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HOW TO MAKE NEW VESSELS?

157 Reduced collateral vessel development and increased fibrosis following hindlimb ischemia in mice with genetic deletion of phosphoinositide 3- kinase gamma

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Purpose: Phosphoinositide 3-kinases (PI3K) belong to a conserved family of enzymes regulating important cellular processes such as cell survival and proliferation. Although PI3K signalling has been linked to vascular endothelial growth factor (VEGF) receptor activation, the specific roles of PI3Ks in the angiogenic process are unknown. In this study we tested the hypothesis that PI3K γ activation is important in the collateral vessel development following hindlimb ischemia. **Methods:** To test this hypothesis, we ligated the femoral artery in wild type mice (129/B6, WT) and in PI3K γ knockout mice (129/B6, PI3K γ -/-). **Results:** Following surgery, PI3K γ -/- mice displayed increased rates of amputation and deambulatory impairment. 28 days after surgery, laser doppler perfusion imaging showed significantly reduced blood flow recovery in PI3K γ -/- mice compared to WT (ischemic over non-ischemic limb blood flow: WT = 0.95 ± 0.04 ; PI3K γ -/- = 0.73 ± 0.03 , $p < 0.01$), increased interstitial fibrosis (% area of fibrosis: WT = 1.7 ± 0.5 ; PI3K γ -/- = 3.2 ± 0.8 , $p < 0.01$) and marked calf muscle atrophy following hindlimb ischemia (30% reduction in calf weight in PI3K γ -/- vs. WT, $p < 0.01$). In contrast to WT mice, hindlimb ischemia did not induce in PI3K γ -/- mice a significant increase in the levels of VEGF, CD4, CD8, interleukin 16 (IL16) and phospho-ERK, suggesting that PI3K γ might play a crucial role in the regulation of multiple signalling pathways involved in collateral vessel development following hindlimb ischemia.

Conclusions: These results show a pivotal role of PI3K γ in regulating collateral vessel development following hindlimb ischemia highlighting novel possible therapeutic strategies to enhance collateral vessel development in response to peripheral ischemia.

158 EDA promotes collateral artery growth through TLR2/TLR4 signaling

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Background: Collateral artery growth (arteriogenesis) is propelled by inflammatory mechanisms, e.g. infiltration of leukocytes and release of pro-inflammatory cytokines. Exogenous application of the Toll Like Receptor 4 (TLR4) ligand LPS has been shown to significantly stimulate arteriogenesis by promoting monocyte infiltration into the perivascular tissue. The extra-domain A (EDA) of fibronectin is an endogenous ligand of TLR 4. We therefore hypothesized that EDA serves as an endogenous stimulator of arteriogenesis through TLR 4 signaling. Furthermore, we hypothesized that TLR 2, previously shown to mediate positive arterial remodeling, is essential for collateral artery growth upon arterial occlusion.

Methods: TLR 4 defective (-/-), TLR 2 -/- mice and their respective genetic backgrounds were subjected to femoral artery occlusion. RT-PCR of EDA was performed at day 3 after femoral artery ligation. At day 7, perfusion measurements were performed to assess the arteriogenic response using fluorescent microspheres injected under maximal vasodilatation. Furthermore, blood was withdrawn for whole blood stimulation experiments and subsequent FACS-analysis of MAC-1 expression as a marker for leukocyte activation.

Results: Detecting MAC-1 on leukocytes after whole blood stimulation, we observed that TLR 4 -/- monocytes did not respond to LPS or EDA stimulation, neither were TLR 2 -/- monocytes activated by PAM3Cys or EDA, indicating that EDA signals via both, TLR 2 and TLR 4. Monocytes from background strains in contrast expressed significantly more MAC-1 upon LPS, PAM3Cys or EDA incubation. After occlusion of the femoral artery, EDA mRNA significantly increased (~80-fold) in the regions of collateral artery formation (i.e. the thigh) as compared to the non-occluded left hind limb. EDA was located in the adventitia of the growing collateral vessels as observed by immunohistochemistry. Seven days after the initial operation, microsphere perfusion measurements elucidated a significant reduction of perfusion restoration in TLR 2 and TLR 4 -/- mice (perfusion occluded vs. non-occluded hind limb: TLR 2 -/-: $38.3 \pm 4.8\%$; C57BL6J: $58.5 \pm 3.1\%$; TLR 4 -/-: $16.3 \pm 2.7\%$; Balb-C: $30.7 \pm 2.2\%$; $p < 0.01$).

Conclusion: Arteriogenesis is mediated by TLR 2 and TLR 4 signaling. EDA is a potential endogenous stimulator of arteriogenesis that requires co-signaling via TLR 2 and TLR 4.

159 Synergistic effect of transplanted human stem cell-derived vascular progenitor cells and adrenomedullin on vascular regeneration

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Background: We and others have demonstrated that adrenomedullin (AM) could potentiate vascular regeneration. We previously isolated vascular progenitor cells (VPC), which can differentiate into both endothelial cells and vascular smooth muscle cells, from mouse, monkey, and human embryonic stem (ES) cells. Herein, we examined the effect of AM on augmented angiogenesis of transplanted human VPC in murine hindlimb ischemia.

Methods: 12-weeks-old of AM-transgenic (AM-Tg) mice, which overproduce AM in their liver, and wild-type (Wt) mice were used for experiments. Undifferentiated human ES cells were induced into VPC differentiation. VEGF-R2+TRA1-VE-cadherin- cells, which we revealed to be defined as VPC, were sorted at day 8 of differentiation and used for transplantation. To obtain vascular cells, that is, endothelial cells and mural cells differentiated from VPC (VPC -VC), VEGF-R2+TRA1-VE-cadherin- cells were recultured with 50 ng/ml of VEGF for 3 passages. VPC and VPC -VC were injected intra-arterially into the middle portion of right femoral artery before ligation. To investigate the augmented effect of AM on endothelial differentiation from ES cell-derived VPC, we sorted VPC on day 8 of differentiation and recultured with VEGF and AM.

Results: The plasma concentrations of total AM in AM-Tg mice were about 100 times more than endogenous AM. Serial follow-up laser Doppler perfusion imaging showed significantly different among groups after day 14. On day 22, accelerated flow improvement was observed in PBS+AM-Tg ($n=12$) vs. PBS+Wt ($n=13$) (0.77 ± 0.09 vs. 0.53 ± 0.08 , $p=0.048$). There was more flow recovery in VPC-VC+Wt ($n=9$) (0.98 ± 0.22 , $p=0.03$) and VPC-VC+AM-Tg ($n=15$) (0.99 ± 0.1 , $p=0.001$) as compared to PBS+Wt but not PBS+AM-Tg. VPC+AM-Tg mice ($n=12$) had the highest flow improvement (1.1 ± 0.05) which was significantly different from PBS+Wt ($p=0.001$) as well as PBS+AM-Tg ($p=0.04$). Total capillary density assessed by mouse PECAM1 staining, an endothelial cell marker, also showed similar pattern of significant differences among groups. Immunofluorescence staining showed that more human PECAM1+ cells appeared, incorporated into host circulating vessel, and formed neovascularization in VPC+AM-Tg than VPC+Wt. On day 8 of incubation, PECAM1+ cells derived from VPC in AM+VEGF groups were much more than VEGF only and negative control.

Conclusions: AM could potentiate the angiogenic effect of transplanted human VPC, partly mediated by enhancing endothelial differentiation. Combination therapy of human VPC and AM may be served as a new promising strategy for therapeutic vascular regeneration.

160 The PPARgamma agonist rosiglitazone inhibits angiogenesis by suppressing CREB activation and COX-2 expression induced by vascular endothelial growth factor in human endothelium

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Background and Aims: The activation of peroxisome proliferator activated receptor (PPAR)gamma following the exposure to the antidiabetic rosiglitazone (RSG) is known to inhibit angiogenesis associated with diabetic vasculopathy, but underlying mechanisms are unknown. The transcription factor cAMP-response element-binding protein (CREB), once phosphorylated in response to vascular endothelial growth factor (VEGF), plays a key role in promoting angiogenesis inducing endothelial proliferation and blood vessel formation, partly by transcriptionally regulating the expression of the pro-angiogenic enzyme cyclooxygenase(COX)-2. We here investigated the effects of PPAR γ stimulation on CREB phosphorylation and COX-2 expression in human umbilical vein endothelial cells (HUVEC) challenged with the pro-angiogenic agents VEGF and phorbol myristate acetate (PMA).

Methods and Results: VEGF induced CREB Ser133-phosphorylation in a dose- and time-dependent manner (Western analysis and gel shift assay) and, correspondingly, upregulated COX-2 mRNA and protein expression (RT-PCR and Western analysis). In the absence of any toxicity and anti-proliferative effects, 10 mmol/L RSG significantly ($p < 0.01$) reduced CREB phosphorylation (Western blot), prevented its binding to CRE within COX-2 promoter (gel shift assay) and inhibited COX-2 expression and activity (by 40%, Western blot and immunoassays for 6-keto-PGF1 α) as induced by VEGF or PMA. These effects were PPARgamma-mediated since they were mimicked by GW1929, another PPARgamma ligand, and completely reverted by the PPARgamma antagonist bisphenol-A-diglycidyl ether (BADGE). Since VEGF signaling pathway involves the activation of protein kinase C (PKC), we explored the involvement of PKC activation on CREB and COX-2 induction by VEGF, observing that PKC down regulation by prolonged treatment with PMA or by pretreatment with Ro31-8220, a non-specific PKC inhibitor, always suppressed CREB activation and COX-2 expression stimulated by VEGF (by 70% and 80%, respectively, Western analysis).

Conclusions: Our findings indicate that VEGF induces CREB activation and

COX-2 expression through a PKC-dependent pathway in human endothelium, and that the anti-angiogenic effect of RSG is due, at least in part, to its interference with the PKC-mediated activation of CREB and the related expression of pro-angiogenic COX-2.

161 Effects of angiotensin II on basal and vascular endothelial growth factor stimulated vascular tube formation by human umbilical vein endothelial cells



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Background: The survival of endothelial cells is critical for angiogenesis and the maintenance of blood vessel integrity. Capillary rarefaction is an early event in patients with cardiovascular risk factors as well in patients with established cardiovascular disease or related disorders. Vascular endothelial growth factor is a specific endothelial cell mitogen that plays a key role in inducing blood vessel formation. As angiotensin II has been implicated in impaired VEGF signalling, we studied the effects of Ang II on basal and VEGF-stimulated vascular tube formation by endothelial cells.

Methods: We grew primary cultures of endothelial cells from human umbilical cords (HUVECs) obtained following elective Caesarean Section with written informed consent and ethical approval. HUVECs at passage 2 were seeded at a density of around 104 cells/ml in Matrigel coated wells in 10% FBS and incubated for 4 hrs. Phase contrast microscopic images of tube formation were digitally captured and tube lengths analyzed using dedicated software. Data are mean $\pm$ SEM. Results were compared by student's two-tailed t-tests.

Results: 4hrs incubation with VEGF 50ng/ml significantly increased HUVEC angiogenic activity vs. 4hr in control medium (total length 5.3 ± 0.2 mm vs. control 4.3 ± 0.3 mm; $P=0.03$). There was little effect of angiotensin II 10nM (total length 4.4 ± 0.2 mm) however angiotensin II 100 μ M reduced tube length markedly (5.0 ± 0.3 mm; $P=0.008$ vs. control) and inhibited the angiogenic effects of VEGF (angiotensin 100 μ M + VEGF 3.5 ± 0.4 mm; $P=0.012$ vs. VEGF alone). The anti-angiogenic effects of angiotensin II 100 μ M were in part prevented by its Type 2 receptor antagonist PD123319 100nM (angiotensin 100 μ M + PD123319 100nM: 3.7 ± 0.3 mm; $P=0.032$ vs. angiotensin II 100 μ M alone).

Conclusions: Our findings support a dose-dependent role for angiotensin II in suppressing both basal and VEGF stimulated angiogenesis. These anti-angiogenic effects of angiotensin II were mediated in part by its Type 2 receptor. This 3D vascular tube model provides an important system for study of mechanisms contributing to capillary rarefaction.

162 First report of an endovascular stent for the delivery of an arteriogenic growth factor



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Background: The stimulation of collateral artery growth (arteriogenesis) using cytokines or growth factors is a promising new treatment strategy for patients with vascular occlusive disease. Continuous local infusion of growth factors via intra-arterial delivery-catheters is the most effective way to induce arteriogenesis. However, this is not feasible in patients, and therefore an alternative mode of delivery is warranted. In the present study we determined the efficacy of a newly developed stent, releasing the pro-arteriogenic cytokine transforming growth factor beta1, to stimulate collateral artery growth in the peripheral circulation of the rabbit.

Methods and Results: A TGF beta1 loaded polymer coating, based on poly(D,L-lactide) was optimized for cytokine release and applied on 15 mm coronary cobalt-chrome alloy stents. A dip-coating method was used, obtaining mounts of coating around 500 μ g. In-vitro testing confirmed elution of about 2.5 μ g active TGF beta1 from these cytokine-loaded stents over the treatment period of seven days. Forty-five rabbits underwent implantation of bare-metal-stents (BMS), polymer-only-coated stents (PCS) or polymer-coated TGF-beta eluting stents (TGF) in the iliac artery and subsequent femoral artery ligation (n=15/group). After seven days, microsphere-based perfusion measurements revealed a significant increase in collateral conductance following TGF beta1-stent implantation compared to the control groups (ml/min/100mmHg: BMS: 47.8 ± 1.0 ; PCS: 44.1 ± 1.6 ; TGF: 91.3 ± 13.3 ; $p < 0.05$). Histological analysis of hindlimb collateral arteries verified a significantly higher proliferation activity of vascular smooth muscle cells (VSMC) in collateral arteries from the TGF beta1-treated group (% of Ki67 pos. VSMC: BMS: 18.9 ± 1.3 ; PCS: 18.4 ± 2.3 ; TGF: 27.4 ± 7.9 ; $p < 0.05$). At seven days, no significant difference in in-stent neointima formation was observed (neointima area in mm²: BMS: 0.34 ± 0.09 ; PCS: 0.32 ± 0.13 ; TGF: 0.32 ± 0.09).

Conclusion: We first describe the use of a cytokine-releasing stent to stimulate collateral artery growth. These results show that intra arterial cytokine-releasing devices may serve as a novel platform for pro-arteriogenic therapy as well as for other applications demanding local delivery of proteins.

STABILIZING OR REVERSING ATHEROSCLEROSIS

163 Chronic activation of soluble guanylate cyclase improves endothelial function and reduces atherosclerosis in apolipoprotein E-deficient mice



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Decreased NO bioavailability due to diminished NO production or increased oxidative stress plays an important role in atherogenesis. Activation of targets downstream of NO may be a therapeutic strategy to inhibit endothelial dysfunction and atherosclerotic lesion formation. Therefore, we investigated the effect of a novel activator of soluble guanylate cyclase (sGC), HMR1766, in a mouse model of atherosclerosis.

Methods and Results: In vitro, HMR1766 activates the heme-oxidized form of sGC, which is insensitive to NO, and increases cGMP accumulation in vascular smooth muscle cells. Apolipoprotein E-deficient (ApoE^{-/-}) mice were fed a high-fat diet containing 1.25% cholesterol for 6 weeks or 0.5% cholesterol for 15 weeks, or the respective cholesterol-rich diets supplemented with HMR1766. At the end of the treatment periods, there were no significant differences in plasma cholesterol concentrations between the groups. Compared to wild-type mice, placebo-treated ApoE^{-/-} mice developed profound endothelial dysfunction, as indicated by an impaired endothelium-dependent vasodilation (organ chamber experiments with isolated aortic segments), and severe atherosclerotic lesion formation in the aortic root and the ascending aorta (oil red O staining; histological morphometric analysis). In contrast, both treatment regimen with HMR1766 significantly reduced atherosclerotic plaque formation and markedly improved endothelium-dependent vasodilation. Treatment with HMR1766 had no effect on endothelium-independent vasorelaxation or vasoconstriction. HMR1766 led to increased expression of vascular P-VASP, a downstream target of sGC, did not alter eNOS and sGC expression (Western blot), and reduced vascular VCAM-1 expression (immunohistochemistry). Aortic release of reactive oxygen species was increased in ApoE^{-/-} mice as compared to wild-type mice, but was not affected by treatment with HMR1766 (L-012 chemiluminescence). There was no significant effect of HMR1766 treatment on systolic blood pressure (tail-cuff measurements).

Conclusions: Treatment with HMR1766, an activator of sGC, improves endothelial function and reduces atherosclerosis in ApoE^{-/-} mice. HMR1766 represents a promising novel therapeutic agent for the treatment of atherosclerosis.

164 Blocking of angio-associated migratory cell protein inhibits smooth muscle cell migration and neointima formation after vascular injury in apolipoprotein E knockout mice



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Purpose: Angio-associated migratory cell protein (AAMP) was described to participate in angio- and cancerogenesis and is predominantly expressed in cells with a migratory phenotype; thus, we investigated the contribution of AAMP to neointima (NI) development.

Methods: Subcellular localisation of AAMP in SMCs was examined using confocal scanning laser microscopy. AAMP contents of smooth muscle cells (SMCs) with different phenotypes were quantified by Western blot. Expression of AAMP and density of SMCs were determined in the atherogenic apolipoprotein E knockout (apoE^{-/-}) mouse model or in the porcine coronary restenosis model by immunohistochemistry and by western blot. Migratory potential of SMCs transiently transfected with AAMP sense expression vectors or treated with anti-recombinant AAMP (anti-rAAMP)-antibody was examined using Boyden chamber assays. After dose-finding studies, apoE^{-/-} mice were treated intraperitoneally with anti-rAAMP antibody, and NI area and SMC density in wire-injured carotid arteries were quantified histopathologically after 4 weeks.

Results: AAMP-transfected SMCs and SMCs of the migratory phenotype displayed intensified AAMP distribution along the filopodia and lamellipodia. SMCs of the migratory phenotype displayed increased AAMP expression (34.9 ± 6.0 intensity/area) compared to the quiescent SMC phenotype (3.8 ± 0.3 ; $P < 0.01$). Vascular injury enhanced AAMP expression in murine arteries ($88.1 \pm 6.0\%$ of NI area) compared to non-injured control (32.2 ± 3.1 ; $P < 0.01$) and in porcine arteries (38.4 ± 6.2 intensity/area) compared to non-dilated control (4.9 ± 1.0 ; $P < 0.01$) after one week. The NI of coronary arteries displayed elevated AAMP content 1 week after dilatation (40.1 ± 6.2 intensity/area) compared to control (10.2 ± 1.1 intensity/area; $P < 0.01$). SMCs overexpressing AAMP displayed increased migratory potential (51.9 ± 4.1 cells/area) compared to mock transfected cells (32.5 ± 2.3 ; $P < 0.01$), and blocking of AAMP reduced migratory potential of medial (21.5 ± 4.0 cells/area) or SMCs of the NI (74.4 ± 11.6) compared to control (49.7 ± 3.8 or 164.5 ± 20.6 ; $P < 0.001$). Blocking of AAMP reduced NI area development ($42.1 \pm 2.8 \mu\text{m}^2$) and NI SMC density ($18.3 \pm 4.2\%$) compared

to isotype control (78.7 ± 3.1 ; $P < 0.01$ and 33.3 ± 5.5 ; $P < 0.01$) in wire-injured arteries.

Conclusions: Upregulation of AAMP in migratory and neointimal SMCs, increased migratory potential of SMCs overexpressing AAMP, and reduced SMC migration, SMC density and NI formation under blockade of AAMP indicate a possible contribution of AAMP to NI formation.

165 Role of α_1 receptor blockade in atherosclerotic plaque stabilization



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Purpose: Clinical trials have demonstrated that agents that inhibit the angiotensin II pathway confer benefit beyond the reduction of blood pressure alone. However, the molecular mechanism underlying this effect has yet to be investigated. Recently, we have reported the overexpression of inducible cyclooxygenase (COX-2) and prostaglandin E synthase (mPGES-1) in human symptomatic plaques, and provided evidence that it is associated with metalloproteinase (MMP)-induced plaque rupture. By contrast, COX-2 overexpression in the presence of high levels of lipocalin type PGD synthase (L-PGDS) is associated with a stable plaque phenotype, possibly through generation of PGD₂ and 15d-PGJ₂, compounds with anti-inflammatory properties. Thus, the aim of this study was to characterize the effect of the α_1 receptor antagonist irbesartan on the inflammatory infiltration and the expression of COX-2, mPGES-1, L-PGDS and MMPs in human carotid plaques.

Methods: Forty patients with symptomatic carotid artery stenosis were randomized to irbesartan (300 mg/d) or chlorthalidone (50 mg/d) for 4 months before endarterectomy. Plaques were analyzed for inflammatory cells, COX-2, mPGES-1, L-PGDS, MMP-2 and MMP-9 by immunocytochemistry and Western blot; zymography was used to detect MMP activity.

Results: Plaques from irbesartan group had fewer macrophages ($7 \pm 4\%$ vs $23 \pm 6\%$), T-lymphocytes ($3 \pm 2\%$ vs $8 \pm 3\%$), and HLA-DR+ cells ($P < 0.0001$), less ($P < 0.0001$) immunoreactivity for COX-2 ($8 \pm 4\%$ vs $22 \pm 3\%$), mPGES-1 ($7 \pm 5\%$ vs $26 \pm 2\%$) and MMP-9 ($8 \pm 2\%$ vs $28 \pm 4\%$), reduced ($P < 0.0001$) gelatinolytic activity and increased ($P < 0.0001$) levels of L-PGDS ($27 \pm 4\%$ vs $8 \pm 3\%$) as compared to plaques from chlorthalidone group.

Conclusions: This study shows for the first time that α_1 blockade may stabilize atherosclerotic plaque by up-regulating the L-PGDS pathway and thus reducing PGE₂-dependent MMP biosynthesis.

166 N-3 polyunsaturated fatty acids stabilize atherosclerotic plaques in humans by inhibiting pge2-dependent matrix metalloproteinase activity



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Purpose: Clinical trials have demonstrated that n-3 polyunsaturated fatty acids (n-3 PUFAs) confer strong protection against fatal myocardial infarction and cardiovascular death. However, the molecular mechanism(s) underlying this effect are not yet completely known. Recently, we demonstrated enhanced expression of the inducible type 1 PGE synthase (mPGES-1) in human symptomatic plaques, and provided evidence that it is associated with metalloproteinase (MMP)-induced plaque rupture. Thus, the aim of this study was to characterize the effect of n-3 PUFAs on inflammatory infiltration and expression of mPGES-1 and MMPs in human carotid plaques.

Methods: Seventy high-risk patients with asymptomatic carotid artery stenosis were randomized in a double blind study to n-3 PUFAs (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] in the ratio of 0.9/1.5, 1 g/day) or placebo for 4 months before endarterectomy. Plaque specimens and plaque-derived macrophages were subjected to analysis of constitutive PGE synthase (cPGES), mPGES-1, mPGES-2, MMP-2 and MMP-9 by immunocytochemistry and Western blot, whereas zymography was used to detect MMP activity and EIA was used to detect PGE₂ and MMP-9 levels. Immunohistochemistry was also used to identify procollagen and interstitial collagen content, and CD68+ macrophages, CD3+ T-lymphocytes, smooth muscle cells (SMCs) and HLA-DR+ inflammatory cells.

Results: Plaques from n-3 PUFA group had fewer ($P < 0.0001$) macrophages, T-lymphocytes, and HLA-DR+ cells; less ($P < 0.0001$) immunoreactivity for mPGES-1 and MMPs; less production of PGE₂ and MMP-9 ($P < 0.0001$); reduced ($P < 0.0001$) gelatinolytic activity; increased ($P < 0.0001$) collagen content. Worth noting is that mPGES-1 inhibition was observed after incubation of monocytes in vitro with EPA or DHA, but not with n-6 or n-9 PUFAs.

Conclusions: This study demonstrates that n-3 PUFAs used as a pharmacological tool decrease inflammation and inhibit mPGES-1 expression in plaque macrophages. This effect in turn may contribute to human plaque stabilization by inhibition of metalloproteinase-induced plaque rupture.

167 Local lentiviral shRNA silencing of CCR2 inhibits vein graft thickening in hypercholesterolemic ApoE3Leiden mice



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Intimal hyperplasia and accelerated atherosclerosis in venous bypass grafts are major causes of graft failure. Inflammatory responses to vascular injury and subsequent smooth muscle cell (SMC) migration and proliferation in the vein are key players in these processes. Therefore, interference in the inflammatory responses by RNA interference seems to be an attractive strategy for inhibiting vein graft disease.

Here, we study the effect of blocking the inflammatory processes by local application of lentiviral short hairpin RNA (shRNA) silencing the MCP-1 receptor (CCR2) on intimal hyperplasia in a murine model for vein graft disease.

The mRNA of murine CC-chemokine receptor 2 (CCR2) is abundantly expressed on vascular SMCs and macrophages as determined by real-time RT-PCR. Next, a lentiviral shRNA was designed targeting murine CCR2. This shCCR2 proved to be able to knock-down CCR2 expression at the mRNA and protein levels in vitro. Moreover, migration of SMCs one day after stimulating SMCs with murine MCP-1 (100 ng/ml), was reduced by 37% in the cells infected with lentiviral shCCR2.

To demonstrate the efficacy of the lentiviral shCCR2 in blocking vein graft disease in vivo, a venous interposition was placed into the carotid artery of recipient hypercholesterolemic ApoE3Leiden mice to induce intimal hyperplasia in vivo. In this interposition, intimal hyperplasia with signs of accelerated atherosclerosis develops within 4 weeks. Directly after graft placement, pluronic gel containing 10E8 pfu lentiviral shCCR2 or a control lentivirus was applied around the vein graft. Mice were sacrificed 28 days after surgery. Morphometric analysis on sections of grafts shows a significant 38% reduction in total amount of intimal hyperplasia in the shCCR2 treated animals (controls: 0.42 ± 0.05 mm², shCCR2: 0.26 ± 0.03 mm², $p = 0.007$).

In conclusion, these data demonstrate that lentiviral shCCR2 reduces migration of SMCs in vitro. Moreover, local application of shRNA against CCR2 to the vessel wall prevents intimal hyperplasia and vein graft disease in a hypercholesterolemic murine in vivo model for vein graft disease. Therefore, this local application of RNA interference is very promising as therapeutic tool to prevent vein graft failure.

168(W) Heparanase and atherosclerosis: lessons from transgenic mice overexpressing the human heparanase gene

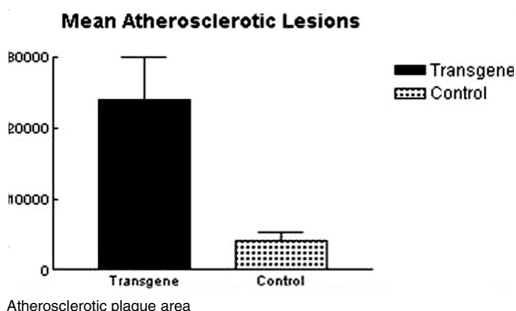


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Objective: To study the effect of heparanase over-expression on the development and progression of atherosclerosis.

Methods: Transgenic mice ubiquitously over-expressing the human heparanase gene were produced. Atherosclerosis in the aortic root of the transgenic mice was compared to control C57BL/6 mice after 6 months of high fat diet. Advanced plaque composition and stability was studied in transgenic mice on the background of Apo E-/- mice. Lipid profile, cytokine profile and lipid uptake by mouse peritoneal macrophages was studied. Apo E-/- mice were transplanted with bone marrow from transgenic mice, C57BL/6 mice and Apo E-/- to study whether the effect is mediated by the hematopoietic system.

Results: Transgenic mice over expressing heparanase had 5 times increased atherosclerotic lesions compared to control mice. Atherosclerotic plaques in Apo E null mice crossbred with heparanase overexpressors were less stable as demonstrated by reduced plaque's collagen to lipid ratio compared to Apo E-/- mice. There was no difference in plasma lipid profile and cholesterol uptake by peritoneal macrophages between the groups. Heparanase overexpressors had higher levels of IFN gamma. Apo E-/- mice over-expressing heparanase only in hematopoietic cells had increased atherosclerotic plaque area compared to control.



Conclusions: Heparanase plays a dominant role in atherosclerosis both in early lesions and mature plaques composition. The effect is at least partially mediated by the hematopoietic system.

CHALLENGING QUESTIONS IN GROWN-UP CONGENITAL HEART DISEASE

169 High pressure at the dark side of the circulation: pulmonary arterial hypertension in adults with congenital heart disease



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Aim: To evaluate the pathogenic role of pulmonary arterial hypertension (PAH) in the morbidity following from congenital heart defects, in particular septum defects and cyanotic disease.

Methods: The data base of the European Heart Survey on adult congenital heart disease, a retrospective cohort study with over 5-year median follow-up, was used to assess the prevalence of PAH, its effect on outcomes, and relations with other markers of pathology. All patients (83% from tertiary referral centres) were selected with an ASD (n=882), VSD (n=628) or cyanotic heart disease (n=390). Presence of PAH was defined as pulmonary artery pressure (PAP) > 40 mmHg as recorded in the patient file (or when qualified as "abnormal" otherwise). The following relations were analysed with standard statistical methods. In patients with unclosed septal defects with or without the Eisenmenger syndrome: presence of PAH and functional limitations (NYHA class > 1). In patients with unclosed septal defects but without Eisenmenger: the relation between baseline PAP and NYHA class worsening (or death). In patients with cyanotic disease: the prevalence of a history of major events (bleedings, thrombotic events) related to parameters of cyanosis.

Results: Overall, the prevalence of PAH was 29%. Among patients with an unclosed septal defect, prevalence was 33% in the case of a VSD, and 30% in the case of an ASD; in patients with closed defects, 12%, respectively 13%; in cyanotic disease other than Eisenmenger syndrome, 19%. Presence of PAH was associated with an 8-fold increased risk of functional limitations, while Eisenmenger syndrome entailed an additional 5-fold increase. Increased PAP was a strong predictor of adverse outcome (NYHA class change or death) in patients with an unclosed VSD (hazard ratio 1.049 for each mmHg; $P < 0.001$), but not in patients with an unclosed ASD. A history of major bleeding events was much more prevalent in patients with the Eisenmenger syndrome compared to those with (non-Eisenmenger) cyanotic heart disease (5% versus 15%; $P=0.002$), independently from the degree of cyanosis.

Conclusions: In this selected population, the prevalence of PAH among patients with septum defects is remarkably high. Presence of PAH is a strong determinant of functional limitations and predictor of adverse outcome. Monitoring of PAP and careful management of pulmonary artery hypertension should be key elements in the care of adults with septum defects.

170 Electrical and structural reverse remodeling after transcatheter closure of Atrial Septal Defects in adults



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The presence of long standing atrial septal defects (ASD) results in electrical and structural remodeling of the human atria susceptible for the development of supraventricular arrhythmias. Objective: To determine the effects of transcatheter closure of ASD's on electrical and structural remodeling.

Methods: Thirty-seven consecutive patients after successful device closure of ASD's were included into this analysis. Patients (mean age: 40 ± 17 years) were assessed by means of standard 12-lead electrocardiography (ECG) and transthoracic echocardiography. Data were obtained before the intervention, at 1 month and 12-month follow-up. The following ECG parameters were collected using conventional measurements: maximal and minimal duration of the P wave (P max, P min), P dispersion (Pmax-Pmin), QT max, QT dispersion (Qtmax-Qtmin). Right ventricular (RV) dimensions were assessed by means of M-mode echocardiography (RVm). Two-dimensional and Doppler echocardiography were used to evaluate the maximal inlet diameter (RVmax), right atrial area (RAA), left atrial area (LAA), end-diastolic RV/LV ratio and the RV systolic pressure (RVSP).

Results: At one-month follow-up P max and QT max showed significant reduction compared with baseline (122 ± 17 ms vs. 117 ± 13 ms, $p=0.02$; 402 ± 18 ms vs. 396 ± 17 ms, $p=0.02$, respectively). There was no significant change in P dispersion, QT dispersion. RAA (18 ± 4 cm² vs. 7 ± 4 cm², $p=0.02$), RVm (31 ± 7 mm vs. 27 ± 6 , $p<0.0001$), RVmax (45 ± 6 mm vs. 43 ± 8 mm, $p=0.02$), RV/LV (0.71 ± 0.18 vs. 0.57 ± 0.13 , $p<0.0001$) and RVSP (38 ± 9 mmHg vs. 29 ± 5 mmHg, $p<0.0001$) decreased significantly. At one-year follow up only P max (95 ± 13 ms, $p<0.0001$), QT max (387 ± 17 ms, $p=0.02$), QT dispersion (40 ± 16 ms to 44 ± 18 ms to 40 ± 16 ms, $p=0.001$), RAA (15 ± 3 cm², $p=0.02$), RVm-mode (23 ± 5 mm, $p<0.0001$), RV/LV (0.48 ± 0.11 , $p<0.0001$) showed further reduction. Sixteen percent of the patients had atrial arrhythmias before the procedure and 60% of them became

arrhythmia-free during the follow-up. Only atrial dimensions were different between patients with and without arrhythmias (RAA: 23 ± 4 cm² vs. 17 ± 4 cm², $p=0.04$; LAA: 20 ± 4 cm² vs. 16 ± 3 cm², $p=0.01$) Conclusions: Electrical and structural reverse remodeling starts early after defect closure and continues at one year follow-up. Our data suggest that structural reverse remodeling may play a role in the reduction of arrhythmia recurrences.

171 Is the presence of an atrial septal defect also related to an increased prevalence of migraine? A prospective multi-centre follow up study



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Background: The prevalence of migraine is 10-12% in the overall population. An increased prevalence is noted in patients with a right-to-left shunt and a patent foramen ovale (PFO). Although an atrial septal defect (ASD) is mainly characterized by a left-to-right shunt, a spontaneous right-to-left shunt is frequently detected on contrast echocardiography. Therefore, we wanted to compare the prevalence of migraine between ASD and PFO patients.

Methodology: All 103 PFO and 72 ASD patients (>16 years), who underwent a percutaneous closure in our centres between November 2003 and December 2005, were included in this prospective trial. They received a structured headache questionnaire immediately before closure. In one arm of the study, changes in prevalence of migraine were recorded by sending a second questionnaire at least two months after ASD closure. A neurologist, blinded to the patients' files, diagnosed migraine with or without aura according to the International Headache Criteria (MA+ or MA-, respectively).

Results: Ninety-eight PFO (95%, 68 males, mean age 51.3 ± 12.1 years) and 63 ASD patients (88%, 16 males - Chi-square, $P<0.001$ vs PFO, mean age 48.1 ± 16.4 years - T-test, $P=0.19$ vs PFO) filled in the questionnaire. The overall prevalence of migraine was 27.5% for the PFO group and 34.9% for the ASD group ($P=0.49$). For MA+ the prevalence was 10.2% and 15.9% for the PFO and ASD group, respectively ($P=0.26$). The prevalence of MA- was 17.3% for the PFO and 19.0% for the ASD group ($P=0.93$). Forty-four ASD patients could be already included in the follow-up arm (median follow-up time 0.5 years (range 0.3-1.4 years)). The overall prevalence of migraine decreased from 34.1% to 25.0% (Mc Nemar, $P=0.34$), MA- from 18.2% to 15.9% ($P=0.99$), and MA+ from 15.9% to 9.1% ($P=0.45$). Two of three non-migraine patients developed MA+, one MA-.

Conclusions: The overall prevalence of migraine is high in both ASD and PFO patients. The prevalence did not differ between patients with an ASD or a PFO. Our prospective preliminary results of ASD closure suggests a tendency to further decrease of migraine. However, a longer follow-up time and a more powered trial will be necessary to answer these remaining questions.

172 Pulmonary regurgitation in Tetralogy of Fallot. How can it be assessed?

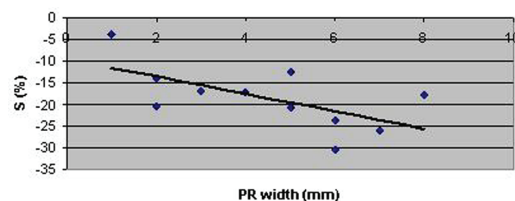


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Background: Pulmonary regurgitation (PR) is associated with an adverse outcome in patients after tetralogy of Fallot (TOF) repair. Accurate ultrasound markers of PR severity are yet poorly defined. The aim of our study was to determine whether ultrasonic tissue indices can be helpful in the detection of significant PR in adults reoperated after total correction of TOF.

Methods: 15 consecutive TOF patients (7F, 8M) (age 25-50 yr) being operated in childhood or adolescent age and reoperated in the further years were examined. They were characterized by the duration of pulmonary regurgitation obtained from the continuous-wave Doppler (PR time) and by the color Doppler pulmonary regurgitant jet width (PR width). The ratio between PR width and pulmonary trunk diameter was defined as pulmonary regurgitation index (PRI). To calculate regional longitudinal systolic and diastolic Strain Rate (SR) and maximal strain (S), GE Echopac 2D was applied. The program allowed an automatic tracking of the region of interest throughout the RV lateral wall as well as the septal and LV lateral wall segments.

Results: PR was detected in 11 out of 15 patients. Mean PR time was 409,5 ms and PR width 4,45 mm. We found a significant correlation between PR width and systolic basal RV S ($r=-0.63$; $p<0.05$) [Fig. 1]. The value of S in mid- and apical RV segments as well as in the septal and LV segments was non-contributory in



PR evaluation

respect to PR characterization. PR time and PRi did not correlate with either of analyzed tissue indices.

Conclusion: PR is common in adults reoperated after total TOF repair. Its significance can be described by increased longitudinal strain in the basal RV segments.

173 Risk of complications during pregnancy in women with congenital aortic stenosis



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Background: To investigate the magnitude and determinants of risk during pregnancy in patients with congenital aortic stenosis (AS).

Methods: Using two adult congenital heart disease (CHD) registries, 117 women with congenital AS receiving care in 6 tertiary medical centres were included: congenital valvular aortic stenosis (n=83), subaortic stenosis (n=32) and supra-aortic stenosis (n=2).

Results: A total of 48 women had 84 pregnancies, including 9 miscarriages (10.7%) and 5 elective abortions. We investigated 70 completed (>20 weeks of gestation) pregnancies in 44 women. Complications were observed during 51 of 70 completed pregnancies (72.9%). The most severe cardiac complication was heart failure (n=3, 4.3%), requiring aortic valve replacement during pregnancy in one patient. Other cardiac complications were clinically significant arrhythmias (n=5, 7.1%), angina pectoris (n=2, 2.9%), syncope (n=1, 1.4%) and transient ischemic attack (n=1, 1.4%). General pregnancy complications were eclampsia (n=1, 1.4%), preeclampsia (n=3, 4.3%) and pregnancy-induced hypertension (n=6, 8.6%). Obstetric complications included placental abruption (n=3, 4.3%), premature labour (n=4, 5.7%), premature rupture of membranes (n=2, 2.9%). There were 54 vaginal deliveries, including 14 instrumental assisted deliveries (20%). Sixteen deliveries (32%) were by caesarean section, most were for obstetric indications. Mean pregnancy duration was 38.3 ± 2.8 weeks, and premature birth occurred in 10 pregnancies (14.3%). Eleven of the 70 children (15.7%) were small for gestational age. There was one neonatal death (1.4%), but no maternal death. Recurrence of CHD in the offspring was documented in 2 pregnancies (3.1%) in patients with supra-aortic AS.

Conclusions: In this largest report on pregnancy in women with congenital aortic stenosis to date, an increased risk of cardiac complications and obstetric interventions was observed. However, pregnancy is generally tolerated well in most patients with congenital aortic stenosis.

174 Warfarin treatment in patients with giant coronary aneurysms caused by Kawasaki disease



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Purpose: To determine the effectiveness and risk of bleeding in patients with giant coronary aneurysms (GA) caused by Kawasaki disease (KD) treated by oral warfarin treatment.

Methods: A multi-institutional cohort study was conducted. Fifty eight (46 male and 12 female) patients with GA > 8 mm in diameter and had been treated for > 3 months were enrolled. Coronary aneurysms were on right coronary artery in 15, left in 12, and both in 31 patients. The diameter of GA was median of 10.3 (8-39.5) mm. The age at KD was median of 2.3 (0.2 - 14.5) years old. Warfarin was started from 0 (0 - 17) months after the onset of KD and had been prescribed for 3.0 (0.3 - 17.6) years giving 235.5 of patient-year. Target international normalized ratio of prothrombin time was 1.5 in 5, 1.5 - 2.0 in 29, 2.0 in 18, and unknown in 6 patients.

Results: During this observational period, 3 patients suffered from acute myocardial infarction (AMI). Of these 3, 1 patient suffered from 2 events of AMI and 1 course of intracoronary thrombolysis (ICT) but died and another 1 patient experienced 4 events of AMI and 4 courses of ICT and alive. Visualization of coronary thrombus formation enforced ICT in 2 patients (1 and 4 times, respectively). Acute coronary event rate was calculated as 4.2 per 100 patient-year. Excluding 6 patients who had acute coronary event prior to warfarin treatment, freedom of acute coronary event was 92% at 1 month and 82% at 10 years. Of note, within 6 months after discontinuation of warfarin, 2 patients suffered from AMI and 1 of them died. Catheter intervention was offered in 6 patients for development of coronary stenosis. Eight hemorrhagic episodes were observed in 5 patients giving 3.4 episodes per 100 patient-year. Of them 4 were caused by blunt hit and 1 was acute subdural hematoma that required emergency operation.

Conclusions: Warfarin treatment is effective to prevent acute coronary event in

most patients with GA caused by KD though it has some risk of hemorrhagic complications. In conjunction with warfarin treatment, regular check up of coronary anatomy and appropriate coronary interventions must be offered.

GROWN-UP CONGENITAL HEART DISEASE: LONG-TERM FOLLOW-UP DATA AVAILABLE?

175 Long-term course in adult patients with atrial septal defect and pulmonary hypertension treated with percutaneous device occlusion

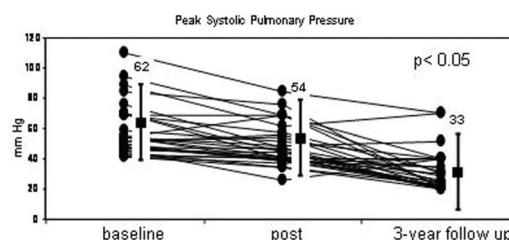


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Background: Percutaneous device occlusion of secundum atrial septal defect (ASD) is an accepted alternative to surgical closure. However, there is limited information on the immediate and long-term effects of percutaneous device occlusion for ASD in middle-aged or elderly patients (pts) with pulmonary hypertension (PHT).

Methods: From a total of 212 pts with ASD treated with percutaneous device occlusion, we selected 40 adult pts (mean age 53 ± 16 years) with a baseline peak systolic pulmonary pressure (PSP) > 40 mmHg. Before treatment, 10 pts (25%) were in functional class III-IV. Seven pts with a mean PSP of 75 ± 22 mmHg had a bi-directional shunt. An Amplatzer occluder (mean device diameter 28 ± 7.4 mm) was successfully implanted in all pts. A new hemodynamic and echocardiographic assessment was performed immediately after treatment. Close clinical follow-up was undertaken in all 40 pts. The last echo-Doppler evaluation was made at a mean follow-up time of 3.4 ± 2.4 years.

Results: There were no major complications. Complete ASD occlusion at discharge was observed by echo-Doppler in 37 pts (92%). The figure shows the course of pulmonary pressure. At the last clinical evaluation, only 1 pt (2%) was in functional class III and 38 (96%) were in class I-II. One pt 72 years-old died of heart failure and respiratory infection 30 months after treatment. One pt has a persistent residual shunt while the remaining 38 have complete ASD occlusion. The subgroup of pts with bi-directional shunt before treatment had significant further decrease in pulmonary pressure at late follow-up (36 ± 20 mmHg; p < 0.05)



Conclusions: Most adult pts with ASD and PHT show a marked clinical and hemodynamic improvement after percutaneous treatment which is maintained long-term follow-up.

176 Homograft survival after tetralogy of Fallot repair: looking for determinants of accelerated homograft degeneration



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Background: Homografts are frequently implanted in patients with tetralogy of Fallot (TOF). However, these homografts have no lifelong survival and surgical re-intervention remains still unavoidable. We were interested in the survival pattern of homografts used in TOF and to determine variables which could influence their survival course.

Methods: All patients with TOF, who were older than 14 years and underwent a surgical intervention with the placement of a homograft in sub-pulmonary position, were selected from our database of congenital cardiology. All patients' files were reviewed to determine demographic, echocardiographic, and peri-operative characteristics. The primary endpoint was defined as homograft replacement or percutaneous balloon-dilatation (PTP > 50 mmHg). Homograft survival was calculated by Kaplan Meier analysis. In addition, stepwise regression analysis was performed to identify variables which determined accelerated homograft degeneration. The latter was defined as the mean increase per year of the homograft gradient. All tests were two-sided, P < 0.05 was considered to be significant.

Results: Sixty-eight TOF patients (71% male, mean age 34 ± 11 years) underwent their first homograft implantation at a median age of 24 years (range 14-49 years). Almost all of these patients (66/68) underwent previously palliative (n = 32) or corrective surgery without an homograft (n = 34). Mean survival time of the first homograft was 14.6 years (CI 12.9 - 16.2 years). Median increase in homograft gradient was 1.1 mmHg/year (range 0.0 - 22.1) for a median follow-up time of 8.4 years (range 1.3 - 17.9 years). Stepwise regression analysis identified the

gradient of the homograft at 1 month after surgery as prognostic for homograft degeneration ($R^2 = 0.23$, $\beta = 0.26$, $P = 0.001$). Immunologic variables, gender, and postoperative inflammatory markers were not related to the degree of increase of homograft gradient. Finally, age at first homograft implantation and previous palliative surgery were significantly associated with the gradient at one month (Spearman's $\rho = -0.41$ and -0.29 , $P = 0.004$ and 0.048 , respectively).

Conclusions: Homograft survival in patients with TOF repair is quite good. However, some patients develop an accelerated homograft degeneration. We found that the gradient of the homograft at one month after surgery is most indicative for accelerated homograft degeneration. We hypothesize that mechanical, and not immunological factors might play an important role in homograft degeneration.

177 Late survival of adults with Mustard repair for transposition of the great arteries

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Introduction/Methods: Late survival patterns of adult patients with Mustard repair for d-transposition of the great arteries (d-TGA) in early life continue to evolve. In a single-centre review, we studied the survival of adults with Mustard repair after transition of care to our institution at the age of 18 years. Only patients with regular follow-up were included.

Results: The outcome of 150 patients (35% female, mean age at last follow-up: 27.8 ± 6.9 years, range 18–53 years) was retrospectively analyzed. Thirteen patients (8.7%) died during follow-up; 11 deaths were cardiac-related. Mean age at death was 26.1 ± 7.0 years. Death rate after 10 years of follow-up was 7.0% (95% CI 3.6–13.7%), and (95% CI 9.2–37.5) after 20 years of follow-up was 19.2%. Non-survivors were less likely to have simple d-TGA (33% vs. 75%, $p=0.002$), were older at the time of Mustard repair (median age 3.0 vs. 1.2 years, $p=0.004$), and were more likely to be in NYHA class > II (58% vs. 5%, $p<0.001$). Five patients who died during follow-up had documented ventricular tachycardia (38% vs. 5% in survivors, $p<0.001$). There was a significant difference in QRS duration on the resting ECG between survivors (109 ± 22 ms) and non-survivors (159 ± 41 ms; $p=0.001$). In a multivariate Cox regression analysis with simple d-TGA anatomy, NYHA class > II, and QRS duration > 140 ms (HR 16.0, 95% CI 1.72–110.2), the latter was the most significant predictor for cardiac death during follow-up (see figure 1).

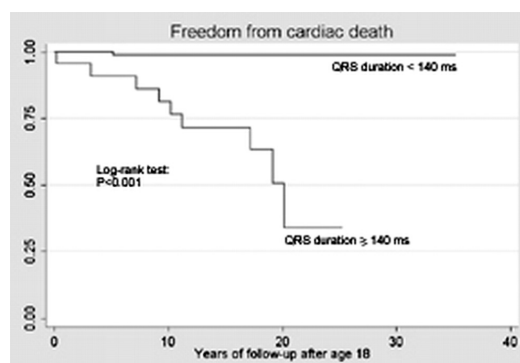


Figure 1

Conclusions: Simple clinical and ECG findings are helpful in identifying adult patients with Mustard repair at increased risk for death. Patients with d-TGA and associated abnormalities (most commonly a ventricular septal defect), poor functional capacity, and QRS duration > 140 ms deserve particular attention.

178 Extended Clinical and Blood Pressure Outcomes in Adults After Stenting of Aortic Coarctation

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Background: Primary stenting has become a preferred method of treatment for adolescents and adults with native or recoarctation of the aorta. While the short term effects are known to be beneficial, the longer term outcomes, especially with regards to control of systemic hypertension are unknown.

Methods: Over a 11 year period, 101 patients underwent stenting for aortic coarctation at the Congenital Cardiac Centre for adults. Of these, 58 patients were followed more than 4 years after the procedure. Complete clinical data was available for analysis in 36 patients <1 year and in 34 patients > 4 years post procedure. A general linear model (SPSS 12.0®) for repeated measures, paired t test and the Chi-square tests were used as appropriate.

Results: There were 19 (53%) males and mean age was 35 (range 15 to 65)

years. There were 22 patients (61%) who were stented for recoarctation from previous surgery. Overall, peak gradient across the coarctation fell from 40 ± 19 mm Hg to 2 ± 4 mm Hg ($p<0.05$) at the procedure and at follow up angiography at 1 year was 4 ± 7 mm Hg ($p<0.05$; compared to baseline). Two patients died during follow up, neither due to coarctation related causes. Two patients (5.5%) developed an aneurysm at the stented site and both these patients were successfully treated by a further transcatheter procedure. No patient required any surgical intervention for the coarctation, although 4 (11%) required other cardiac surgery during follow up. The outcomes for blood pressures are given in Table 1.

Table.1

	Baseline	Short term (<1 year)	Longer term (>4 years)
Mean follow up period (days)	Pre-procedure	225±27	2095±945
Right arm systolic BP(mmHg)	156±28	130±16*	132±16*
Right leg systolic BP(mmHg)	113±14	120±19	124±19
Mean # of antihypertensive medications	1±1.0	0.4±0.7*	0.7±1.0*
# of patients receiving no antihypertensives	13 (38%)	24 (71%)*	21 (62%)*

*P<0.05 as compared to baseline

Conclusions: Stenting of aortic coarctation in adults leads to a significant improvement in hypertension, which is sustained in the longer term. The majority of patients do not appear to require antihypertensive medications and the longer term clinical outcomes appear to be good. Close observation remains necessary to monitor for aneurysm formation and other cardiac issues which may require further intervention.

179 COArctation Long-term Assessment (COALA-Study): perioperative and long-term mortality of surgical coarctation repair

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Aim of the study: to assess survival and the cause of death after surgical coarctation repair.

Patients and Methods: From 1974 to now 404 patients born before 1.1.1965 underwent surgery for isolated aortic coarctation in our hospital. In the COALA study their follow-up was investigated. In deceased patients the cause of death was extracted from hospital charts, from personal reports of relatives, or from the German death register.

Results: In total, 22 patients (5.4%) died at surgery and during the follow-up of up to 30 years. One 10 days old infant died at coarctation repair (year 1981). Six infants, all under the age of 2 months, died postoperatively (year 1976–1983). There were no other perioperative deaths. At logistic regression analysis only young age at surgery was an independent risk factor.

At long-term follow-up 2 patients died from an ascending aorta aneurysm, one of them with a genetic mosaic of Turner syndrome at the 35th week of her second pregnancy. Three patients died from 'heart failure' (16, 19, 49 years old) and in 8 patients (24, 34, 36, 38, 40, 41, 44, 60 years) cause of death could not be assessed. In another 2 patients a cardiac cause could be excluded: one died at a car accident (18 years) and one of cancer (44 years).

COX regression analysis revealed an older age at surgery ($p=0.0005$) as single risk factor for late mortality with patients older than 20 years being at higher risk ($p<0.0005$). Surgical technique and sex were not independently significant.

Conclusion: Perioperative mortality at coarctation repair was confined to infants who could not be stabilized preoperatively. Late mortality after repair is primarily related to a higher age at surgery.

180 Bosentan shows persistent benefit in functional class and exercise capacity amongst Eisenmenger patients in the BREATHE-5 open label extension study

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No evidence-based treatment approach currently exists for patients with the most advanced form of pulmonary arterial hypertension (PAH) related to congenital heart disease (CHD), namely Eisenmenger patients (EP). Endothelin (ET) is a central mediator in the pathogenesis of PAH and Bosentan, a dual ET_A/ET_B receptor antagonist, was recently shown to improve exercise capacity of EP over 16 weeks (Chest 2005;128:496S). However, longer term experience with Bosentan in EP is lacking. After completion of the 16-week treatment with Bosentan or placebo in BREATHE-5, eligible patients were transitioned to Bosentan in the open-label (OL) extension study. We report the 6-month results of this study, investigating further the effects of Bosentan on exercise capacity, WHO functional class (FC), oxygen saturation (SpO_2) and overall safety and tolerability in Eisenmenger patients. Eleven EP from the ex-placebo (plac/bos) and 26 EP from the ex-Bosentan (bos/bos) group were followed up for 6 to 10 months on bosentan

treatment. Mean age was 45.9 (standard deviation 9.3) years for plac/bos and 37.2 (SD 12) yrs for bos/bos patients. Ventricular septal defects were predominant in both groups (70%). From baseline of the OL study to 6 months, mean 6-minute walk distance (6MWD) improved in the plac/bos group by 33.2 (standard error 23.9) m, whereas 6MWD continued to improve in the bos/bos group with a mean increase of 6.7 (SE 10) m. Therefore, in this bos/bos group, the total improvement in mean 6MWD from BREATHE-5 baseline to end of OL (10 months) was 61.3 (SE 8.1) m. For plac/bos, both WHO FC II patients remained in FC II, and 5 of 9 FC III patients improved to FC II. For bos/bos, 9 of 9 FC II patients remained in FC II, and 8 of 17 FC III patients improved to FC II. No patient declined to FC IV. Mean SpO₂ remained stable throughout the study. Two patients discontinued prematurely, 1 withdrawing consent and 1 due to an adverse event. Four patients experienced serious adverse events. Improvement in exercise capacity shown in BREATHE-5 persisted in this OL extension study, including the ex-placebo group. Bosentan improved WHO FC and was well tolerated. These longer-term results combined with the randomised placebo controlled data suggest that Bosentan is a new treatment option for EP.

COMORBIDITIES AND CORONARY ARTERY DISEASE OUTCOME

181 Impact of body mass index on hospital and long-term outcome in consecutive patients with acute ST-elevation myocardial infarction

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Background: Obesity is a traditional risk factor of cardiovascular disease. However, recent studies have described obesity to be associated with a better survival in acute coronary syndromes.

Methods: Analyzing data of the German MITRA PLUS registry, 10648 consecutive patients with acute ST-elevation myocardial infarction (STEMI) were investigated. Obesity (body mass index > 30 kg/m²), overweight (25-29.9 kg/m²), normal (18.5-24.9 kg/m²) and lean weight (<18.5 kg/m²), were compared.

Results: Obese STEMI-patients were younger, had a higher rate of diabetes mellitus and hypertension, and more often received reperfusion therapy than patients with normal or lean weight. Obese STEMI-patients had the lowest hospital mortality (6.0%) and the lowest one-year mortality (6.1%) of all compared groups. Lean STEMI-patients had a very high one-year mortality with 28.0% and a high rate of MACCE (death, reinfarction, stroke) (31.2%). After adjustment for differences in baseline characteristics and treatment in a multivariate analysis, obese patients had a significantly reduced one-year mortality compared to patients with normal (OR 0.68, 95% CI 0.53-0.88) or lean weight (OR 0.44, 95% CI 0.24-0.79). Analyzing the different BMI-groups and reperfusion therapy versus no reperfusion therapy, in all BMI-classes PCI-patients had the lowest mortality, followed by thrombolysis-patients and patients without reperfusion therapy. Lean patients without reperfusion therapy had the highest mortality (47.6%).

Conclusions: In 10648 consecutive STEMI-patients a strong impact of BMI on outcome was found. In the clinical practice of STEMI, obese patients had a reduced hospital and long-term mortality compared to patients with normal or lean weight, even after adjustment in a multivariate analysis. Lean patients had an increased risk for mortality, especially if no reperfusion therapy has been performed.

182 Plasma concentration of soluble intercellular adhesion molecule-1 and risk of incident cardiovascular events

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Background: Some studies have suggested a positive relationship between elevated levels of soluble intercellular adhesion molecule-1 (ICAM) and cardiovascular (CVD) events. However, prospective cohort follow-up data that examine the association between baseline ICAM levels and incident CVD events are sparse, particularly in women.

Methods and Results: We measured baseline ICAM levels among 23,984 apparently healthy women who were followed for a mean of 10 years for the development of myocardial infarction, ischemic stroke, coronary revascularization or death from cardiovascular causes. At baseline, women in the highest quintile of ICAM were more likely to be overweight, hypertensive, diabetic, have elevated lipid levels and a family history of myocardial infarction (MI) than women in the lowest quintile (all $p_{trend} < 0.001$). While age-adjusted Cox-proportional hazard models revealed an association between increasing quintiles of ICAM level and risk of CVD events [Hazard ratios: 1.0, 0.9, 1.0, 1.3, 2.1; $p_{trend} < 0.001$; Chi-squared for non-linearity = 14.4, degrees of freedom = 3, $p = 0.002$], this effect was markedly attenuated after adjustment for low density lipoprotein, high density lipoprotein, body mass index, history of hypertension, history of diabetes, family history of myocardial infarction < 60 years old, alcohol use, physical activity and C-reactive protein, the relationship between baseline ICAM levels and subsequent CVD risk was markedly attenuated and was no longer statistically

significant (1.0, 0.9, 0.8, 1.0, 1.1; $p_{trend} = 0.07$). Stratification by use of hormone replacement therapy did not alter this relationship. However, in analyses adjusting for these covariates, there was a statistically significant relationship between increasing baseline ICAM concentrations and total coronary heart disease (CHD) [MI, CHD death, and coronary revascularization]; 1.0, 1.1, 1.1, 1.3, 1.5 ($p_{trend} = 0.01$), a result that appears to be driven by the effect of coronary revascularization (1.0, 1.4, 1.3, 1.6, 1.8; $p_{trend} = 0.005$).

Conclusion: In this cohort of initially healthy women, baseline levels of ICAM are not an independent risk factor for incident occlusive cardiovascular events, but might predict anginal events due to the robust relationship with coronary revascularization.

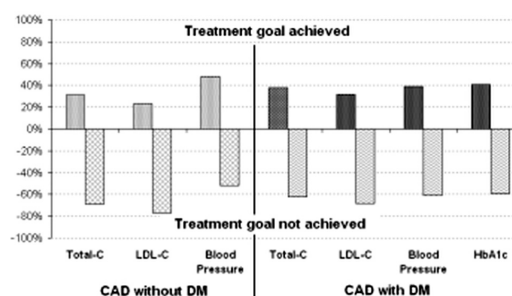
183 Guideline based therapy of coronary artery disease: where do we stand? Results from the German Coronary Risk Management (CoRiMa) study

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Background: Optimal secondary prevention is a key factor for the reduction of morbidity and mortality in patients with Coronary Artery Disease (CAD). The aim of the CoRiMa study was to investigate the efficacy of coronary risk factor treatment in patients with CAD in the "real world" of primary care based on most recent guidelines.

Methods: In selected (general practitioner and internal medicine) physician offices in Germany, all patients with CAD seen between January 1998 and June 2005 were identified. The data were exported anonymously and were transferred into the project database. Age, sex, blood pressure, serum lipids, HbA_{1c} levels and information regarding risk factors were analyzed. The last office visit of each patient was used for the analysis of treatment goals based on reference values stated in current guidelines.

Results: 48.742 patients with CAD were included in the study. More than 17.000 of these patients also had diabetes mellitus (DM). Achievement of treatment goals is presented in the following graph. Moreover the analysis revealed that over 11.000 patients with a total cholesterol over 190 mg/dl were not diagnosed as patients with hyperlipidemia.



Conclusion: (1) Based on treatment goals of current guidelines, risk factors of CAD are not effectively treated in almost 2/3 of patients with CAD with and without DM. Economical pressure on physicians treatment regimen as well as insufficient patient compliance may be potential explanations. (2) The lack of diagnosis of hyperlipidemia underscores the significance of risk factor management in patients with CAD.

184 Under-use of guidelines-recommended treatment in elderly patients admitted for acute myocardial infarction

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Background: Elderly patients (pts) (>80 years) admitted for acute myocardial infarction (MI), with or without ST segment elevation, often receive less effective treatment. It is unclear whether this under-use corresponds to more contra-indications, and what its clinical impact is.

Methods: Prospective multicenter registry, including all cardiology centers (n=10) of the Franche-Comte region (1.2 million inhabitants) in France. Demographic and clinical characteristics at admission, in-hospital treatment prescription or contra-indications and 1-month all-cause mortality were recorded. "Compliance" was defined as treatment actually given when indicated or treatment not given because of contra-indication.

Results: After 6 months of recruitment, 535 pts were included (411 males, mean age 67±14 years), 262 STEMI and 273 NSTEMI. Risk characteristics except age (history of heart failure or previous MI, renal function, diabetes and hemodynamic

conditions at admission) were comparable in both groups. Compliance to recommendations regarding reperfusion strategy, use of GP2b/3a inhibitors, statins and beta-blockers was lower among elderly pts, but was similar for aspirin and ACE inhibitors. As a result, 1-month mortality was doubled in the elderly compared to pts <80 years (10.7% vs 5.2% respectively, $p < 0.001$). This difference remained significant after adjustment for risk characteristics (except age).

	STEMI <=80 (n=214)	STEMI >80 (n=48)	NSTEMI <=80 (n=197)	NSTEMI >80 (n=76)
Reperfusion <12h	161/195 (83)	15/23 (65)		
Angioplasty	117/195 (60)	11/23 (48)		
Thrombolysis	44/195 (23)	4/23 (17)		
GP2b3a inhibitors			145/191 (76)	28/57 (49)
Aspirin	210/214 (98)	48/49 (98)	190/195 (97)	70/74 (95)
ACE inhibitors	158/200 (79)	31/45 (69)	154/193 (80)	66/73 (90)
Beta blockers	138/185 (76)	19/38 (50)	144/176 (82)	37/62 (60)
Statins	202/212 (95)	34/48 (71)	186/194 (96)	62/74 (84)
1-month death	13/214 (6.1)	9/48 (18.7)	8/197 (4.0)	4/76 (5.3)

All values are actual/eligible (%)

Conclusions: Despite the absence of contra-indications, pts aged >80 years admitted for acute MI less frequently receive guidelines-recommended treatment, contributing to a twofold increase in 1-month mortality.

185 Predicting cardiovascular events in patients with end-stage renal disease on the waiting list for renal transplantation - to invade or not to invade?



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Background: Patients (pt) with end-stage renal disease (ESRD) have an increased risk of major adverse cardiovascular events (MACE), most likely due to coronary artery disease (CAD). Current guidelines for cardiovascular assessment of pt with ESRD on the waiting list for renal transplantation recommend non-invasive testing for risk stratification, and the need for further workup, which then might include coronary angiography. There is controversial data regarding the appropriateness of this strategy.

Objective: To investigate the value of combining cardiac scintigraphy and coronary angiography in predicting the occurrence of MACE in pt with ESRD on the waiting list for renal transplantation.

Methods: 217 pt with ESRD on dialysis (56±8 years-old, 73% men) at high-risk for CAD were enrolled. All pt underwent myocardial perfusion assessment by cardiac scintigraphy (SPECT) with dipyridamole, and coronary angiography, regardless of symptoms or results of non-invasive tests. The median follow-up was 24 months (range=2 to 90). Cox proportional hazards models were used to determine the association between myocardial perfusion defects (reversible and/or fixed), significant CAD (stenosis >70%), and the risk of fatal/non-fatal MACE.

Results: There were 74 fatal/non-fatal MACE. In pt with normal perfusion scans (n=114), there were 36 (32%) with significant CAD at angiography. In this group, the risk ratio (RR) and 95% confidence intervals (95%CI) for MACE were 2.02 (1.39-3.00; $P=0.0002$). On the other hand, in pt without significant CAD (n=117), finding an abnormal myocardial perfusion scan was marginally associated with an increased risk of MACE (RR=1.52, 95%CI=1.00-2.33; $P=0.052$), whereas in pt with significant CAD (n=100), finding a normal perfusion scan was not associated with a lower rate of events (RR=0.98, 95%CI=0.72-1.31; $P=0.92$).

Conclusions: In pt with ESRD and high-risk for CAD, in those with normal myocardial perfusion scans the prevalence of significant CAD is high. Moreover, in pt with normal perfusion scans, coronary angiography does help to identify pt at risk of MACE, should significant CAD be found. An abnormal myocardial perfusion scan was marginally associated with an increased risk of MACE only in pt without significant CAD. On the other hand, in pt with significant CAD, the risk of MACE seems to be independent of the results of perfusion scans. These data suggest that the strategy of initially relying solely on non-invasive testing for risk stratification and the need for additional workup in pt with ESRD should be reviewed.

186 Prognostic value of moderate renal dysfunction in patients with acute coronary syndromes



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Introduction: The prognostic importance of mild degrees of renal impairment in patients (pts) who have had an acute coronary syndrome (ACS) is not established. The purpose of this study was to quantify the impact of baseline renal dysfunction assessed by estimated glomerular filtration rate (GFR) on mortality in pts admitted with an ACS.

Methods: We studied all pts with an ACS consecutively admitted to a Coronary Care Unit over 18 months. The GFR was estimated by means of the four-component Modification of Diet in Renal Disease equation. Pts were grouped according to their estimated GFR (<45.0; 45.0 to 59.9; 60.0 to 74.9; and at least 75.0 ml/min/1.73 m²).

Results: The mean age of the 589 study pts was 64 years, 73% were male, and 49.2% had ACS with ST-segment elevation. Arterial hypertension, diabetes mellitus, prior myocardial infarction, and a Killip class>1 were incrementally more common across increasing renal dysfunction strata ($p < 0.01$). The use of beta-blockers and coronary angioplasty was lower in groups with a reduced estimated GFR ($p < 0.001$). In-hospital mortality was 6.1%; six-month mortality was 13.6%. Using the group with an estimated GFR of at least 75.0 ml/min/1.73 m² as the reference group yielded odds ratio (OR) for in-hospital and 6-month mortality that increased as the degree of renal impairment increased (Table). After adjusting for baseline characteristics and treatment, impaired renal function remained associated with increased mortality (Table). The multivariable-adjusted OR for 6-month mortality in pts with mild renal impairment (GFR, 60.0-74.9 ml/min/1.73 m²) was 2.71 (95% CI 1.09-6.69).

Odds Ratio for Death According to GFR

Outcome	GFR<45.0 (N=60)	GFR 45.0-59.9 (N=81)	GFR 60.0-74.9 (N=103)	GFR≥75.0 (N=345)
In-hospital mortality (%)	21.7	16.0	2.9	2.0
Unadjusted OR (95% CI)	13.36 (5.07-35.17)	9.23 (3.55-23.99)	1.45 (0.37-5.71)	1.0*
Adjusted OR (95% CI)	3.98 (1.17-13.53)	3.16 (1.04-9.61)	0.90 (0.21-3.88)	
Six-month mortality (%)	42.9	37.2	12.1	3.6
Unadjusted OR (95% CI)	20.00 (9.15-43.74)	15.78 (7.55-32.98)	3.68 (1.60-8.47)	1.0*
Adjusted OR (95% CI)	8.10 (3.18-20.60)	7.53 (3.21-17.71)	2.71 (1.09-6.69)	

*This group served as the reference group.

Conclusions: Baseline renal dysfunction, as assessed by the estimated GFR, is a potent and easily identifiable determinant of outcome after an ACS. Even mild levels of renal impairment are independently associated with increased mortality after an ACS.

PROGNOSIS AFTER ACUTE MYOCARDIAL INFARCTION

187 Inadequate performance of the TIMI risk prediction score for patients with ST-elevation myocardial infarction treated according to current guidelines



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Background: Mortality prediction of patients admitted with ST elevation myocardial infarction (STEMI) is currently based on models derived from randomised controlled trials performed in the 1990's, with selective inclusion and exclusion criteria. It is unclear whether such models remain valid in community-based populations in the modern era.

Methods: The AMIS (Acute Myocardial Infarction in Switzerland)-Plus registry prospectively collects data from ACS patients admitted to 56 Swiss hospitals. We analysed hospital mortality for patients with ST-elevation myocardial infarction (STEMI) included in this registry between 1997-2005, and compared it to mortality as predicted by the benchmark risk score from the TIMI study group. This is an integer score calculated from 10 weighted parameters available at admission. Each score value delivers a hospital mortality risk prediction (range 0.7% for 0 points, 31.7% for >8 points).

Results: Among 7875 patients with STEMI, overall hospital mortality was 7.3%. The TIMI risk score overestimated mortality risk at each score level for the entire population. Subgroup analysis according to initial revascularisation treatment (PCI [n=3358], thrombolysis [n=1842], none [n=2675]) showed an especially poor performance of the TIMI risk score for patients treated by PCI. In this subgroup no relevant increase in mortality was observed up until 5 points (actual mortality 2.7%, predicted 11.6%), and remained below 5% up till 7 points (predicted 21.5%) (Figure 1).

Conclusions: The TIMI risk score overestimates the mortality risk and delivers poor stratification in real life patients with STEMI treated according to current guidelines.

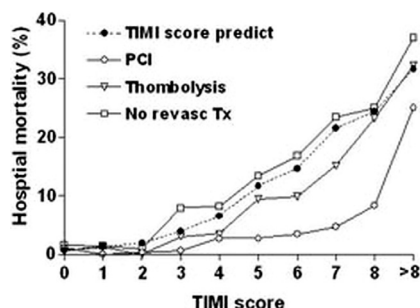


Figure 1

188 ECG insights into the unexpected outcome of ASSENT-4 PCI



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The ASSENT 4 PCI trial of ST-elevation MI patients (STEMI) revealed that routine PCI following an experimental tenecteplase (TNK)/antithrombotic regimen vs. PCI alone was associated with an increase in major adverse events. In order to assess myocardial reperfusion status, a systematic ECG evaluation at baseline, 60 and 180 minutes after randomization was undertaken in 1128 pts who underwent PCI within this interval. Baseline Σ ST deviation was similar but we found a modest advantage at 60 min for TNK+PCI vs. PCI alone in complete ST elevation resolution i.e. STR > 70%, (25% vs. 16%, $p=0.001$). However, more TNK+PCI pts showed worsening of ST resolution vs. PCI alone between 60 and 180 min (14.7% vs. 9.7% $p=0.011$), yet they had similar rates of complete STR at 180 min (50% vs. 51%). The table shows clinical outcomes within each treatment group according to whether or not there was ST worsening between 60 and 180 min.

STR change 60-180 min	TNK/PCI			PCI only		
	ST worse (>10%) N=84	ST ok N=487	P	ST worse (>10%) N=54	ST ok N=503	P
60' STR % (median)	61(29.80)	35(0.65)	<0.001	58(36.84)	25(7.56)	<0.001
60' STR						
<30%	25	46.6	< 0.001	16.7	53.9	< 0.001
30% to 70%	36.9	30.8		46.3	32.4	
≥70%	38.1	22.6		37	13.7	
30-day ReMI	12.2	3.9	0.005	3.7	2.6	0.649
30d death/ReMI	14.6	7.5	0.050	5.6	4.0	0.482

Despite achieving better early reperfusion with TNK + PCI, those undergoing PCI alone had significantly better 30-day outcomes. Worsening STR was more common in the TNK+PCI group and was associated with an especially high reMI rate suggestive of a prothrombotic effect as manifested by early reocclusion.

189 Grade 3 ischemia on the admission electrocardiogram predicts failure of ST resolution and of adequate flow restoration following primary angioplasty for acute myocardial infarction



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Background: Failure of ST resolution (STR) is a strong adverse predictor following primary angioplasty (PPCI) but cannot be reliably predicted on admission. Grade 3 ischemia (G3I) is a measure of the severity of ischemia in patients with STEMI, defined by absence of S waves in the right precordial leads or take-off the ST segment at >50% of the R wave in other leads. ST elevation that does not fulfill criteria for G3I is defined as grade 2 ischemia (G2I). We recently showed that G3I on admission is the strongest predictor of failure to achieve STR after lysis. G3I on admission predicts mortality after PPCI but the mechanism is unknown.

Methods: We prospectively studied all patients who had PPCI for a first STEMI between 7/04 and 4/05 (N=100). Multiple variables available on admission were analyzed as predictors of STR. ECG's were read blindly in a core lab. Angiograms were analyzed by an angiographer who was blinded to the clinical and ECG data.

Results: Seventy one patients (71%) had G2I and 29 (29%) had G3I. G2I patients did not differ from G3I patients in terms of age, sex, medical therapy, diabetes, time to treatment and pre-infarction angina. 70% STR was observed in 42/71 patients with G2I (59%) as compared to 8/29 patients with G3I (28%) ($p=0.004$). In a model adjusting for age, sex, time to treatment, pre-infarction angina, previous medical therapy, diabetes, grade of ischemia and Q waves on admission, G3I remained the sole predictor of failure of STR (OR: 0.26, 95% CI=0.1-0.72). Similar findings were obtained when the analysis was repeated with 50% STR as the end point (OR: 0.41, 95% CI= 0.04-0.56). Positive and negative predictive values for failure to achieve 70% STR were 72% and 60%, respectively. Patients with G3I had higher peak CK levels (2992 ± 2501 vs. 1763 ± 1756 $p=0.02$) and a higher rate of significant LV dysfunction (78% vs. 55% $p=0.05$). The post PCI corrected TIMI frame count was 11 ± 6 vs. 20 ± 22 in patients with G2I and G3I, respectively ($p=0.003$). Multivariate analysis showed that G3I was the strongest independent predictor of failure to achieve TIMI grade 3 flow (OR: 0.06, 95% CI=0.01-0.33) and TIMI myocardial blush 3 (OR: 0.08, 95% CI=0.02-0.31).

Conclusion: G3I is the strongest independent predictor available on admission of failure to achieve myocardial reperfusion after PPCI, as assessed both electrocardiographically and angiographically. This association may underlie the larger infarcts associated with G3I and may allow the identification upon admission of patients who require more aggressive management to improve reperfusion.

190 Relative 50%-reduction of hospital mortality by primary PCI as compared to thrombolysis for STEMI in the high risk population of diabetics in clinical practice - results of the ACOS registry



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Background: Current guidelines for the management of acute ST-elevation myocardial infarction (STEMI) and guidelines for PCI recommend primary PCI as reperfusion-therapy of first choice as it was shown to be superior to thrombolysis. No data from randomised controlled trials exist for the comparison of primary PCI and thrombolysis in the high risk population of diabetics.

Methods: Between 2000 and 2002 a total of 16816 consecutive patients with acute coronary syndromes were enrolled into the multicenter ACOS-registry in Germany. We examined the impact on the hospital mortality of primary PCI versus thrombolysis in Diabetics with STEMI in clinical practice.

Results: Out of 8303 patients presenting with STEMI, 2202 were diabetics (26.5%), of whom 880 (40%) did not receive any reperfusion therapy, 810 (37%) primary PCI and 512 (23%) thrombolysis. After adjustment for differences in the baseline characteristics, concomitant diseases and the prehospital delay, primary PCI as compared to thrombolysis was associated with a significant lower hospital mortality in the high risk population of diabetics (OR 0.50, CI 0.34-0.73).

Primary PCI vs Thrombolysis in Diabetics

	Primary PCI n=810	Thrombolysis n=512	p-value
Age [years]	66	67	ns
Female Gender	32.8%	35.0%	ns
Prior MI	18.6%	19.1%	ns
Prior PCI	12.0%	6.3%	<0.001
Prior CABG	5.9%	5.3%	ns
Prior Stroke/TIA	8.0%	7.6%	ns
Hypertension	72.8%	70.7%	ns
Hyperlipidemia	64.4%	61.1%	ns
Renal Failure	5.1%	4.5%	ns
Prehospital Delay [min]	270	141	<0.001
Hospital Mortality	7.3%	13.3%	<0.001

Conclusion: In consecutive diabetics with STEMI, reperfusion by primary PCI as compared to thrombolysis was associated with a 50% reduction in hospital mortality in clinical practice. According to current guidelines for the management of STEMI primary PCI is the preferred treatment of reperfusion and should especially be offered to high risk patients as diabetics.

191 Impact of new cases of diabetes mellitus in patients with AMI treated with primary angioplasty



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Purpose: The high prevalence of glucose metabolism disorders (including diabetes mellitus) not previously diagnosed in patients (pts) with acute myocardial infarction (AMI) has been shown in several recently published trials. It was our objective to evaluate the prevalence and prognostic impact of glucose metabolism disturbances suggesting diabetes, by measuring admission glucose levels in patients with AMI treated with primary angioplasty (P-PCI).

Methods: In-hospital, 30 days and 6 months mortality were evaluated in 435 consecutive pts with ST elevation AMI treated with P-PCI. Pts in cardiogenic shock (16.1% of the total) were included. Glucose blood levels were measured on admission and pts were divided in 3 groups: without previously known diabetes and admission glucose <200 mg/dl (Group 1); with previously known diabetes (Group 2); without previously known diabetes and admission glucose >200 mg/dl (Group 3). In a subgroup of 149 pts, glycosylated hemoglobin (HbA1c) was also determined on admission.

Results: 94 (21.6%) pts had previously known diabetes. In the remaining, 39 (9.0%) had admission glucose >200 mg/dl. HbA1c >6% were observed in 23.8%, 74.1% and 70.6% of patients in Groups 1, 2 and 3 ($p<0.001$). Pts in Group 3 ("new cases of diabetes") had in-hospital, 30 days and 6 months major events (death, myocardial infarction or target vessel revascularization) rates significantly higher than patients in Group 1 and comparable to patients in Group 2 (Table). In-hospital (9.3%, 13.8% and 23.1%, $p=0.03$) and 6 months mortality (12.4%, 20.2%, 29.4%, $p=0.01$) was also significantly higher in Group 3. Pts in Group 3 presented more frequently in cardiogenic shock (30.8%, vs. 18.1% and 13.6% for Groups 1 e 2, $p=0.05$).

Conclusions: The measurement of admission glucose blood levels in pts with AMI treated with P-PCI identifies a subgroup of pts with glucose metabolism disturbances suggesting diabetes, not previously known and associated with a worst prognosis.

Major Events (death, myocardial infarction, target vessel revascularization in Groups 1, 2 and 3

	N	Group 1	Group 2	Group 3	P Value
In-Hospital events	435	11.6%	18.1%	25.6%	0.03
30 days events	417	12.9%	19.6%	28.9%	0.02
6 months events	385	17.6%	27.4%	41.2%	0.003

192 Spontaneous ST resolution is not an indicator for coronary reperfusion during ST elevation myocardial infarction (STEMI)



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Background: It has been shown that ST segment resolution in response to reperfusion therapy for STEMI is an indicator of coronary and myocardial reperfusion. The purpose of this study is to evaluate whether spontaneous ST resolution (sSTr) prior to any revascularization therapy is an indicator of an open culprit coronary artery.

Methods: 400 consecutive STEMI patients were admitted and treated with immediate angiography and PCI. The ECG was recorded on admission and again immediately pre PCI. TIMI flow in the culprit artery was evaluated by angiography. The sensitivity and specificity of sSTr to indicate good TIMI flow was calculated.

Results: sSTr was recorded in 57 (13.7%) patients. An initial good TIMI flow (2/3) was demonstrated in 41 (71.9%) of them. Among the 343 patients with persistent ST elevation a good TIMI flow was demonstrated in 250 (69.6%) cases. sSTr was calculated to have a sensitivity of 25.3%, specificity of 93.9%, positive predictive value of 71.9% and negative predictive value of 72.9% for good TIMI flow. A statistical analysis using Mann Whitney U test found that sSTr is correlated with lower CPK elevation (sigma CPK at admission and after 6, 12, 18, 24, 48 hours 3304±3836 vs. 6483±6721, Z=-3.858, p<0.001), fewer days in ICCU (1.29±0.6 vs. 2.65±3, Z=-4.729, p<0.001 and total hospitalization days (3.8±1.17 vs. 6.23±4.58, Z=-5.527, p<0.001).

Conclusion: Spontaneous ST segment resolution in STEMI patients has a relatively low sensitivity and positive predictive value to indicate coronary reperfusion. Never the less it correlate with smaller infarct size, and shorter hospitalization length, but should not be relied upon to deferred planed direct PCI.

NUTRITION, ALCOHOL AND COFFEE

270 Nut consumption and protection against coronary heart disease death in the European Prospective Investigation into Cancer and Nutrition (EPIC)



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Purpose: Nuts have been suggested to be protective of coronary heart disease. However, all epidemiologic information to date is derived from cohorts based on American populations, which may have different dietary backgrounds and nut intake patterns than other populations.

Methods: The association of nut intake and coronary heart disease mortality was examined in 399,633 subjects, including 1158 cases, enrolled in the EPIC study, a large prospective cohort of subjects recruited from 23 centres in 10 different European countries. Nut intake was assessed by country-specific validated dietary questionnaires completed by all subjects and was corrected for measurement errors across countries with standardized 24-hour recalls obtained from a subset of 36,900. Hazard ratios (HR) were obtained from four categories of nut intake and from linear models estimating the risk for 8g/day increments in intake.

Results: When comparing the highest (>13g/d) and the lowest (<1g/d) nut intake categories, the HR was 0.60, (95% CI, 0.43-0.83) and after adjustments for coronary risk factors and dietary variables the HR was 0.71 (95% CI, 0.51-0.98). A HR of 0.74 (0.57-0.96) was estimated for every 8g/day of increased nut intake, and after adjustments the HR was 0.89 (0.74-1.08).

Conclusions: Nut intake is associated with a decreased risk of coronary heart disease mortality. In a population where approximately half rarely consume nuts, an intake of only two servings of nuts per week (8g/d) may reduce coronary heart disease mortality by 11%.

271 Effect of alcohol consumption on arterial elasticity in coronary artery disease



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Purpose: Observational studies demonstrate that moderate alcohol consumption improves the prognosis in coronary artery diseases (CAD). The increase of HDL cholesterol and beneficial effect on blood clotting are some of possible explanation. However, all mechanisms responsible for such protective effect of alcohol were not yet established. The main cause of CAD - atherosclerosis is connected with the increased arterial stiffness. Pulse wave velocity (PWV) provides an indirect, non-invasive assessment of the mechanical properties of arteries. The aim of our study was to assess the influence of alcohol consumption on large arteries elasticity.

Methods: The study group consisted of 46 pts with stable CAD who seldom consumed alcohol. In all of them PWV was evaluated using a computer system

COMPLIOR-Colson to assess the mechanical properties of arteries. For automatic measurement of PWV pressure waveforms were digitized at rate 500 Hz for carotid-femoral distance. 10 healthy volunteers constituted a control group. After PWV measurement 26 patients (Group 1) were asked for regular consuming one or two drinks per day. The remaining 20 (Group 2) did not change their mode of alcohol consumption. Groups were comparable according to demographic characteristics and treatment of CAD. After 6-month follow-up period the PWV assessment was performed again.

Results: PWV in control group remained unchanged following study period (7.01±0.6 m/s initial vs 7.2±0.4 after 6 months). Initial PWV in both CAD groups was similar (12.2±0.4 m/s in Group 1 vs 12.0±0.8 m/s in Group 2). After 6 months PWV in Group 1 significantly decreased (10.5±0.7 m/s, p<0.05 vs initial). In Group 2 PWV decreased to 11.9±0.2 m/s but this value did not differ significantly from the initial measurement. Groups did not differ in regard to total plasma cholesterol level. HDL-cholesterol was higher in Group 1 but the difference was not significant (42, 1±9 mg/dl vs 38±11 mg/dl).

Conclusions: 1. Moderate alcohol consumption improves arterial elasticity in patients with CAD. 2. The influence of systematic moderate alcohol consumption on mechanical properties of arteries could be one of the possible explanations of its protective effect in CAD.

272 PAI-1, tPA, endothelin-1 and hsCRP levels after short-term consumption of different types of alcohol in healthy male volunteers



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Purpose: Moderate alcohol consumption reduces coronary artery disease morbidity and mortality. This effect can be mediated by favourable influence on fibrinolysis, endothelial function and inflammatory process. The study was designed to clarify the impact of short-term consumption of different types of alcoholic beverages on haemostatic factors, C-reactive protein and endothelin-1 plasma levels.

Methods: The study group consisted of 57 healthy male volunteers, seminarians of Diocesan Theological Seminary, aged 20-29 years. All were non-smokers and abstainers. No subject was taking cardiovascular medication or lipid-lowering agents. Subjects were randomized to consume 300 ml of either: red wine (Cabernet Sauvignon), white wine (Chardonnay), 14% ethanol solution, blackcurrant juice or water, for a period of five days. Fasting blood samples were collected for C-reactive protein, t-PA antigen, PAI-1 antigen and endothelin-1 determination at baseline, day 2, and day 6.

Results: Statistically significant differences could only be observed after dividing the study group regarding consumption of alcohol of any kind. The type of alcohol had no impact on final results. C-reactive protein levels were not affected by consumption of any sort of beverage.

tPA, PAI, endothelin-1 concentrations

	Alcohol (n=34)	No alcohol (n=23)	
tPA antigen [ng/ml]	1	3.65	3.17
	2	4.17	3.77
	3	5.03*	3.35
PAI-1 antigen [ng/ml]	1	44.75	44.80
	2	54.07*	39.73
	3	44.80	42.84
endothelin-1 [fmol/ml]	1	0.42	0.46
	2	1.01*	0.75
	3	0.97**	0.60

Median values of tPA antigen, PAI-1 antigen, endothelin-1 plasma concentration at baseline (1), day 2 (2) and day 6 (3). *p<0.05; **p<0.001 (difference from baseline)

Conclusion: Short-term alcohol consumption increases tPA, PAI and endothelin-1 plasma levels in a universal manner, independent of the kind of beverage. That effect can have an unfavorable impact on fibrinolysis and regulation of regional blood flow.

273 Drinking modulates monocyte migration in healthy subjects: A randomised intervention study of water, ethanol, beer and red wine with or without alcohol



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Background: Monocyte migration into and accumulation in the arterial wall is supposed to be a crucial step in early atherosclerosis. In observational studies moderate alcohol consumption has consistently been shown to be associated with reduced cardiovascular mortality compared to non-drinking and heavy drinking. We assessed the effect of consumption of moderate amounts of alcoholic and non-alcoholic beverages on monocyte migration in vitro.

Methods: Forty-two non-smoking healthy men and women aged 22-55 years were included in this randomised intervention study. After a wash-out period of at least 2 weeks the participants were randomly assigned to the following interventions for 3 weeks: either ethanol (concentration 12.5%), beer (5.6%), or red wine (12.5%) equivalent to 30 grams of ethanol per day for men and 20 g/d for women or the same amount of the same but de-alcoholised beer or red wine or just water.

Fasting venous blood was drawn before and after intervention. Monocyte migration was evaluated ex vivo using a modified Boyden chamber. After stimulation with either FMLP (N-formyl-methionyl-leucyl-phenylalanine) or MCP-1 (monocyte chemoattractant protein-1) as chemoattractant migration was assessed before and after intervention.

Results: Monocyte migration was inhibited by both consumption of non-alcoholic and alcoholic beverages compared to consumption of water. Using FMLP as chemoattractant this was statistically significant for consumption of ethanol (2.37-fold induction before and 1.40-fold induction after intervention, $p < 0.05$) and de-alcoholised red wine (2.17/1.39, $p < 0.05$). Using MCP-1 monocyte migration was also significantly inhibited by either ethanol (1.78-fold induction before/0.75 after intervention, $p < 0.01$) or consumption of de-alcoholised red wine (1.96/1.25, $p < 0.05$).

Conclusion: Short term intervention with intake of moderate amounts of alcohol either by drinking low-concentrated ethanol, red wine or beer as well as with de-alcoholised red wine and de-alcoholised beer inhibits monocyte migration in vitro. This might represent a mediating mechanism by which moderate alcohol consumption can lower cardiovascular risk.

274 Genetic variation in alcohol dehydrogenase and beneficial effect of alcohol consumption on myocardial infarction. Results from the MONICA/KORA study



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Background: Epidemiological studies show that moderate alcohol consumption lowers the risk of coronary heart disease (CHD). Recently, it has been suggested that alcohol metabolizing enzyme alcohol dehydrogenase 3 (ADH3 or ADH1C) modifies the association between alcohol consumption and CHD risk. We highlight the current scientific evidence and investigate the relationship between alcohol intake and CHD with regard to ADH3 in a German population.

Methods: We used data from the population-based MONICA/KORA Augsburg study. Alcohol consumption was assessed at baseline among 3674 men and women aged 25-74 who were followed from 1995 to 2002 with respect to coronary events. ADH3 genotype ($\gamma 1\gamma 1$ = fast alcohol metabolism; $\gamma 1\gamma 2$ = intermediate alcohol metabolism; $\gamma 2\gamma 2$ = slow alcohol metabolism) was specified. The association between alcohol intake and CHD according to ADH3 genotype was investigated using multivariate Cox proportional hazards models.

Results: Mean age was 48.6 years in both men and women. During follow-up, 53 myocardial infarctions (MI) occurred among males and 19 among women, respectively. Distribution of ADH3 genotype among males was as follows: homozygote fast 38.7%; homozygote slow 15.1%; and the remaining 46.2% heterozygote. Males with either homozygote or heterozygote slow allele and 20 grams alcohol intake/day had a CHD-risk of 0.69 (95% CI 0.18-2.55). Risk of CHD in males with any slow allele decreased with increasing alcohol intake while CHD risk in those with homozygote fast alleles showed a J-shaped function.

Conclusions: ADH3 genotype may modify the association between alcohol consumption and CHD. Males with slow allele may profit particularly from moderate alcohol consumption.

275 Effect of coffee consumption and nutritional factors in the development of acute lone atrial fibrillation



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Objectives: The study evaluated the relationships between espresso coffee consumption and nutritional factors and the development and the spontaneous cardioversion of acute lone atrial fibrillation (LAF).

Methods: The study group included 116 patients (pts) with LAF cardioverted within 48 hours of the onset of LAF. The nutritional parameters (diet, alcohol and espresso coffee consumption, smoking and body mass index=BMI) were investigated. Pts underwent a series of cognitive tests to evaluate acute psychological stress (mean life acute stress score). A control group age and sex matched was selected and compared.

Results: Spontaneous conversion of LAF to sinus rhythm was observed in 72 pts (63%). In univariate analysis alcohol consumption and smoking habits did not influence spontaneous conversion of LAF. The mean life acute stress score among patients with LAF was 56 ± 33 , while in control was 34 ± 27 ($p < 0.01$). In the logistic regression analysis, the presence of spontaneous conversion of sinus rhythm was used as the dependent variable. Independent variables were indicator variables representing categories of stress, espresso coffee consumption and BMI. Pts with an acute stress showed the highest probability of spontaneous conversion followed by pts with TAB. High espresso coffee consumption more than 3 cups/day (RR 0.39%; CI 0.11-0.49; $p = 0.008$) and BMI > 27 were associated with a significantly greater risk of persistent atrial fibrillation (RR 1.55%; CI 1.2-1.7; $p = 0.012$).

Conclusions: High espresso coffee consumption and high BMI were associated with an increase risk of persistent AF. Pts that developed LAF after an acute stress showed the highest probability of spontaneous conversion. Others socio-economics factors exert a lower influence on spontaneous conversion of LAF.

ENVIRONMENT, POLLUTION

276 Burden of cardiovascular diseases attributable to passive smoking in Germany - a sensitivity analysis



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Background: Passive smoking is associated with increased risk of coronary heart disease (CHD) and stroke. The burden of passive smoking on a population level is currently unclear and depends on several assumptions. We investigated the public health impact of passive smoking in Germany with regard to cardiovascular diseases (CVD).

Methods: We computed attributable morbidity and mortality risks due to environmental tobacco smoke (ETS) considering CHD and stroke. Frequency of passive smoking was derived from the German national health survey. Sensitivity analyses were performed using different definitions of exposure to passive smoking.

Results: In total, 5613 incident fatal and non-fatal events every year in Germany are estimated to be caused by exposure to passive smoking at home (CHD 3776, stroke 1837). Overall, 2922 CVD-deaths per year are estimated to be caused by ETS at home (CHD 2148, stroke 774). Two thirds of these events occur among women. Additional consideration of passive smoking at workplace increased the number of CVD-deaths to nearly 3500. Considering any exposure to passive smoking and also active smokers who report exposure to passive smoking increased the number of deaths further.

Conclusions: Passive smoking has an important impact on cardiovascular morbidity and mortality in Germany. Even the most conservative estimate using exposure to ETS at home came up with about 3000 CVD-deaths every year related to passive smoking in Germany.

277 Impact of smoking cessation on C-reactive protein, and the role of life-time and passive smoking



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CRP levels predict CHD risk. Smoking increases CRP but results conflict as to whether this is dose-dependent. Studies differ on CRP trends post smoking cessation. Some suggest it reverts to normal at five years, some 20 years and some never. Life-time consumption may be more important than time from cessation, and passive smoking may play a role.

We analysed cross-sectional data on a representative sample of 8,305 adults. 594 were excluded because of prevalent CHD. CRP, cotinine and self-reported smoking status were available on 4,259. Among the 1,343 current smokers, there was a univariate correlation between CRP and smoking duration ($p < 0.001$), number of cigarettes ($p < 0.001$) and pack years ($p < 0.001$). These remained significant after adjustment ($p = 0.036$, $p = 0.008$, $p = 0.006$ respectively).

CRP fell with time from cessation but was still raised after 20 years ($p = 0.001$). After adjustment for age, sex, BMI, deprivation and diabetes, ex-smokers had higher CRP levels up to 5 years post cessation ($p < 0.001$) but not thereafter. The difference persisted after adjustment for pack-years. Exposure to passive smoking was greater among ex-smokers than never smokers (median cotinine 0.7 vs 0.5, $p < 0.001$). When passive smoking was added to the model the difference was no longer significant.

Previous studies on smoking cessation have been limited by lack of objective evidence of smoking status, inadequate adjustment for confounders, or lack of adjustment for life-time consumption or passive smoking. Our results demonstrate that CPR remains elevated more than 20 years post cessation, but this is explained by demographic and comorbid confounders plus greater exposure to passive smoking.

278 Abnormal pattern of myocardial perfusion in warfare patients intoxicated with mustard gas



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Background: Mustard agents are of the major chemical agents used during Iran-Iraq war. There are no reports concerning long-term cardiac effects. The aim was to assess the scintigraphic pattern of myocardial perfusion in patients intoxicated with blistering gases.

Method: We analyzed myocardial perfusion scans of 22 consecutive intoxicated patients (21 male and 1 female, all < 44 years) and compared results with 14 controls. Only those patients and controls were entered whose 10-year risk of coronary artery disease (Framingham criteria) was $< 5\%$. Also only those patients were experimented upon that had currently other confirmed complications of intoxication (respiratory, cutaneous and ocular complications). All patients underwent a 1-day stress and rest protocol using ^{99m}Tc -MIBI. Images were assessed visually and quantitatively using Cedars Sinai program.

Results: The prevalence of nonhomogeneity of uptake and left and right ven-

tricular enlargement in both visual and quantitative analyses were higher in the mustard exposed patients than unexposed controls. It was observed that 13 warfare patients (59.1%) and none of the controls had dilated right ventricular chambers. The prevalence of ischemia was higher in exposed patients ($P < 0.05$). The average values of quantitative ischemic measurements including SSS (Summed stress score), SRS (Summed rest score), and SDS (Summed difference score) were 3.7 ± 2.8 , 1.1 ± 1.6 and 2.6 ± 2.3 correspondingly in the warfare patients while the corresponding values for the control group were 1 ± 0.9 , 0.4 ± 0.7 and 0.6 ± 0.8 (all P values < 0.01). Non-homogeneity of nuclide uptake was defined as the standard deviation of the 20 regions of the left ventricle of each patient and control. The standard deviation was 14.6 ± 3.8 in mustard exposed patients while it was equal to 11.4 ± 2.8 in the control group ($P = 0.001$). Cavity to myocardium ratio, as an established and validated measure of ejection fraction, was also significantly lower in the patients than the controls.

Conclusion: In so far it lies in our knowledge, this is the first report concerning the scintigraphic pattern of myocardial perfusion in mustard intoxicated patients. Based on the results, the pattern of myocardial perfusion in these patients is significantly different from normal controls, which could resemble either coronary artery disease or mild cardiomyopathic changes. Findings must be confirmed in larger series of patients.

279 Meteorological effects on cardiovascular mortality in the Athens territory



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Background: Seasonal variations in the development of coronary artery death and associations with low atmospheric temperatures have been reported from mortality data and hospital admission registries. Aim of the present study was to evaluate the impact of meteorological variables on daily and monthly rates of death due to cardiovascular causes with the exception of strokes.

Methods: We analyzed all the death certificate data from the Athens territory, for cardiovascular deaths for the year 2001. Daily mean atmospheric temperature (Celsius), pressure (millibars) and humidity (%) were obtained from the National Meteorological Society for the Athens territory and the same year.

Results: The total number of cardiovascular deaths in the Athens area was on an annual basis 9007 (4702 males/4305 females) from a population of 2,664,776 (0.338%). A significant seasonal variation in deaths was observed: the mean daily number of deaths in winter was 22% higher than in summer (mean difference 5.1 deaths per day, $p < 0.001$). Forward linear regression analysis revealed that the average of the mean daily atmospheric temperature of the previous 7 days was the most powerful predictor among the meteorological variables of the daily number of deaths ($R = -0.327$, $p < 0.001$). Considering monthly cardiovascular death rates, mean monthly humidity was independently associated with total cardiovascular deaths ($R = 0.682$, $p = 0.015$).

Conclusions: A significant seasonal variability in cardiovascular deaths was found in this study, as previously reported. Even in the mild climate of a Mediterranean city like Athens, meteorological variables, namely the average of the mean temperatures of the previous 7 days and, on a monthly basis, mean monthly humidity were shown to be independently associated with deaths from cardiovascular causes.

280 Cold exposure is associated with acute coronary syndromes, especially in the elderly, irrespective of air pollution

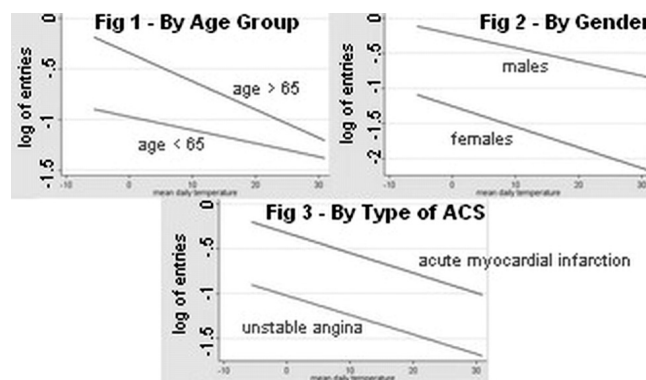


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Background: Associations between coronary heart disease occurrence and ambient temperature have been repetitively detected. However, the potential confounding effect of air pollution has not been taken into account. Aim: We investigated the impact of ambient temperature on admissions for acute coronary syndromes (ACS) in free of air pollution rural Greece. Moreover, we evaluated the role of gender, age and type of ACS as effect modifiers in this setting.

Method: Daily data on ACS admissions and daily mean temperature were obtained for a period of one year, from October 2003 to September 2004, in 5 major hospitals in rural Greece. Gender, age (over 65 or not) and type of ACS (acute myocardial infarction or unstable angina) were recorded. The data were analyzed in a poisson regression and a linear relationship between admissions and temperature was assumed.

Results: 1608 patients (1229 men/329 women, 964 over 65/644 under 65 and 1071 with discharge diagnosis of acute myocardial infarction/537 with unstable angina) were enrolled. For a 1°C decrease in daily mean temperature there was a 1.6% increase in hospital admissions due to ACS (95% CI 0.9% to 2.2%, $p < 0.001$). This effect was more prominent in the elderly [2.2% (95% CI 1.4% to 3.1%, $p < 0.001$) increase in the number of admissions for patients over 65 versus 0.7% (95% CI -0.4% - 1.7%, $p = 0.199$) for those under 65] ($p = 0.031$ for the interaction term, fig. 1). No such difference was detected when stratifying according to gender ($p = 0.222$, fig. 2) or type of ACS ($p = 0.935$, fig. 3).



Regression Lines Of Entries

Conclusion: This study corroborates the importance of implementing measures against cold exposure in coronary heart disease prevention, especially in the elderly and irrespective of air pollution.

281 Particulate matter air pollutants (PM10) and cardiovascular hospitalizations



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Background: High levels of Particulate Matter Air Pollutants (PM₁₀) have been associated with an increased incidence in cardiovascular (CV) events. In Brescia, in the last years, many variations of PM₁₀ upon very high values were detected. Moreover the greater part of the acute CV hospitalizations (H) is concentrated on our hospital, so that our institution is representative of air pollution effects in urban area.

Aim: To evaluate a possible relationship between daily variation of PM₁₀ under usual cut off ($50 \mu\text{g}/\text{m}^3$) and number of CV H in Brescia and its suburbs in 2005.

Methods: Days of the year were divided into three categories: high, mean and low PM₁₀ air concentrations ($\text{PM}_{10} \geq 50 \mu\text{g}/\text{m}^3$, $\text{PM}_{10} \geq 40$ and $< 50 \mu\text{g}/\text{m}^3$ and $\text{PM}_{10} < 40 \mu\text{g}/\text{m}^3$). Afterwards, we have evaluated the number of admissions to ICU for acute coronary syndrome (ACS), acute heart failure (AHF) and sustained ventricular arrhythmias (ICD intervention) recorded during high, mean and low pollution days. PM₁₀ concentration could influence the number of CV events in the two days following each episode of PM₁₀ increase too. So we have considered also CV events during following two days.

Results: During the year 2005 we recorded 148 high, 66 mean and 152 low PM₁₀ concentration days. The number admission for ACS, AHF, ICD intervention, for each level of PM₁₀ concentration are shown in the table.

CV Hospitalizations and PM10 levels

	PM10 < 40 $\mu\text{g}/\text{m}^3$		PM10 > 40 and < 50 $\mu\text{g}/\text{m}^3$		PM10 > 50 $\mu\text{g}/\text{m}^3$		%	p
	Total (N/year)	Daily (N/day)	Total (N/year)	Daily (N/day)	Total (N/year)	Daily (N/day)		
ACS	385	2,53	171	2,59	447	3,02	+14.1	*
HF	147	0,97	110	1,67 ¹	253	1,71	+75.4	***
Arrhythmias	23	0,15	12	0,18	31	0,21	+32.8	**
Total	555	3,65	293	4,44	731	4,94	+41.4	**

Data from Spedali Civili Brescia and ARPA Lombardia (Significance: High vs Low: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; Mean vs Low (1) $p < 0.05$)

Conclusions: The increase of PM₁₀ ($> 50 \mu\text{g}/\text{m}^3$) was related to a significant increase of CV hospitalizations for AHF, ACS and arrhythmias. Particularly AHF hospitalizations increased also for mean value of PM₁₀ (> 40 and $< 50 \mu\text{g}/\text{m}^3$).

NEWS ON NATRIURETIC PEPTIDES IN HEART FAILURE

282 B-type natriuretic peptide can predict the medium-term risk in patients with acute heart failure: The BIC study



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Background: Neurohormonal activation characterizes heart failure and measurement of plasma B-type natriuretic peptide (BNP) indicates the severity of left ventricular dysfunction.

The purpose of this study was to test the hypothesis that measurement of BNP levels in patients with acute HF can predict the occurrence of cardiovascular events in the next six months.

Methods and Results: We enrolled 1000 consecutive patients admitted to the

Outpatient Heart Failure Clinic (OHFC), on stabilization after an episode of acute HF. Standard echocardiography was performed and left ventricular systolic/diastolic function was assessed. Plasma BNP levels were measured on admission to OHFC. Patients were followed up for six months; the main end point combined cardiovascular death or re-admission for HF. Multivariate Cox regression showed that the cut-off values identified by ROC analysis (200 - 500 pg/ml) of the neurohormone are the most accurate predictors of events ($P < .01$) and ($P < .001$) respectively for 201-499 pg/ml and > 500 pg/ml ranges.

Conclusion: This is the largest study on the prognostic value of BNP in patients with acute HF. BNP level is a strong predictor for cardiovascular mortality and early readmission in patients with HF. The results suggest that BNP levels might be used successfully to guide the intensity of follow-up after a decompensation, since increased BNP levels were associated with a progressively bad prognosis.

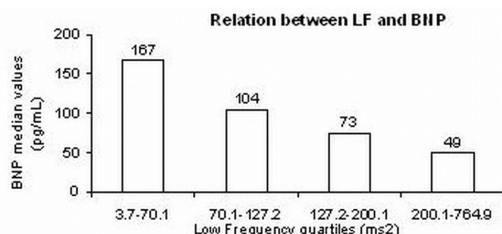
283 Heart rate variability in the LF band is closely related to BNP levels in heart failure. Data from the multicenter Valsartan Heart Failure Trial (Val-HeFT)

A. Mortara¹, H. Krum², H. Sondermeijer¹, S. Barlera³, R. Maestri⁴, S. Masson², R. Latini², L. Tavazzi⁵ on behalf of Valsartan Heart Failure Trial (Val-HeFT). ¹Policlinico Di Monza, Dept. Of Cardiology, Monza, Italy; ²Monash University, Melbourne, Australia; ³Istituto M.Negri, Milano, Italy; ⁴Fondazione S.Maugeri, Montescano (Pv), Italy; ⁵Policlinico S.Matteo, Pavia, Italy

Background: In heart failure (HF) sympathetic overactivity, parasympathetic withdrawal and reduced heart rate variability (HRV) particularly in the low frequency spectral band (LF, 0.04-0.15 Hz) are associated with high morbidity and mortality. Such sympathovagal imbalance may also be a stimulus for natriuretic peptides secretion. The aim of the present study was to test the relationship between autonomic activity as determined by HRV and BNP levels in a subgroup of patients randomized in the Holter sub-study of ValHeFT.

Methods: A total of 415 HF patients in sinus rhythm had a baseline 24-h Holter recording to test the relationship with plasma natriuretic peptides (BNP, IRMA Shionogi). Holter measures (mean heart rate, SDNN and LF power) were divided into quartiles and tested in univariate and multivariate regressive model to adjust for the possible concomitant effect of left ventricular dysfunction on both parameters.

Results: The median values of BNP were significantly different across quartiles of SDNN ($p < 0.001$) and LF ($p < 0.0001$, see Figure), but not for those of mean heart rate. After adjustment for NYHA class, LVEF, beta-blockade therapy, it was shown that for each ms2 of LF decrease, BNP increased by 0.247 pg/mL, (p value=0.0016).



Conclusions: In HF patients, a strong inverse relation between measures of HRV, as markers of sympathovagal imbalance, and BNP has been observed. High adrenergic tone and/or reduced parasympathetic activity may significantly contribute to natriuretic peptide secretion independently of severity of ventricular dysfunction.

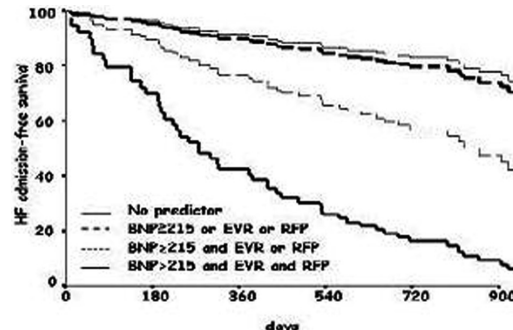
284 The combination of brain natriuretic peptide, enhanced ventilatory response to exercise and echocardiographic indexes improves risk stratification in patients with chronic heart failure

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Background: Whether brain natriuretic peptide (BNP) combined to the enhanced ventilatory response (EVR) during cardiopulmonary exercise test or echocardiographic indexes of diastolic dysfunction, improves prognostic stratification in systolic heart failure (HF) is currently unknown.

Methods and Results: Median BNP plasma levels, measured in 134 consecutive stable outpatients with mild to moderate HF and LV ejection fraction (LVEF) $< 40\%$, who performed a maximal exercise test, were 214 [96, 508] pg/ml. EVR, assessed as slope of the relation between minute ventilation and carbon dioxide production (VE/VCO_2 slope) ≥ 35 , was found in 60/134 patients (45%). A restrictive filling pattern (RFP), defined as presence of E/A ratio > 2.0 cm/sec and E deceleration time < 140 ms, was present in 25/128 patients with Doppler data available (19.5%). During 717 ± 244 follow-up days, 50 patients died or

were admitted for worsening HF. By multivariate analysis, independent predictors of outcome were RFP (HR 2.867, 95% CI 1.459 to 5.633, $p = 0.002$) and EVR (HR 2.80, 95% CI 1.414 to 5.546, $p = 0.003$). The addition of RFP or EVR to BNP levels ≥ 215 pg/ml determined a three-fold increase in risk (HR 2.987, 95% CI 1.376 to 6.483, $p = 0.006$), while the combination of the three predictors identified the patient population with the worst outcome (HR 9.631, 95% CI 4.375 to 21.69, $p < 0.0001$). E vent-free survival rates were 75% in patients without predictors, 73% in those with one, 49% in those with two, and 11% in subjects with three prognostic factors.



Conclusions: In systolic HF, EVR and RFP are the strongest predictors of outcome, while plasma BNP levels ≥ 215 pg/ml have an additive prognostic value.

285 Mid-regional Pro-atrial Natriuretic Peptide (MR-proANP) better than N-terminal Pro B-type Natriuretic Peptide (NT-proBNP) predicts survival in Chronic Heart Failure (CHF)

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Background: Natriuretic peptides are powerful predictors of survival in CHF. ANP comprises 98% of all natriuretic peptides in the circulation. Its relative instability compared to other natriuretic peptides limits its prognostic value. Mid-regional proANP (MR-proANP) is highly stable in vivo and ex vivo.

Methods: We investigated 536 CHF patients (age 61 ± 12 yrs, NYHA class 2.6 ± 0.8 , LVEF $30 \pm 10\%$, N-terminal pro-B-type natriuretic peptide [NT-proBNP] 3581 ± 6513 pg/mL, serum creatinine 112 ± 43 μ mol/L, 94% male, 71% ischemic etiology) from 5 European centers. MR-proANP was detected using a novel assay (Luminescence Immuno Assay). The functional assay sensitivity (inter assay CV $< 20\%$) is 20 pmol/L, and the stability of MR-proANP at room temperature is > 24 hours. Median MR-proANP in 325 healthy individuals in previous investigations was 45 pmol/L (95% CI 43-49 pmol/L).

Results: Mean MR-proANP in our CHF population was 334 ± 306 pmol/L (range: 24.5-2280). MR-proANP increased with NYHA class (I: 133 ± 94 , II: 243 ± 202 , III: 379 ± 301 , IV 626 ± 446 pmol/L, $p < 0.0001$ for all comparisons except NYHA I vs II [$p = 0.0269$]). In a multivariate model, MR-proANP correlated with NT-proBNP ($r = 0.49$, $p < 0.0001$), serum creatinine ($r = 0.24$, $p < 0.0001$), NYHA class ($r = 0.18$, $p < 0.0001$), and LVEF ($r = -0.13$, $p = 0.0002$), but not with etiology, age, and sex (all $p > 0.3$). During follow-up (92 to 4879 days in survivors, median 467 days), 149 patients (28%) died after 1 to 3678 days (median 310 days). The 1- and 5-year mortality were 15% (95% CI 11-19%) and 41% (95% CI 36-47%), respectively. In univariate Cox proportional hazard analysis, MR-proANP (chi square 102.4), NT-proBNP (chi square 73.6), NYHA class, serum creatinine, LVEF (all $p < 0.0001$), and age ($p = 0.003$) all predicted survival. Increasing MR-proANP was a predictor of poor survival (hazard ratio 1.100 per 100 pmol/L, 95% CI 1.047 to 1.156, $p = 0.0002$), independently of NT-proBNP, age, sex, etiology, LVEF, NYHA class, and creatinine. In this model, NT-proBNP did not predict survival ($p = 0.1149$). 18-month mortality was 4% (95% CI 0-8%), 24% (95% CI 14-34%), 37% (95% CI 25-49%), and 77% (95% CI 67-87%) in ascending quartiles of MR-proANP ($p < 0.0001$).

Conclusions: MR-proANP is a powerful new predictor of mortality in patients with CHF independently of established prognosticators. Its predictive power exceeded that of NT-proBNP in our study population.

286 Significance and therapeutic potential of C-type natriuretic peptide in myocardial infarction

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Background: Left ventricular (LV) remodeling after myocardial infarction (MI) is a major cause of subsequent heart failure and death. In this study, to clarify the

role of local cardiac C-type natriuretic peptide (CNP), the third member of the natriuretic peptide family, we investigated endogenous cardiac CNP expressions after MI. In addition, we assessed the hypothesis that the in vivo administration of CNP might attenuate cardiac remodeling after MI.

Methods and Results: Experimental MI was induced by coronary ligation in male Sprague-Dawley rats. We found that cardiac CNP gene expressions were dramatically increased in the infarct region and moderately increased in the non-infarct region on day 3, and subsequently decreased gradually after MI. In addition, immunohistochemical study was performed to localize CNP in ventricular myocardium after MI and revealed that CNP was stained mainly in fibrotic area of the infarct and border region on day 7 after MI. Furthermore, LV enlargement and dysfunction induced by MI was significantly attenuated by CNP infusion at 0.1 µg/kg/min for 2 weeks. CNP infusion significantly attenuated an increase in morphometrical collagen volume fraction in the non-infarct region. CNP also significantly improved capillary density in the non-infarct region. To evaluate whether CNP has direct effects on coronary endothelial cells, we further explored the capillary network formation of cultured human coronary artery endothelial cells (HCAECs) by Matrigel assay in the presence of CNP or a cGMP analog, 8-Br-cGMP. CNP and 8-Br-cGMP significantly promoted spontaneous capillary network formation of HCAECs compared to control.

Conclusions: In the present study, we found that cardiac CNP gene expressions were increased in the infarct region and non-infarct region after MI. We also demonstrated that CNP was stained mainly in fibrotic area of MI. These results suggest that endogenous local CNP might play an important role in the ischemic heart. In addition, our study has demonstrated that continuous administration of CNP improved LV dysfunction and attenuated the development of cardiac remodeling after MI, via improvement in collagen synthesis and angiogenesis in the non-infarcted region. Therefore, CNP is potentially useful as a new cardioprotective agent through its novel mechanism of action.

287 Anemia elevates plasma brain natriuretic peptide concentration in healthy subjects: possible explanation for gender-related difference

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Purpose: Plasma brain natriuretic peptide (BNP) is widely used as a biomarker for the diagnosis and prognosis of heart failure (HF). However, its concentration is often found high even in apparently healthy subjects. A few studies suggest that both age and gender influence plasma BNP concentration even in healthy subjects. In this study, we examined the effects of gender, age and anemia (blood hemoglobin and hematocrit) on plasma BNP concentration in healthy subjects.

Methods: Study population consisted of 1036 healthy subjects who received the annual health examination in a company. Subjects were defined as those who did not have a history of HF, coronary artery disease, atrial fibrillation or renal failure. There were 874 women and 162 men, ranging in age from 30 to 63 years (mean 41).

Results: Plasma BNP was abnormal (>18.4pg/ml) in 292 (28%) subjects. The incidence was significantly higher in women than in men (31% vs 14%, $p<0.01$). Mean plasma BNP was higher in women than in men. The difference was associated with the difference in blood hemoglobin, hematocrit and age. When multiple step-wise regression analysis was performed with hematocrit, aging, gender, creatinine clearance and systolic blood pressure as independent variables, the results showed the combination of blood hematocrit and age yielded a better correlation with logarithmically transformed BNP concentration ($r=0.35$, $p<0.01$). Logarithmically transformed BNP concentration correlated inversely with blood hematocrit ($r=-0.31$, $p<0.01$ for all; $r=-0.23$, $p<0.01$ for women; $r=-0.16$, $p<0.05$ for men). The regression line was considered identical between women and men.

Differences Between Women and Men

	Hb (g/dl)	Ht (%)	Age (years)	BNP (pg/ml)
Women	13.2±1.3	40.6±3.3	40±8	16.7±15.4
Men	15.5±0.9	47.0±2.6	45±9	10.0±11.6
p value	<0.01	<0.01	<0.01	<0.01

mean±SD

Conclusions: Plasma BNP concentration was higher in women than in men. Anemia was a factor that elevates plasma BNP concentration in healthy subjects, and may at least partially explain the gender-related difference in plasma BNP concentration.

NOVEL BLOOD MARKERS PREDICTING OUTCOME IN HEART FAILURE

288 Mid-regional pro-adrenomedullin as a novel and prognostic marker in chronic heart failure (CHF)

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Recent studies have suggested adrenomedullin (ADM) to be a predictor of survival in CHF patients. Its precursor mid-regional pro-ADM (MR-proADM) is significantly more stable in the circulation and ex vivo.

Methods: We investigated 417 CHF patients (age 63±12 yrs, 95% male, NYHA 2.6±0.8, LVEF 32±10%, serum creatinine 113±42 µmol/L, 73% ischemic etiology, N-terminal pro B-type natriuretic peptide [NT-proBNP] 3582±6980 pg/ml). MR-proADM was detected using a novel assay (Luminescence Immuno Assay). The functional assay sensitivity (inter assay CV < 20%) is 0.12 nmol/L, and the stability of MR-proADM at room temperature is >72 hours. The median of MR-proADM in healthy controls is 0.33±0.07 nmol/L (range: 0.10-0.64 nmol/L, n=264).

Results: In our CHF population mean MR-proADM in plasma was 0.62±0.53 nmol/L (range: 0.05-3.53). MR-proADM increased with NYHA class (I: 0.29±0.18; II: 0.46±0.33; III: 0.67±0.50; IV: 1.20±0.78 nmol/L, $p<0.0001$ for all comparisons except NYHA I vs II [$p=0.06$]). In a multivariate model, MR-proADM related to NT-proBNP ($r=0.26$, $p<0.0001$), serum creatinine ($r=0.32$, $p<0.0001$), NYHA class ($r=0.26$, $p<0.0001$), and sex ($r=0.14$, $p=0.0007$), but not to etiology, age, and LVEF (all $p>0.1$). During follow-up (median 577 days in survivors), 128 patients died (31%). The 1- and 5-year mortality were 14% (95% CI 10-18%) and 40% (34-46%), respectively. In univariate Cox proportional hazard analysis, MR-proADM, NT-proBNP, NYHA class, LVEF, age, and serum creatinine (all $p<0.001$) all predicted survival. Increasing MR-proADM was a predictor of poor survival (hazard ratio 1.066 per 0.1 nmol/L [1.022-1.113], $p=0.0032$), independently of age, sex, etiology, LVEF, NYHA class, creatinine, and NT-proBNP. 18-month mortality was 13% (95% CI 7-19%), 17% (95% CI 7-27%), 31% (95% CI 17-45%), and 65% (95% CI 53-77%) in ascending quartiles of MR-proADM ($p<0.0001$).

Conclusions: MR-proADM is a powerful new predictor of mortality in patients with chronic heart failure, independently of established prognosticators including several markers of neurohormonal activation. Its abundance in the circulation and high sample stability make it a good candidate for screening tests and epidemiological studies.

289 Prognostic risk stratification in acute heart failure with Cystatin C -a novel marker of renal function

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Background: Acute heart failure (AHF) has poor long-term prognosis and renal dysfunction is associated with increased mortality in heart failure. Our goal was to investigate the prognostic value of Cystatin C (CysC), a novel marker of renal function, in the setting of acute heart failure.

Methods: FINN-AKVA is a national, prospective, multicenter study on AHF conducted in 14 hospitals in Finland. Consecutive patients presenting with symptoms and signs of AHF and requiring hospitalisation were enrolled during three months in 2004. Blood samples were obtained on admission and 48 h later. The population in the present study consists of 480 patients with measurements of CysC available at 48 h from admission. In the mortality analysis several clinical and biochemical variables were included. Creatinine clearance (CrCl) was calculated by the Cockcroft-gault formula. Analysis was performed by multivariate Cox proportional hazards model and Kaplan Meier survival curves.

Results: All-cause mortality at 12 months was 25.4%. Creatinine values >120 µmol/L was found in 20% of patients. When assessed by CysC, 43% had impaired renal function and moderate renal insufficiency by CrCl <60 ml/min was present in 42% of the study population.

CysC level over the median of 1.30 mg/l was found to be the strongest predictor of outcome, adjusted HR 2.7 (95%CI 1.6-4.5) $p<0.001$. Other variables independently associated with outcome were older age, male gender, NT-proBNP levels >median (3916 pg/ml) and creatinine >120 µmol/L. CysC >1.30 mg/l remained the most powerful risk marker also when compared to CrCl <60 ml/min on multivariate analysis.

Mortality increased significantly by tertile of CysC: 9.9%, 24.8% and 41.8% from the first to the third tertile, log rank $p<0.01$ between each tertile. Combining tertiles of CysC and NT-proBNP stratified patients in groups with mortality risk ranging from very low (5.2%) in the first to very high (48.7%) in the third dual biomarker tertile. In patients with normal plasma creatinine, elevated CysC level was as-

sociated with significantly higher mortality at 12 months compared to patients with both markers of renal function within the normal range; 40.4% vs 12.6%, $p < 0.0001$. Furthermore, in patients with normal CrCl > 90 ml/min, mortality was 50% if CysC levels were above normal ($p < 0.0001$).

Conclusion: CysC enables comprehensive mortality risk stratification of patients hospitalised with AHF and identifies patients with poor prognosis despite normal plasma creatinine or normal CrCl. In addition, CysC is a strong and independent predictor of outcome at 12 months.

290 Plasma phosphate as a marker of poor prognosis in congestive heart failure



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Numerous physiological processes depend critically on phosphate availability. Many alterations in phosphate metabolism have been shown in myocytes and skeletal muscles in heart failure. Phosphate has been also postulated as possible determinant of muscle fatigue. Recently, association between plasma inorganic phosphate (PIP) and mortality has been shown in hypolipidemic patients (Circulation 2005;112:2627). In heart failure patients prognostic importance of PIP and its relation to clinical and laboratory variable have not been studied. Our aim was to assess relation between PIP and clinical, laboratory and body composition variables in patients with heart failure and to establish the prognostic role of PIP in this population. In 332 patients (266 M, 66 F, age 53 ± 13 years, NYHA 2.8 ± 0.8 , EF 25 ± 6 , 77% ischemic etiology, we assessed PIP, performed DEXA scanning to measure muscle mass and patients were prospectively followed for median period 466 days (1-988). We calculated Pearson's correlations coefficients for relations between PIP and various parameters. There was negative correlation between PIP and muscle mass ($r = -0.34$, $p < 0.00000$). There was also clear relationship between PIP and NYHA class with increasing values from class I to IV ($p < 0.001$ for trend) (see table 1). 66 patients (20%) died during follow up. Multivariate regression model was used to establish prognostic importance of different variables. PIP and NTproBNP levels were independent of age, gender, etiology of heart failure, MDRD GFR and ejection fraction predictors of mortality OR=10.8, 95% CI 1.4-82, $p < 0.02$ and 105, 95% CI 6-1676, $p < 0.001$ for PIP and NTproBNP respectively.

NYHA class and plasma phosphate

NYHA	I N=5	II N=133	III N=160	IV N=34
PIP [mmol/L]	1.03 ± 0.23	1.09 ± 0.23	1.17 ± 0.23	1.31 ± 0.23

Conclusion: In heart failure PIP is independently associated with poor prognosis, our study suggests the link between muscles and PIP.

291 Serum pentosidine, an Advanced Glycation End product (AGE), is a risk factor for heart failure



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Oxidative stress and inflammation play an important role in the pathogenesis of heart failure. AGEs induce activation of intracellular signaling and production of pro-inflammatory cytokines and free radicals. Pentosidine is an AGE formed by glycation and oxidation. We studied clinical significance of serum pentosidine level in patients with heart failure. Serum pentosidine was measured in 141 patients with heart failure. Patients were followed up for median 479 days (range 5 to 1095 days) with the end points of cardiac death and progressive heart failure requiring rehospitalization. Serum pentosidine level was significantly increased in patients with New York Heart Association (NYHA) class III/IV than in those with NYHA class I/II ($P < 0.001$). During follow-up periods, 32 patients had cardiac events. Pentosidine level was significantly higher in patients with cardiac events than in those without cardiac events ($P < 0.0001$). In univariate Cox hazard analysis, age, NYHA class, pentosidine, creatinine, estimated glomerular filtration rate, uric acid and B-type natriuretic peptide were risk factors for cardiac events. In multivariate analysis, serum pentosidine level was an independent risk factor for cardiac events (hazard ratio 1.60, 95% confidence interval 1.17 to 2.19, $P < 0.01$). Patients were divided into 4 groups based on pentosidine levels (1st < 22.9 , 2nd 23.0-31.9, 3rd 32.0-46.5, 4th > 46.6 ng/ml). Risk ratios for cardiac events in-

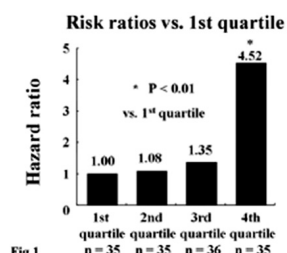


Fig.1

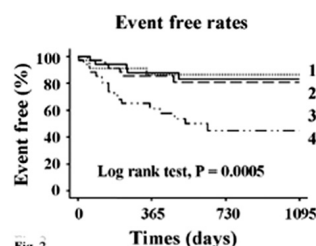


Fig.2

creased as serum pentosidine level rose from the 1st to 4th quartile (Figure 1). Kaplan-Meier analysis (Figure 2) demonstrated that event free rate was the lowest in the 4th quartile (the highest pentosidine level). Serum pentosidine level was a novel prognostic factor in heart failure.

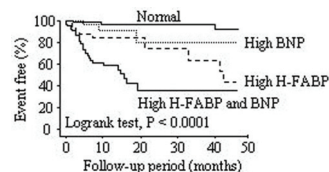
292 A combination of heart-type fatty acid binding protein and brain natriuretic peptide can reliably risk stratify patients hospitalized for chronic heart failure



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Background: Heart-type fatty acid binding protein (H-FABP) is a small cytosolic protein and released into the circulation when the myocardium is injured. Brain natriuretic peptide (BNP), secreted from the ventricles by mechanical overload, is a well-established prognostic factor in chronic heart failure (CHF) patients. We prospectively studied whether the combination of a marker for myocardial cell injury (H-FABP) and a marker for ventricular overload (BNP) at admission can reliably risk stratify patients hospitalized for CHF.

Methods and Results: We measured serum H-FABP levels and plasma BNP levels at admission in 186 consecutive patients hospitalized for CHF. During a mean follow-up period of 534 ± 350 days, there were 44 cardiac events, including 16 cardiac deaths and 28 readmissions for worsening heart failure. Normal upper limits for H-FABP and BNP levels were determined from the receiver operating characteristic (ROC) curves (4.3 ng/ml for H-FABP and 200 pg/ml for BNP). A stepwise Cox regression analysis demonstrated that high H-FABP (hazard ratio 5.416, $P = 0.0002$) and high BNP (hazard ratio 2.411, $P = 0.0463$) were independent predictors of cardiac events. High levels of both H-FABP and BNP at admission were associated with the highest incidence in cardiac mortality and cardiac events. Kaplan-Meier analysis also showed that a combination of H-FABP and BNP levels could reliably stratify patients for cardiac events (figure).



Kaplan-Meier analysis

Conclusion: Combined measurements of H-FABP and BNP levels at admission may be a highly reliable evaluation for risk stratifying patients hospitalized for CHF.

293 Multiple anabolic deficiency in men with chronic heart failure: detrimental impact on long-term survival



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Background: Multiple age-related depletion in three main endocrine anabolic axes in men, assessed by circulating total testosterone (TT), dehydroepiandrosterone sulphate (DHEAS) and insulin-like growth factor 1 (IGF-1), is related to increased morbidity and mortality. We studied the prevalence of these anabolic derangements in men with chronic heart failure (CHF), and assessed the long-term prognostic consequences of multiple anabolic deficiencies.

Methods: Serum hormone levels were measured using immunoassays in 208 men with stable CHF (median age: 63 years, median left ventricular ejection fraction [LVEF]: 33%, NYHA [New York Heart Association] class [I/II/III/IV]: 19/102/70/17, ischaemic aetiology: 81%), and in 366 healthy men aged 35-80 living in the same area.

Results: Deficiencies in TT, DHEAS and IGF-1, defined as serum level $\leq$ the 10th percentile of healthy age-matched controls, were present in 22%, 58% and 64% of men with CHF, respectively. Depletion in none, one, two and three anabolic axes was found in 11%, 41%, 41% and 7% of men with CHF, respectively. All these endocrine abnormalities were seen across all age categories. TT and DHEAS (not IGF-1) were inversely related to NYHA class, irrespective of aetiology (both $p < 0.0001$). Only DHEAS correlated positively with LVEF, and inversely with plasma NT-proBNP (both $p < 0.01$). During follow-up (mean: 930 ± 434 days, median - 1144 days, > 3 years in all survivors), 75 (36%) patients died. Circulating TT, DHEAS and IGF-1 levels were prognostic markers, independent of each other, in multivariate models when adjusted for established prognostic factors, including plasma NT-proBNP (all $p < 0.05$). Men with CHF and normal levels of all anabolic hormones had the lowest 3-year mortality rate (17%, 95%CI: 2-33%), compared to those with deficiencies in one (26%, 95%CI: 16-35%), two (45%, 95%CI: 34-55%), and all three (73%, 95%CI: 51-95%) anabolic endocrine axes ($p < 0.0001$).

Conclusions: In male CHF patients, anabolic hormone depletion is common.

Deficiency of each anabolic hormone constitutes an independent marker of poor long-term prognosis. Depletion in more than one anabolic endocrine axis identifies groups with a higher mortality.

OPTIMIZING STEM CELL THERAPY

303 The response of progenitor cells to vascular endothelial growth factor is amplified under acute inflammatory conditions



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It has been reported that bone marrow-derived progenitor cells (PC) contribute to the recovery of myocardial function following ischemia. Growth factors, such as members of Vascular Endothelial Growth Factor (VEGF) family, are released during hypoxia and increase the number, proliferation, and homing of PC. Of clinical relevance, we analyzed the response of PC to VEGF in subjects with chronic and acute coronary artery disease. This was correlated with cardiovascular risk burden and inflammatory status.

Prior functional analysis, the number and phenotype of circulating PC (specific stem cell markers, VEGF receptor-1 and -2) were characterized using flow cytometry. PC were isolated from peripheral blood as CD133+ cells using a positive MACS isolation. The migratory response of freshly isolated PC towards members of VEGF family (VEGF-A, PlGF-1, and VEGF-E) was analyzed in a chemotaxis assay. Three groups were compared: (i) patients with stable coronary artery disease (CAD)(n=25), (ii) patients early (days 2-4) after onset of acute myocardial infarction (AMI)(n=45), and (iii) healthy controls (n=20).

No significant change in PC number was observed in CAD, while a tendency towards an increased number was noticed early post-AMI (HC, 2182 ± 391 ; CAD, 2062 ± 514 ; AMI, 3777 ± 464 cells/mL blood).

In HC, PC responded significantly to VEGF ligands (average of 1.5-folds increase to unstimulated PC, $p < 0.001$).

In contrast, PC from CAD showed a lower response to VEGF stimulation. In particular, PC response to PlGF-1, specific ligand for VEGF receptor-1, was attenuated in comparison to HC ($p < 0.001$). No clear correlation with the presence of cardiovascular risk factors was registered.

Interestingly, PC from AMI responded differently than those from CAD. Following AMI, PC showed a clear upregulation of their response to VEGF ligands in a time dependent fashion (day 2, 1.7-folds increase, $p < 0.05$; day 4, 2.2-folds increase, $p < 0.02$). This was correlated with the increase of CK-max ($R = 0.81$, $p < 0.02$), and C-reactive protein serum levels ($R = 0.68$, $p < 0.001$).

To conclude, chronic CAD burden negatively influences PC response to VEGF ligands, while acute inflammatory conditions, such as early post-AMI, are associated with a stimulation of the migratory response of PC.

304 HMG-CoA reductase inhibitors enhance cardiac stem-progenitor cell activation and new myocyte formation after diffuse myocardial damage



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Purpose: HMG-CoA reductase inhibitors (statins) have been shown to favourably impact pathologic cardiac remodeling. Statins exert pleiotropic, cholesterol-independent effects on cardiac repair, which are not yet fully understood. The adult mammalian heart possesses c-kit-positive cardiac stem/progenitor cells (CSCs), which are clonogenic, self-renewing and multipotent and are activated in cardiac disease. Here we tested whether statin treatment affects CSC activation and resultant myocyte differentiation in an in vivo myocardial-regeneration assay.

Methods: A single high dose of isoproterenol (ISO, 5mg/kg) was employed to induce diffuse myocyte damage in Wistar rats. We have demonstrated that this damage determines CSC activation and new myocyte formation. Saline was used in control rats (CTRL). ISO-treated rats were administered simvastatin (SIM, 50mg/kg) or placebo (PL). Animals were sacrificed 3, 7 and 14 days after ISO. Myocardial repair was tracked by BrdU administration and myocyte apoptosis (hairpin 1), proliferation (BrdU/Ki67), c-kit-positive CSC number and their myocyte-committed progeny (c-kit-positive/MEF2C-positive) were evaluated by confocal microscopy.

Results: Myocyte hypertrophy was evident 3 days after ISO, compared to CTRL. SIM administration blunted ISO-induced hypertrophy. The fraction of apoptotic myocytes increased 1 through 3 days after ISO (0.4%) in PL-treated rats, but was almost abolished by SIM administration (0.02%). Conversely, the number of c-kit-positive CSCs increased progressively in SIM-treated rats compared to PL, 3, 7 and 14 days after ISO, respectively. Myocyte progenitors (c-kit-positive/MEF2C-positive) were increased in SIM as compared to PL, 3 to 14 days after ISO. Accordingly, the fraction of newly-formed myocytes (BrdU-positive) in PL-treated rats reached ~4% by 14 days after ISO, but they form earlier and reach up to 36% higher number in SIM-treated animals at 14 days after ISO. Importantly, new my-

ocytes showed almost complete mature size in SIM-treated rats at 14 days after ISO. Finally, SIM-treatment resulted in an improved LV function, compared to PL-treated animals.

Conclusions: Statins blunt myocardial remodeling by a combination of reversal processes: preventing myocyte apoptosis and hypertrophy while stimulating new myocyte formation through cardiac stem cell activation. These data add a new piece to the puzzle of the beneficial myocardial effects of HMG-CoA reductase inhibitors in the treatment of cardiac disease.

305 Cell isolation matters: a comparison of different isolation protocols of bone marrow mononuclear cells for cell therapy in acute myocardial infarction



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Cell therapy of patients with myocardial infarction improves neovascularization and heart function in experimental studies and clinical trials. However, despite the use of similar cell populations, recent randomized studies showed striking differences in functional improvement of patients after treatment with bone marrow mononuclear cells. Whereas the REPAIR-AMI trial showed a significant improvement of ejection fraction, no change in function was detected in the ASTAMI trial. Therefore, we compared the functional activity of bone marrow mononuclear cells isolated by the protocols of the REPAIR and the ASTAMI trial. Bone marrow mononuclear cells were isolated according to the protocol used in the REPAIR-AMI trial, which includes Ficoll gradient centrifugation followed by storage of the cells at room temperature in x-vivo 10 medium and 20% autologous serum, or the ASTAMI protocol, which used LymphoprepTM gradient centrifugation and stored the cells at 4°C in 0.9% NaCl and 20% Heparin-plasma. The recovery of total cell number, colony forming units (GM-CFU) and the number of mesenchymal stem cells was significantly reduced to $77 \pm 4\%$, $83 \pm 16\%$ and $65 \pm 15\%$, respectively, when using the ASTAMI protocol compared to the REPAIR-AMI protocol. The capacity of the isolated BMC to migrate in response to SDF-1 was abolished when using the ASTAMI isolation procedure ($40 \pm 7\%$ compared to the REPAIR-AMI protocol). Infusion of BMC in hind limb ischemia model demonstrated a significantly higher improvement of neovascularization by BMC isolated by the REPAIR-AMI compared to the ASTAMI protocol ($57 \pm 5\%$ reduction of ASTAMI compared to REPAIR-AMI), although the same number of cells were infused. Comparison of the individual steps in the isolation protocols identified the use of NaCl and plasma for cell storage as major factors, which led to a functional impairment of the BMC. Cell isolation protocols have a major impact on the functional activity of cells isolated for cell therapy. The analysis of cell number and CFU may not entirely reflect the functional capacity of cells in vivo. Additional functional testing by using migration assays and particularly in vivo monitoring of cell function in animal models appears to be mandatory to assure proper cell function before embarking on clinical cell therapy trials.

306 Retrograde intracoronary infusion as a route for cell transplantation for treating post-infarction chronic heart failure



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Intracoronary infusion is a useful cell-delivery route which enables dissemination of cells into the host myocardium with less myocardial injury and less inflammatory response as compared to intramuscular injection (IM). Antegrade intracoronary infusion is commonly used in clinical cell therapy but has a risk of coronary embolism. This can be serious particularly when treating post-infarction chronic heart failure where the lumen of responsible coronary arteries is often diffusely narrowed. In contrast, retrograde intracoronary infusion (RIC) is considered to obviate such a risk. In the present study, we estimated the efficiency of RIC implantation of bone marrow cells for treating post-infarction chronic heart failure by comparing with IM injection.

[Methods and Results] 10 million bone marrow mononuclear cells derived from male GFP transgenic rats were implanted into female wild-type rat hearts that had undergone left coronary artery ligation 3 weeks before. Cell implantation was performed by either RIC infusion into the left cardiac vein which drains the whole left ventricular free wall (RIC group) or IM injection into border zones surrounding the infarct (IM group). At 4 weeks after cell implantation, echocardiography showed that left ventricular ejection fraction was similarly improved in the RIC ($47.8 \pm 4.2\%$, $p < 0.001$, $n = 10$) and IM ($46.6 \pm 2.4\%$, $p < 0.001$, $n = 10$) groups, compared to the hearts before cell therapy ($34.4 \pm 1.8\%$). Noticeably, continuous ECG monitoring by a radio-telemetry unit demonstrated a large number of ventricular premature contractions (VPC), including multiform, consecutive VPCs and VT, in the IM group with a peak at day 7. The number of VPC was 14.7 ± 5.2 , 17.4 ± 5.1 , 108.2 ± 73.0 , 38.3 ± 30.1 , 2.8 ± 2.7 /hour at day 1, 3, 7, 14, 28, respectively ($n = 4$ or 5 at each point). In contrast, only a small number (< 5 /hour) of VPC was found in the RIC and control groups (PBS injection by either RIC or IM route) throughout the period studied. Quantitative PCR for male specific Sry gene detected a larger number of surviving grafted cells in the RIC group compared to the IM group ($11.2 \pm 7.2 \times 10^3$ vs $1.7 \pm 0.7 \times 10^3$, $p < 0.001$, $n = 5$) at day 7. Histological study

demonstrated that cells grafted by IM injection, but not RIC infusion, formed islet-like cell clusters together with many accumulating inflammatory cells. Such a local heterogeneity appeared to disturb myocardial construct, disrupting intraventricular conductance.

[Conclusion] RIC infusion is a more efficient, safer route, compared to IM injection, for implantation of bone marrow cells for treating post-infarction chronic heart failure.

307 Therapeutic myocardial neovascularization using human embryonic stem cell-derived endothelial progenitor cells



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Objective To investigate the efficiency of human embryonic stem cells (hESCs) differentiation into endothelial progenitor cells (EPC) within embryoid bodies (EBs) transduced with adenoviral vector expressing human VEGF₁₆₅ gene (ad-hVEGF₁₆₅) and the effect of transplanting the EPCs in a myocardial infarction (MI) model.

Methods Single cells from EBs were transduced with ad-hVEGF₁₆₅ for four hours for three consecutive days. EPC differentiation was analyzed through immunohistochemical analysis with endothelial-specific markers and RT-PCR of vascular-related gene markers. ELISA was performed to measure hVEGF₁₆₅ protein expression. The 4,6-diamidino-2-phenylindole (DAPI)-labeled cells were transplanted into rodent ligation models. The animals were randomized to receive intramyocardial injection of DMEM (group-1; n=25), null-Ad transduced cells (group-2; n=25) and VEGF-transduced cells (group-3; n=25). Six weeks post-treatment, heart function was assessed by echocardiography. Hearts were harvested for morphometric and immunohistochemical studies.

Results There was a significant increase in AC133 and CD31-positive cells. $48.4 \pm 11.3\%$ and $49.1 \pm 12.5\%$ of ad-hVEGF₁₆₅-transduced cells were positive for AC133 and CD31 respectively. Upregulation of vascular-related genes expression in ad-hVEGF₁₆₅-transduced cells including EPC markers such as Flk-1 and AC133 was observed. These cells secreted functional hVEGF protein over 30 days, peaking on day 8 post-transduction ($23.1 \pm 6\text{ng/ml}$). Transplantation of ad-hVEGF₁₆₅-transduced cells into the ligation models showed improvement in left ventricular ejection fraction in group-3 ($72.85 \pm 4.7\%$) as compared to group-1 ($38.22 \pm 5.4\%$, $p < 0.05$) and group-2 ($51.16 \pm 3.4\%$, $p < 0.05$). This was accompanied with significant reduction of infarct size in group-3 ($28 \pm 6.2\%$) as compared to group-1 ($76 \pm 4.3\%$, $p < 0.001$) and group-2 ($51 \pm 4.5\%$; $p = 0.008$). Histological examination revealed that DAPI-labeled cells were incorporated into the newly formed blood vessels. Fluorescent immunostaining of von-Willebrand factor and smooth muscle actin at high microscopic field showed enhanced blood vessel density in group-3 (29.35 ± 1.02 ; 25.62 ± 0.94 , $p < 0.05$) as compared to group-1 (5.25 ± 0.73 ; 2.41 ± 1.26 , $p < 0.05$), group-2 (11.36 ± 1.57 ; 5.82 ± 1.19 , $p < 0.05$).

Conclusion Ad-hVEGF₁₆₅ transduction into differentiating cells from EBs enhanced EPC differentiation. These EPCs demonstrated therapeutic potential in myocardial regeneration as they induced neovascularization upon transplantation.

308 Human embryonic stem cells are immunogenic in allogeneic and xenogeneic settings



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Background Human embryonic stem cells (HESCs) can potentially replace damaged and dysfunctional cells in different clinical settings. Recent studies have suggested that HESCs are immune-privileged and may thereby circumvent rejection.

Methods The expression of immunologically active molecules was studied by micro-array analysis. The expression of HLA molecules after incubation with interferon- γ (IFN- γ) was analysed by flow cytometry. HESCs were transplanted into immunologically competent mice and traced by fluorescence in situ hybridization (FISH) and immunohistochemistry. The ability of HESCs to directly and indirectly induce immune responses in CD4+ T-cells from naïve and transplanted mice was studied. HESCs ability to induce immune responses in human CD4+ T-cells, when cultured in the presence of dendritic cells (DCs) syngeneic to responder T-cells, was also analysed.

Results HESCs demonstrated expression of HLA class I but low levels of other immunologically active molecules and expressed low levels of HLA class II after incubation with IFN- γ . HESCs could be demonstrated by FISH until three days after transplantation and were surrounded by heavy infiltrates of T-cells and macrophages. HESCs induced a similar immune response as human fibroblast cells (HFibs) on naïve and immunized T-cells, both directly or in the presence of syngeneic DCs. A similar response was observed on human T-cells stimulated by syngeneic DCs. Undifferentiated HESCs in combination with syngeneic DCs also stimulated proliferation of alloreactive primary human T-cells.

Conclusion HESCs are immunogenic and do not inhibit immune responses during direct or indirect antigen presentation and they were acutely rejected. HESCs induce an immune response similar to other cell transplants and show no signs of being immune-privileged.

STEM CELL THERAPY: FOCUS ON THE CARDIAC MYOCYTE

309 Paracrine effects of cell transplantation on recipient cardiomyocytes in a rat model of heart failure



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Cell transplantation has been shown to enhance cardiac function in several animal models of heart failure. However, the low numbers of surviving transplanted cells can not explain the functional myocardial improvement directly, and the cellular mechanisms responsible remain unknown. We investigated the effects of transplantation of bone marrow mononuclear cells or skeletal myoblasts on the recipient cardiomyocytes in a rat model of heart failure.

Myocardial infarction was induced in adult female Sprague-Dawley rats by left coronary artery ligation (HF). Bone marrow cells (BM) or skeletal myoblasts (SK), both from GFP-expressing rats, were injected into the heart.

After 4 weeks both cell types improved ejection fraction (BM from $36.8 \pm 1.7\%$ to $46.8 \pm 2.1\%$ [16] (Mean $\pm$ SEM [n]) $p = 0.0013$; SK from $35.5 \pm 1.5\%$ to $41.72 \pm 2.1\%$ [16] $p = 0.02$) whereas there was no difference after PBS injection only.

Isolated ventricular myocytes were GFP-negative. Projected 2-dimensional cell area was larger in heart failure compared to sham-operated hearts (SHAM). This hypertrophy was reduced following cell transplantation (area, in μm^2 : SHAM 3074 ± 61 [220]; HF 4143 ± 68 [225]; BM 3732 ± 66 [259]; SK 3657 ± 53 [328]). Calcium transients developed more slowly in HF, but transplantation of either cell type abolished this delay ((Indo-1 time-to-peak, in ms): SHAM 36.9 ± 0.81 [53], HF 43.1 ± 1.15 [46], BM 39.1 ± 0.87 [44] ($p < 0.01$ vs HF), SK 37.1 ± 0.91 [41] ($p < 0.001$ vs HF)). L-type calcium-current density was increased in SK compared with HF but was unchanged in BM ((in pA/pF, at 0 mV) SHAM -4.61 ± 0.28 [28], HF -3.42 ± 0.22 [22], BM -3.54 ± 0.35 [15], SK -4.83 ± 0.40 [23] ($p < 0.05$ vs HF)).

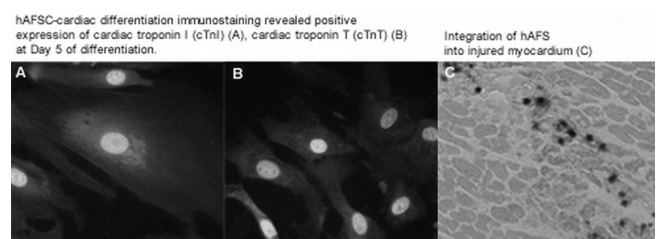
This increased calcium trigger can be responsible for the faster calcium release in the SK-treated cardiomyocytes. This study strongly suggests that the improvement in heart function following cell transplantation is at least partly mediated by a paracrine effect on recipient myocyte calcium homeostasis.

310 Amniotic fluid derived stem cells for cardiac therapeutics



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Cell therapy has been proposed as a means to promote the regeneration of damaged heart muscle. We have established lines of broad spectrum multipotent stem cells derived from primitive fetal cells present in human and mouse amniotic fluid (AFSC). These cells can be induced to differentiate in vitro into a wide variety of cell types, including all three embryonic germ layers. In this study, we hypothesize that AFSC can be used for cardiac regeneration. We utilized treatment with 5-aza-2-deoxycytidine to induced cardiogenic differentiation. The cells were analyzed for expression of myogenic and cardiogenic markers. AFSC-derived cardiomyocytes were seeded on collagen scaffolds and preconditioned in a bioreactor system with cyclic strain stimulation, mimicking the wall motion of the native heart muscle. Lastly, we used an ischemic injury model in mice to test the ability of the cells to survive and integrate after direct injection into the myocardium. We observed that by 10 to 20 days after induction, AFSC cells stained positively for cardiomyocyte markers including troponin I, troponin T, α -actinin. RT-PCR analysis revealed expression of cardiomyocyte markers including GATA-4 and MEF2C. AFSC-derived cardiomyocytes preconditioned in the bioreactor showed muscle tissue organization and contraction. Histological assessment of AFSC-derived cardiomyocytes injected into injured mouse hearts indicated that these cells survived and integrated into the myocardium. These results demonstrate that multipotent stem cells derived from amniotic fluid can be used for cardiac regeneration. Amniotic



Cardiac Differentiation of hAFS

fluid derived stem cells represent a promising novel source of cells for regenerative therapies in cardiac diseases.

311 Wnt signaling and the polycomb-group gene Bmi-1 modulate cardiac stem cell fate



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Purpose: The mammalian heart undergoes significant changes in cell composition during development, adulthood, aging and disease. These changes in the cellular repertoire are generated by a resident cardiac stem cell (CSC) compartment. These CSCs are clonogenic, self-renewing and multipotent, giving rise to the 3 main cardiac cell lineages: myocytes, smooth muscle and endothelial cells. In order to exploit the regenerative potential of these unique cells, it is imperative to obtain a better understanding of their biology and the signalling cascade regulating CSC fate.

Methods: To this aim, c-kit-positive CSCs were isolated from the hearts of C57J-B6 mice and examined in vitro for clonogenicity, self-renewal, proliferation and differentiation.

Results: A cardiosphere-forming protocol (an assay of multipotency), real time RT-PCR and Western Blot analysis showed a high expression of Bmi-1, β -catenin and Wnt1-related proteins in the more primitive, undifferentiated CSCs. When CSCs were grown in the presence of Wnt3a (one of the Wnt-1 group of secreted proteins), CSC proliferation and clonal efficiency increased. Furthermore, Wnt-3A stimulated the formation of primary and secondary cardiospheres. This cellular effect is mediated by activation of the canonical Wnt pathway, through inhibition of β -catenin phosphorylation and hence its degradation. β -catenin stabilization leads to its nuclear accumulation and co-localization with the transcription factor Tcf. β -catenin down regulation through specific mouse si-RNA transfection reduced cardiosphere formation and CSC proliferation. Accordingly, it also abolished the cellular effects of Wnt3a. The polycomb family transcriptional repressor Bmi-1 is required for the self-renewal and post-natal maintenance of hematopoietic and neural stem cells. Our results show that CSC "stemness" also requires Bmi-1 expression. Transfection of a lentivirus expressing Bmi-1 increased CSC clonal efficiency, cardiosphere formation and BrdU incorporation. When a specific mouse siRNA for Bmi-1 was transfected, these in vitro events were all significantly impaired.

Conclusions: These findings reveal a key role for the Wnt1 group and Bmi-1 in CSC biology, modulating clonogenesis and self-renewal of these primitive cardiac cells. The ability to modulate growth and self-renewal of CSCs is of great interest to manipulate myocardial cell regeneration and cardiac tissue engineering.

312(W) Sonic hedgehog (Shh) promotes cardiac differentiation in embryonic stem cells and increases gene expression of the pacemaker channel HCN4 in combination with bone morphogenetic protein (BMP) 4



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[Aim] Pluripotent embryonic stem (ES) cell is one of the most promising cell source for cardiac regeneration therapy. However, efficient method to induce cardiac differentiation remained to be established. Recently, an extracellular signaling molecule, Shh, has been reported to induce cardiomyogenesis in P19 embryonal carcinoma cells. The aim of the present study is to investigate the effects of Shh on cardiac differentiation of ES cells. [Methods] Nkx2.5-GFP knock-in murine ES cells (Hidaka et al., FASEB J. 2003) were cultured for 10 days to form embryoid bodies. The efficiency of cardiac differentiation was evaluated by flow cytometry as proportion of GFP-positive cells. Shh was applied to the culture medium at various concentration (1, 10, 100, 1000, 10000 ng/ml) and at various stages (Stage 1: Day 0-3, Stage 2: Day 4-5, Stage 3: Day 6-7, Stage 4: Day 8-10). Then, efficiency of cardiac differentiation was evaluated as compared to the control medium without Shh (CONT). We also examined the expression levels of cardiac genes such as GATA4, Tbx5, myosin heavy chain, Mef2C, Oct3/4, brachyury and HCN4 by RT-PCR. The effect of combined application of Shh and BMP4 was also examined. [Results] The application of Shh significantly increased the fraction of GFP-positive (cardiac-differentiated) cells at 100, 1000 and 10,000 ng/ml (1.8, 2.1, 2.9 times compared to CONT, respectively. $n=3$, $p<0.05$). When Shh applied at Stage 3 of development, the efficiency of cardiac differentiation was highest. In RT-PCR experiments, gene expression of cardiac transcriptional factors, GATA4 (1.8 times, $p<0.05$) and Tbx5 (1.9 times, $p<0.0005$) were significantly increased in embryoid bodies cultured with Shh-added medium compared to CONT. Considerable increase of gene expression of myosin heavy chain was also observed. In combined application of Shh and BMP4, gene expression of brachyury, the marker of mesoderm, was significantly increased (4.1 times, $n=3$, $p<0.05$). On the other hand, Oct3/4, the marker of the undifferentiated ES cell, was downregulated when ES cells were cultured in the conditioned medium (0.45 times, $n=3$, $p<0.02$). Interestingly, HCN4 gene encoding the pacemaker chan-

nel was significantly increased with the combined application of Shh and BMP4. [Conclusion] Shh promoted cardiac differentiation in embryonic stem cells. Combined application of Shh and BMP4 increased mRNA expression of HCN4. The results suggest that Shh could be one of the crucial signaling factors for cardiac differentiation. In addition, Shh may be related to further differentiation into certain subtype of cardiac cells.

313(W) Cardiac engraftment of undifferentiated murine embryonic stem cells (ESC) causes teratoma formation in allotransplant and induces apoptosis, probably through leukemia inhibitory factor (LIF) secretion



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Aim: The aim is to investigate the risk and efficacy of ES transplant, focusing on 1) tumorigenesis by undifferentiated ES cells (u-ES) in allo- or xeno-transplant, and 2) induction of apoptosis in host myocardium.

Methods: GFP-labeled u-ES were engrafted to mouse hearts with myocardial infarction (allotransplant). Two to four weeks later, the hearts were excised and subjected to immunohistochemistry for cardiac-specific troponin I (cTnI) and TUNEL stain. For xenotransplant, murine u-ES were engrafted to 8 wks-old Wistar rat hearts. To investigate the mechanisms of u-ES induced apoptosis, LIF (100 U/ml) was applied to cultured mouse cardiomyocytes (CM) and the number of TUNEL-positive cells was estimated with flow cytometry.

Results: In allogeneic transplant ($n=3$), u-ES formed teratoma composed of tubular grand- and cartilage-like immature tissues (Figure 1). Expression of cTnI was not observed in ES, suggesting a failure of post-graft differentiation. TUNEL-positive cells were considerably recognized in the host myocardium surrounding u-ES, but not in u-ES graft itself. Xenotransplant of u-ES to rat heart, in contrast, did not form teratoma ($n=4$), and there was no appreciable differentiation to cardiac cells. CM cultured with u-ES showed prominent apoptotic cell death. Application of LIF, secreted from u-ES as reported recently, to cultured mouse cardiomyocytes significantly increased TUNEL-positive population (from 1.8 ± 1.5 to $6.0\pm2.0\%$, $p<0.05$, $n=3$).

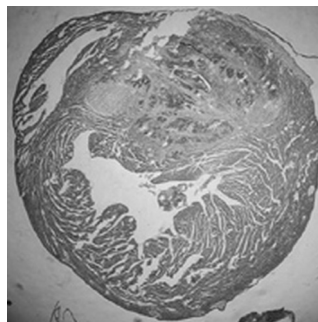


Fig. 1

Conclusion: Cardiac engraftment of u-ES formed teratomas in allotransplant, but not in xenotransplant. u-ES transplant also caused apoptosis in the host mouse myocardium probably through LIF secretion. These results suggest serious limitation in the feasibility of undifferentiated ES allograft in cardiac regeneration therapy.

HEART FAILURE IN THE REAL-WORLD

333 Prescription of HF drugs, diagnostic procedures and costs of heart failure in Italy, 2004

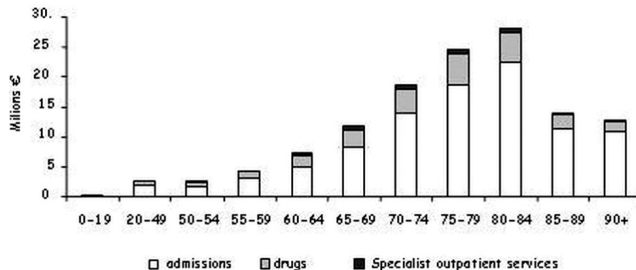


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Purpose: Heart failure (HF) is highly prevalent and costly. We evaluated health care expenditure for hospital admissions, outpatient specialist services and cardiologic drug prescription in 2004 from record linkage of administrative databases (ADB) in 5 regions in Italy among a total population of over 4.7 million residents.

Methods: We identified patients with HF as those who had had between January 2001 and December 2004 either a hospital admission with a primary or secondary diagnosis ICD9 428.xx or certification of chronic HF state by a cardiology specialist during the same period ($n=65.850$, mean age 75.7 ± 1.6 yrs).

Results: In 2004, 40% of the above identified HF patients underwent an ECG and 26% an echocardiogram; 70% of patients were prescribed ACE-inhibitors (ACE-I), 22% angiotensin-receptor blockers (ARB), 27% beta-blockers and 23% aldosterone antagonists (Figure). Total health care costs for HF in 2004 in the study population were € 126.2 millions: € 96.8 millions for hospital admissions (77%); € 4.2 millions for specialist outpatient services (3%); € 25.2 millions for cardiological drug prescription (20%). Average HF-related per capita expenditure was € 1.917. The age-related trend in costs per type of expenditure is shown in Figure.



Conclusion: Unlike ACE-I/ARB, the proportion of patients treated with betablockers remains inadequate. The proportion of health expenditure due to hospital admissions increased with age. Hospitalizations of patients aged 75-85 were the main determinant of HF-related costs in Italy in 2004. HF management programs targeted to this population segment should be implemented to impact on disease-specific resource consumption.

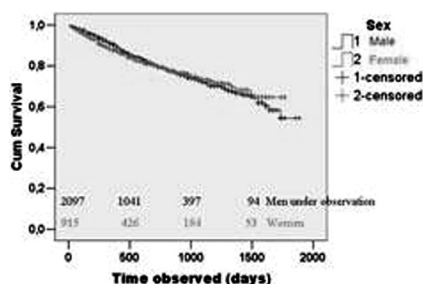
334 Mortality from heart failure is high despite adherence to guidelines

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Objectives: To evaluate heart failure (HF) patient's characteristics, management and outcome in nurse based hospital outpatient heart failure clinics.

Methods: From the year 2000, patients with HF, NYHA functional class I-IV, diagnosed according to current guidelines were registered consecutively in the registry of 24 hospitals, and with follow-up data from the first and last visit at the clinic. Mortality is monitored continuously including after the last visit.

Results: A total of 3011 patients with HF were included in this survey, 2097 men and 915 (30%) women, mean age 71 ± 11.7 years. The aetiology of HF was coronary artery disease in 58%, dilated cardiomyopathy in 14%, hypertension in 9%, valvular heart disease in 7% and other and unknown 13%. Atrial fibrillation was present in 30% and diabetes mellitus in 20%. There were 16% smokers. 47% of the patients were in NYHA class I and II, 51% in class III and only one % in class IV. At the last visit ACE inhibitors or angiotensin receptor blockers were taken by 87%, beta blockers 83%, spironolactone 27%, loop diuretics 85% and thiazides 3% of the patients. At one and two years of follow up 8.8 and 19.2% of the men, and 11.1 and 19.0% of the women had died, respectively. Mortality was significantly positively related to NYHA functional class, age and a history of cerebrovascular accident, and significantly negatively related to blood haemoglobin, calculated creatinine clearance, sex, statin use and s-cholesterol.



Kaplan Meier curve of survival

Conclusion: Despite adherence to current guidelines in the management of patients with HF, our results show that the outcome is still reduced. Thus, there is requirement for further improvement.

335 Heart failure and trial generated patients' profile for implant with electrical devices: real-world prevalence, outcomes and public health implications

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Background: The ongoing production of major clinical trials is leading clinicians to reason in terms of "patient profiles" generated by these trials. While this can favor evidence-based decision making, it can also lead to simplistic cataloging of individual patients. Little is known about the real prevalence of these subgroups in the real world and about patients' outcome.

Aims: To estimate baseline prevalence and 1-year mortality of SCD-HeFT-like, MADIT-II-like and CARE-HF-like patient profiles within a multicenter national registry on heart failure patients (IN-CHF). Data were collected from 1995 to 2000 in an outpatient setting.

Results: Baseline clinical, ECG, and echocardiographic data were available for 4977 patients (mean age $\pm$ SD = 63 ± 12 years; female 26%). Table 1 depicts patients profile and 1-year mortality in the IN-CHF registry and in clinical trials.

Table 1

	SCD-HeFT profile	MADIT II profile	CARE-HF profile
IN-CHF baseline prevalence	47.9% (n=2385)	14.5% (n=722)	6.8% (n=337)
IN-CHF 1-yr total (and SCD) mortality	13.7% (SCD=6%)	16.2% (SCD=7.8%)	19.9% (SCD=7.7%)
Original trial 1-yr mortality: device group	6.1%	9%	9.7%
Original trial 1-yr mortality: control group	5.9%	10%	12.6%

Legend: 1-yr = one-year; SCD = sudden cardiac death.

Conclusions: Our study provides the first data on prevalence in the real world of "patient profiles" generated by clinical trials testing devices. These data are potentially relevant for public health decisions. One-year total mortality and sudden cardiac death rate of non implanted patients in the nationwide registry are much higher compared with both device treated and control patients in the original trials. Suboptimal medical treatment and comorbidities can partly explain these differences.

336 New onset atrial fibrillation is an independent predictor of in-hospital mortality in patients admitted with heart failure. Results of the Euro Heart Failure Survey

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Background: The prognostic significance of atrial fibrillation (AF) in patients admitted due to heart failure (HF) remains poorly understood. Objective: To evaluate in what way AF, and its different presentations, affect in-hospital mortality in patients admitted with HF.

Methods: The Euro Heart Failure Survey was conducted to ascertain how hospitalized HF patients are managed in Europe. The survey enrolled 10701 patients over a 6-week period in 115 hospitals from 24 countries. For this analysis patients were divided in 3 groups according to the type of AF: persistent-AF (patients with known history of AF), new onset-AF (no history of AF with AF diagnosed during hospitalization) and no-AF (no history of AF and no AF during hospitalization). Clinical variables, treatment, duration of hospitalization and survival status were assessed and compared among groups.

Results: Table 1 summarises the clinical characteristics and in-hospital evolution of the different groups. In the univariate analysis the type of AF (but not the presence of AF), fast AF (> 120 beats/min), age, female gender, ejection fraction (EF), moderate or severe left atrial (LA) dilatation, use of antiarrhythmic drugs (AAD) and inotropic treatment were predictors of mortality. When including these variables in a multivariate model, new onset-AF (not fast AF) remained an independent predictor of mortality (OR 1.5 [CI, 1.1-2.0]).

Table 1

	No AF (n=6027)	Persistent AF (n=3673)	New Onset AF (n=1001)	P value
Mean age (SD)	70 (13)	73 (12)	73 (12)	<0.001
Male (%)	54	51	52	0.005
Fast AF (%)	0	27	77	<0.001
EF < 50%	42	43	42	0.012
Mod/Sev LA dilation (%)	13	28	17	<0.001
AAD (%)	7	22	32	<0.001
ACEI/ARB (%)	65	67	61	0.01
Beta blocker (%)	40	33	36	<0.001
Digoxine (%)	21	56	52	<0.001
Days CCU (SD)	1 (3)	1 (3)	2 (4)	<0.001
Mortality (%)	7	7	12	<0.001

Conclusion: In patients admitted with HF new onset AF is an independent predictor of in-hospital mortality.

337 Predictors of betablocker uptitration success in patients treated in nurse-based heart failure clinics. Results from the Danish Heart Failure Clinics Network

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Background: In recent years nurse-based clinics dedicated to the care of heart failure (HF) patients have emerged. One major argument for initiating such clinics was to promote the time-consuming and difficult task of initiation and uptitration of beta-blockade. In Denmark 14 different clinics share a common electronic patient file system (Hjerterplus), which also serves as a clinical database. Using data from this database the aim of the present study was to determine 1) the rate of success in betablocker (BB) uptitration after three months and 2) to identify potential predictors of uptitration success and failure in these patients.

Methods and patients: 2448 outpatients followed in specialized nurse based HF clinics from April 2002 to November 2005. BB treatment (yes/no) and doses were recorded three months after the initial visit in the clinic. Mean age was 68,3 (SD 11,7) years and 28% were women. Left ventricular systolic dysfunction (LVEF < 0,45) was present in 96%.

Results: At referral 18% were treated with BB. After three months 79% were treated with BB and 90% received an angiotensin-blocking drug. Mean BB dose (relative to target dose) was 49,6 (SD 3,9) %. More men (81%) than women (74%) received a BB at three months ($P < 0.001$), and BB doses in women were lower (mean dose relative to target 42% vs. 52%, $P < 0.001$). Furthermore BB treatment and doses at three months depended on age (mean age for patients on BB vs. patients off BB: 67,7 vs. 72,1 years, $P < 0.01$). The effect of sex on BB treatment and dose was independent of the effect of age (multivariable analysis). Diabetes, atrial fibrillation, heart rate, blood pressures and LVEF at baseline did not predict BB treatment or dose at three months.

Conclusion: This large registry of HF outpatients demonstrates that nurse-based HF clinics are effective in initiating BB treatment, but doses could probably be increased. Women and elderly patients appear to be less optimally treated with BB. Particular attention should be paid to these groups during BB uptitration.

338 Frailty is an independent prognostic variable in very elderly patients with heart failure

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Background: Despite remarkable advances in diagnosis and therapy over the past decade, the prognosis of elderly HF patients remains poor. Frailty, a clinical state of increased vulnerability to adverse outcomes such as disability and mortality, is frequent in older HF pts. Aim of the study was to evaluate the clinical and prognostic profile of frail HF elderly pts living in the community and treated with optimized HF therapy in specialized heart failure clinics.

Methods: A cohort of 190 outpts aged >70 yrs (77±5, range 70-94, 53.7% males) with clinically stable HF were prospectively studied. A frailty staging system (FSS) was used as an index of severity of functional impairment. The FSS combines three core domains of functioning (cognitive status, mobility, and urinary continence) into four stages (1-4) of increasing impairment.

Results and Conclusions: Mean ejection fraction (EF) was 32.9±10, mean NYHA class was 2.7±0.6 (61.6% NYHA 3-4); anemia (Hemoglobin [Hb] <12 g/dl) was found in 42.6%; renal dysfunction (RD)(creatinine clearance <60 ml/min) was present in 85.7%; pts were treated with optimized HF therapy (betablockers [BB] 52%, ACE-i/ARB 94%, spironolactone 35%).

Frailty (FSS 2-4) was present in 76 pts (40%). There was an association between increasing frailty stages (1-4) and 1-year mortality: 14,9%, 30,2%, 54,5% and 100,0% ($p < 0.0001$) or HF re-admissions: 21,1%, 47,6%, 81,8%, 100,0% ($p < 0.0001$) respectively.

At multivariate analysis, advanced age (RR 1,1085 [1,024-1,149]), EF <20% (2,936 [1,533-5,623]), SBP <100 mmHg (4,585 [1,814-11,587]), anemia (2,237 [1,069-4,678]), no BB therapy (0,435 [0,220-0,862]) and Frailty (1,739 [1,100-2,751]) were independent predictors of 1-year mortality.

BB showed a similar improvement in survival both in frail and non frail patients. Frailty (3,111 [1,605-6,031], NYHA 3-4 (5,3 [2,51-11,19]), no BB therapy (0,357[0,207-0,615] and SBP <100 mmHg (2,75[1,33-5,685] were also predictors of 1-year HF hospital re-admissions.

In conclusion, in this cohort of community-living elderly HF patients, despite optimized therapy, Frailty: 1) is frequent also in non-institutionalized individuals; 2) represents a new independent predictor of worse prognosis; 3) does not influence the favourable impact of BB on survival; thus, awareness of this syndrome and its risks can help us care for these patients more confidently and decrease their risk for adverse outcomes.

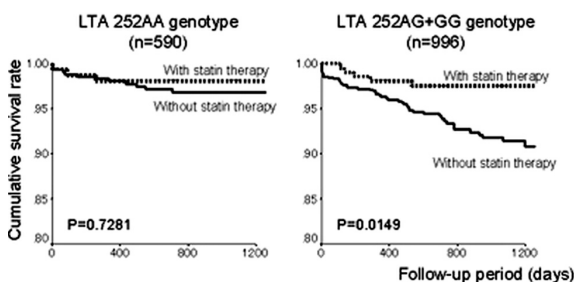
NEW DATA ON CURRENT AND DEVELOPPING CHRONIC HEART FAILURE THERAPIES

339 Effect of statin treatment on mortality after Myocardial Infarction is modified by A252G polymorphism at Lymphotoxin Alpha gene

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Background: Many studies have established the favorable effects of statin therapy in the patients of myocardial infarction (MI). For research of precise mechanism and efficient use of medical resource, it is necessary to find subgroup of patients who enjoy the most benefit of this drug. We have previously reported that 252G allele of lymphotoxin alpha (LTA) is associated not only with increased inflammatory response but also with higher mortality after MI. In this study, we tested the hypothesis that statin has more favorable effect in patients with this allele. Patients and Methods. Among consecutive Japanese patients with MI, 1586 survivors were included in this study. Patients were divided into subgroups according to LTA 252 allele. In each subgroup, survival curve was constructed by Kaplan-Meier method and the difference between patients with and without statin treatment was evaluated. Multivariate Cox regression model was used to evaluate Hazard ratio of statin use.

Results: During mean follow-up of 831 days, 76 patients died. Overall, statin use was associated with lower mortality (HR=0.46, $p=0.029$). In subgroup analysis, this association was significant only in the subgroup of patients with LTA 252G allele. On the other hand, in the subgroup of patients with LTA 252AA genotype, the mortality was relatively low and there were no significant differences according to statin use.



Conclusions: In this study, statin use was associated with lower mortality only in patients with LTA 252G allele. This allele is reported to evoke inflammation, so we guess the benefit of statin in this subgroup is at least due to its antiinflammatory effects. Although further study will be needed, carriers of this allele might be new targets of statin therapy.

340 Effect of telmisartan added to angiotensin converting enzyme inhibitors in reducing morbidity and mortality in haemodialysis patients with chronic heart failure

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Purpose: Congestive heart failure is common in patients with end-stage renal disease (ESRD), occurring in up to 64% of patients referred to nephrologists. The presence of CHF in patients with ESRD increases the risk of mortality and rehospitalisation, and ARBs have not been shown to reduce this risk. This study investigated whether prognosis in this particular population could be improved with telmisartan, a once-daily, long-acting ARB, added to ongoing, ACE inhibitor-based treatment.

Methods: A placebo-controlled, double-blind, study investigated whether mortality and rehospitalisation could be reduced by adding telmisartan to standard therapy with ACE-inhibitors. Data were collected in 31 Italian clinics belonging to a clinic network using a prospective database (Euclid). Patients were in receipt of haemodialysis and had CHF (class II or III with left ventricular ejection fraction <40%). The target telmisartan dose was 80 mg once daily, and mean (SD) follow-up was 35 (5) months. All patients received angiotensin converting enzyme (ACE) inhibitors at baseline and throughout the study, along with other ongoing therapy as indicated. The primary outcomes were all-cause mortality, cardiovascular mortality, and CHF hospitalisation.

Results: Data from 303 patients were analysed. Telmisartan reduced the incidence of all cause mortality compared with placebo (58.3% vs 73.1%, relative risk reduction [RRR] 20.2%, $P < 0.01$). The incidence of cardiovascular death was 39.0% and 49.3% in the telmisartan and placebo groups, respectively (RRR 20.9%, $P < 0.001$). CHF hospitalization occurred in 37.7% of telmisartan patients and 66.4% of placebo patients (RRR 44.9%, $P < 0.0001$). Approximately 60% of patients received beta-blockers. There was no interaction between outcome and treatment with ACE inhibitors, beta-blockers, or the combination. Withdrawals were 13.2% in telmisartan group and 10.7% in placebo group, with a trend to

wards increased hypotension with telmisartan (6.1%) compared with placebo (4.3%).

Conclusion: The addition of telmisartan 80 mg/day to ongoing ACE inhibitor therapy (including beta-blockers in most cases) in patients with CHF and receiving haemodialysis significantly reduces mortality and morbidity with low adverse effects. This multicentre study, the largest yet conducted in this particular population, may be contrasted with the lack of effect on CV mortality in CHF patients not receiving haemodialysis in previous study with ARBs.

341 Testosterone therapy in men with moderate severity heart failure: a double blind RCT

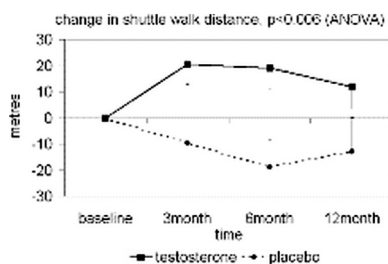


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Background: Chronic heart failure is associated with maladaptive and prolonged neurohormonal and pro-inflammatory cytokine activation causing a metabolic shift favouring catabolism, vasodilator incapacity, and loss of skeletal muscle bulk and function. In men, androgens are important determinants of anabolic function and physical strength and also possess anti-inflammatory and vasodilatory properties.

Methods: We conducted a randomised, double blind, placebo-controlled parallel trial of testosterone replacement therapy (5mg Androderm[®]) at physiological doses in 76 men (mean $\pm$ SD age 64 ± 9.9 years) with heart failure (ejection fraction $32.5\% \pm 11\%$) over a maximum follow-up period of 12 months. The primary endpoint was functional capacity as assessed by the incremental shuttle walk test (ISWT).

Results: At baseline, 18(24%) had serum testosterone below the normal range and bioavailable testosterone correlated with distance walked on the initial ISWT ($r=0.3$, $p=0.01$). Exercise capacity significantly improved with testosterone therapy compared with placebo over the full study period (mean change $+25 \pm 15$ m) corresponding to a $15 \pm 11\%$ improvement from baseline ($p=0.006$ ANOVA)(figure). Symptoms improved by at least one functional class on testosterone in 13(35%) vs 3(8%) on placebo ($p=0.01$). No significant changes were found in handgrip strength, skeletal muscle bulk by cross-sectional computed tomography or in tumour necrosis factor levels. Testosterone therapy was safe with no excess of adverse events although the patch preparation was not well tolerated by the study patients.



Conclusions: Testosterone replacement therapy improves functional capacity and symptoms in men with moderately severe heart failure.

342 The effects of initial monotherapy with bisoprolol or enalapril followed by their combination on renal function in patients with chronic heart failure - results of CIBIS-III trial



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Background: Renal insufficiency is a common comorbid condition in chronic heart failure (CHF) predicting risk of an adverse outcome. However, it remains unclear how life-saving therapies with ACE inhibitors and beta-blockers influence renal function in CHF. In CIBIS III initial monotherapy with either bisoprolol (B) ($n=505$) or enalapril (E) ($n=505$) for 6 months, followed by their combination for 6-18 months similarly influenced mortality and morbidity in patients ≥ 65 years old, with stable, mild/moderate systolic CHF. We compared the effects of B-first and E-first regimens on renal function.

Methods: Renal function was expressed on the basis of glomerular filtration rate estimated using Cockcroft-Gault formula (eGFR), and eGFR < 60 ml/min was defined as renal dysfunction. Deterioration in renal function was prospectively defined as an increase in serum creatinine level by 0.5 mg/dl or serum creatinine level > 2.4 mg/dl.

Results: At baseline eGFR was similar in the 2 groups (median eGFR: 60.9 ml/min (B-first) vs 60.8 ml/min (E-first); $p=ns$) and 486 (48.1%) patients demonstrated impaired renal function. During the study period there was a gradual decline in eGFR in both treatment arms. The within-group means of eGFR decrease adjusted for baseline eGFR are given below, together with between-groups difference and 95% confidence interval. At the end of the monotherapy phase (week 24): -3.2 ml/min vs -2.2 ml/min, -0.8 ml/min (-2.5 , 0.9). At the end of the study: -5.4 ml/min vs -6.6 ml/min, 1.2 ml/min (-2.5 , 4.9), B-first vs E-first, respectively, $p=ns$ in both comparisons. Deterioration in renal function was observed: at the end of the monotherapy phase - in 4.4% vs 3.9% and during the combined phase - at the end of week 48 in 8.9% vs 7.6%, at the end of week 100 in 14.4% vs 14.7% patients, B-first vs E-first, respectively, $p=ns$ in all comparisons.

Conclusions: Both treatments similarly influence renal function. However, despite optimal pharmacological treatment with ACE inhibitor and beta-blocker, progressive loss in renal function occurs during the natural course of CHF.

343 Impact of statin therapy on survival in patients with diastolic heart failure



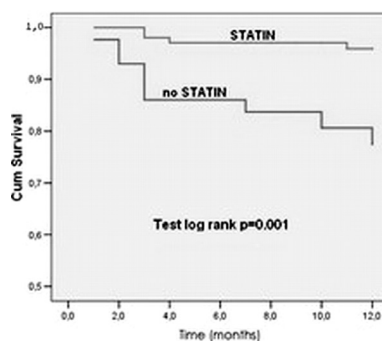
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Background: Despite advances in pharmacological and interventional therapy morbidity and mortality due to heart failure remain high. No therapy has been shown to improve survival in heart failure (HF) with preserved left ventricular function.

Aim: The aim of the study was to assess the impact of statin therapy in pts with diastolic heart failure on 1 year mortality.

Methods: We enrolled 146 consecutive pts with HF and preserved left ventricular function (ejection fraction ≥ 45) with performed ECHO. We divide the pts into the statin therapy ($n=103$, mean age 69 ± 11 , male 52) and without statin therapy ($n=43$, mean age 66 ± 16 , male 25). The effect of treatment received at study on discharged was analyzed. Laboratory data were measured during the hospital stay. Pts were followed up for one year.

Results: The age, male gender, renal dysfunction, COPD, diabetes mellitus did not differ between group. The pts which received statin therapy were more frequent of ischemic etiology, hypertensive and had previous myocardial infarction ($p < 0.001$). In clinical presentations we did not observed differences in NYHA class, ejection fraction assessed by ECHO (58% vs 55%, $p=NS$) and laboratory data (BUN, creatinine level, hemoglobin level, choletsreol level). Pts receiving statins had lower mortality (4% vs. 21%, $p < 0.001$) and rehospitalisation rate (43% vs. 69%, $p < 0.002$). After adjustment for differences in baseline clinical variables and drug used statin therapy was associated significantly reduced mortality in 12-month follow-up ($p < 0.001$, figure 1).



Kaplan-Meier curve

Conclusions: Statin therapy is associated with better survival rate in pts with HF and preserved EF. Further study are needed to confirmed this observation.

344 Influence of baseline ejection fraction on effects of nebivolol (Beta-1 blocker) in elderly patients with heart failure



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Background: Benefits of beta blockers (BB) in patients(pts) with heart failure (HF) and reduced ejection fraction (EF) are well established. The SENIORS study

showed nebivolol (N) reduced composite of all cause mortality or cardiovascular hospital admission (CV hosp) vs placebo (P) in 2128 pts with HF $\geq$ 70 yrs with a median EF of 34% (36% with EF $>$ 35%) followed for mean of 21 months (31.1% & 35.3% respectively, HR 0.86; 95% CI 0.74-0.99; $p=0.04$). We explored pts characteristics and outcomes stratified by baseline EF in SENIORS.

Methods: EF was used as continuous and categorical variable ($\leq 35\%$ vs. $> 35\%$). We explored treatment effects on time to first event in these subgroups for primary outcome (death/CV hosp), & all cause mortality, separately.

Results: Pts in grps $\leq 35\%$ vs. $> 35\%$ were 1369 and 752 respectively and mean age of pts was the same in both groups (76.1 years). Proportions of women 30% vs. 50%, NYHA II 53% vs 63%, NYHA III 42% vs. 32%, prior MI 49% vs. 34%, and hypertension 53% vs. 78% resp (all comparisons $p < 0.001$). There was no significant interaction between EF as a continuous variable and clinical outcomes. Results for death/CV hosp, and all cause mortality are shown in the table (ARR = absolute risk reduction)

Table 1

	N	P	ARR	HR and 95% CI	p
Death/CV hosp					
EF $\leq 35\%$ (n= 1369)	31.1%	36.3%	5.2%	0.87(0.73-1.04)	0.14
EF $> 35\%$ (n=752)	28.9%	33.6%	4.7%	0.82(0.63-1.05)	0.12
All cause mortality					
EF $\leq 35\%$ (n= 1369)	17.0%	19.8%	2.8%	0.86(0.67-1.10)	0.23
EF $> 35\%$ (n=752)	13.7%	14.8%	1.1%	0.92(0.63-1.34)	0.66

Effect of Nebivolol (beta-1 blocker) versus placebo on clinical outcomes in elderly with heart failure based on baseline LVEF.

Conclusions: Elderly pts with preserved EF are more likely to be hypertensive, whereas those with lower EF are more likely to have had prior MI, supporting the hypothesis that diastolic dysfunction contributes to HF in the elderly. These data support the role of this agent in elderly pts with a wide range of EF. There are perhaps similar benefits of nebivolol on composite of death/CV hosp irrespective of baseline EF. CV hosp may be a more influenced outcome in the elderly with HF that can be beneficially influenced by BB irrespective of EF

"NAVIGARE NECESSARE EST." NOVEL APPROACHES TO GUIDE AND OPTIMISE LV LEAD PLACEMENT, CONFIGURATION AND CRT PROGRAMMING

362 Magnetic navigation of guidewires in the coronary sinus with the NIOBE-system

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Purpose: The clinical benefit of cardiac resynchronization therapy depends on accurate placement of the left ventricular pacemaker lead. We evaluated whether a novel magnetic navigation system can be used for left ventricular lead implantation.

Methods: A biventricular ICD device was implanted for cardiac resynchronization therapy using the magnetic navigation system Niobe (Stereotaxis Inc., USA) for left ventricular lead placement in a coronary sinus side branch. The navigation system is made up of two computer-controlled permanent magnets creating a steerable magnetic field of 0.08 Tesla. Guide-wires with integrated magnets align to the magnetic field and are used for over-the-wire implantation of pacemaker leads in the coronary sinus.

Results: In 24 patients (4 female, 65 ± 8 years) magnetic navigation was used for left ventricular lead placement. In 19 patients a new triple-chamber ICD implantation was planned. In 4 patients an existing pacemaker system was upgraded to a triple chamber ICD and in one patient left ventricular lead placement was performed after prior lead dislocation. Magnetic guidewire navigation with subsequent left ventricular lead placement was successful in 23 patients. In one patient no left ventricular lead was implanted due to inferior hemodynamics during intraprocedural biventricular pacing.

Conclusions: Left ventricular lead placement for cardiac resynchronization can be successfully performed with magnetic guide-wire navigation to engage the desired coronary sinus side branch.

363 Impact of left ventricular lead position on left ventricular function and remodelling after cardiac resynchronization therapy using myocardial deformation imaging

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Aims: This study sought to assess if myocardial deformation imaging (MDI) allows definition of an optimal left ventricular (LV) lead position for improved effectiveness of cardiac resynchronization therapy (CRT).

Methods: MDI based on tracking of acoustic markers within 2D echo images (GE Ultrasound) was performed in 47 heart failure patients (pts., 51 ± 5 years, 31 men) at baseline and 8 months follow up. Ejection fraction (EF), peak oxygen consumption (VO2max), LV endsystolic/diastolic volume (LVESV, LVEDV) were determined before and after CRT. In a 36 segment LV model based on 6 short axis views the

segment with latest peak systolic circumferential strain was determined. Additionally, the segment with maximal temporal difference of peak strain between pre- and post-CRT was defined as the segment with greatest benefit of CRT and assumed to be location of the LV-lead. Optimal LV lead position was defined as concordance or immediate neighbouring of the segment with latest myocardial deformation prior to CRT and the segment with maximal temporal difference of peak strain pre- and post-CRT.

Results: 21 pts. showed optimal, 26 pts. non-optimal position of the LV lead based on this definition. Preop EF, VO2max, LVESV and LVEDV were similar in both groups (table). After 8 months there was greater increase of EF and VO2max and greater decrease of LVESV and LVEDV in the optimal compared to the non-optimal LV lead position group (table).

Results

	optimal	non-optimal	p
EF(%)	31 $\pm$ 6	30 $\pm$ 6	ns
Δ EF(%)	12 $\pm$ 3	7 $\pm$ 3	<0.001
VO2max(ml/min/kg)	14.1 $\pm$ 1.8	14.0 $\pm$ 2.3	ns
Δ VO2max(ml/min/kg)	2.8 $\pm$ 0.9	1.6 $\pm$ 0.9	<0.001
LVESV (ml)	246 $\pm$ 88	242 $\pm$ 92	ns
Δ LVESV (ml)	27 $\pm$ 7	15 $\pm$ 5	<0.001
LVEDV (ml)	302 $\pm$ 90	297 $\pm$ 82	ns
Δ LVEDV (ml)	33 $\pm$ 7	21 $\pm$ 6	<0.001

Conclusions: MDI is a new 2D based imaging modality which allows detailed analysis of the myocardial contraction sequence. Optimal LV lead position in CRT defined by MDI with the segment with latest contraction prior to CRT results in greater improvement in LV function and remodelling than non-optimal LV lead position.

364 Effectiveness of cardiac resynchronization therapy with left ventricular pacing from an antero-lateral vein

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Introduction: Cardiac resynchronization therapy (CRT) has exhibit the greatest efficacy when the left ventricular lateral wall is paced. The use of an anterolateral vein (drains in the anterior interventricular vein) is controversial as an alternative for pacing, when the implant in a target vein in the postero-lateral or lateral region of the left ventricle is not possible.

Objective: To evaluate the effects of CRT in patients with and electrode implanted in an antero-lateral vein.

Material and Methods: In 16 out of 143 consecutive patients treated with cardiac resynchronization therapy (age 63 ± 9 years, 12 males, QRS duration 159 ± 17 ms, sinus rhythm 88%), an electrode was implanted in the antero-lateral vein. The antero-lateral vein was identified by occlusive venography in LAO view to confirm its drainage in the anterior interventricular vein. The spontaneous VV interval was 102 ± 17 ms. An echocardiographic study was performed, before and in the midterm follow-up, and parameters like left ventricular dimensions, volumes, ejection fraction, quantification of mitral regurgitation, inter and intraventricular asynchrony were obtained. The mean time follow-up was 16 months (range 3-36).

Results: See table.

Mid-term Follow-up Changes after Cardiac Resynchronization Therapy from the antero-lateral vein

	NYHA	LVEDV (mL)	LVESV (mL)	EF (%)	MR (cm ²)	dP/dt (mmHg/s)	InterV delay (ms)	IntraV (ms)
Basal	3.31 $\pm$ 0.6	260 $\pm$ 103	206 $\pm$ 99	22 $\pm$ 10	13 $\pm$ 15	517 $\pm$ 69	56 $\pm$ 32	198 $\pm$ 144
After	1.9 $\pm$ 0.6	223 $\pm$ 78	157 $\pm$ 66	36 $\pm$ 9	4 $\pm$ 2	640 $\pm$ 192	40 $\pm$ 33	73 $\pm$ 53
p	<0.001	0.048	0.049	0.003	0.059	0.092	ns	0.017

Conclusions: CRT with pacing from an antero-lateral vein is effective and should be considered as an alternative when the electrode implantation is not possible at the postero-lateral region of the ventricle.

365 Echocardiography performed by emergency physicians versus NT pro-BNP in patients with acute dyspnea

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Introduction: Acute dyspnea is one of the main reason of Emergency Department (ED) admission. The rapid and accurate identification of etiologic cause, especially acute left ventricular congestive heart failure (LVCHF) remain a clinical challenge.

Objective: Investigate the feasibility of Emergency Echocardiography (EEC) performed by Emergency Physicians (EP) in patients with acute dyspnea and compare the accuracy of EEC and NT pro-BNP in differentiating LVCHF from other causes of acute dyspnea.

Methods: 145 consecutive patients, presenting to ED for dyspnea underwent NT pro-BNP assay and bedside EEC on admission. EEC studies were performed by

4 EP after a 30 hours EEC course. Primary goal was the recognition of the following parameters expressed as present or absent: left ventricular (LV) dilatation, reduced LV ejection fraction (LVEF), "restrictive" pattern on pulsed Doppler analysis of mitral inflow defined as E/A ratio >2 , $1 < E/A < 2$ and E-wave deceleration time (DT) <130 ms or DT <130 alone in case of atrial fibrillation. EEC exams were recorded and subsequently reviewed by a cardiologist echocardiographer in a blinded fashion. Final etiologic diagnosis was established by 3 physicians blinded to NT pro-BNP and EEC results after review of patients clinical data.

Results: Final etiologic diagnosis was LVCHF in 65 (45%). NT pro-BNP level <300 pg/ml was optimal for ruling out LVCHF and >2000 pg/ml was highly sensitive and specific for the diagnosis of LVCHF ($P < 0.0001$). Echocardiographic examination took 5 minutes ± 2 and was not feasible in 5 patients (3%). At cardiologist revision the overall accuracy for the 3 EEC parameters was 97%. The restrictive pattern was the most accurate EEC parameter for the diagnosis of LVCHF (Area under ROC curve 0.84, $P < 0.0001$). Restrictive pattern and NT pro-BNP level were both superior to standardized clinical criteria for diagnosis of congestive heart failure (Boston criteria) ($P < 0.0001$ and $P = 0.036$ respectively). Among the 39 (27%) patients with NT pro-BNP level between 300 and 2000 pg/ml, the area under ROC curve of restrictive pattern was significantly higher than that obtained combining clinical judgment and NT-pro BNP levels ($P < 0.0001$).

Conclusion: Emergency echocardiography performed by EP is feasible and accurate in patients with acute dyspnea. In this setting, restrictive pattern on pulsed Doppler analysis of mitral inflow is the most accurate echocardiographic parameter for diagnosis of LVCHF, being particularly useful in patients with inconclusive NT pro-BNP levels.

366 Simultaneous biventricular stimulation versus optimized V-V delay in CRT. Echocardiographic observations from the RHYTHM II ICD trial

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Study objectives and methods: RHYTHM II was a randomized trial comparing the 6-month clinical outcomes of recipients of cardiac resynchronization therapy devices with cardioverter-defibrillator capabilities (CRT-D) in whom the delay between delivery of ventricular pulses (V-V) was optimized (OPT) during Doppler echocardiographic imaging (DOP-ECHO) before hospital discharge, versus patients (pts) assigned to simultaneous (SIM) biventricular stimulation. All pts underwent detailed, protocol-mandated, M-mode, 2-dimensional and DOP-ECHO at baseline and 6 months after CRT-D system implantation. Images were acquired in the parasternal long and short-axes, apical-4, apical-2, apical long axis, and in the subcostal 4-chamber and short axis views. All records were analyzed by the Cleveland Clinic, Echo Core Laboratory.

Results: The trial randomized in a 1:3 ratio 121 pts, including 30 pts assigned to SIM (mean age $=67.6 \pm 8.7$ y, 22 men) and 91 pts to OPT (66.7 ± 8.6 y, 78 men). The mean baseline left ventricular (LV) ejection fraction (EF) was $21.8 \pm 6.0\%$ in the SIM group and $22.2 \pm 7.3\%$ in the OPT group (ns). The 2 patient groups were similar with respect to all other baseline characteristics. It is noteworthy that the OPT V-V = 0 ms in 28.4% of pts.

	Baseline		6 months	
	SIM	OPT	SIM	OPT
LV EDD, mm	69.2 $\pm$ 9.0	65.6 $\pm$ 6.9	64.7 $\pm$ 6.1*	62.6 $\pm$ 8.4*
LV ESD, mm	60.2 $\pm$ 9.9	56.4 $\pm$ 7.3	55.1 $\pm$ 6.8*	52.6 $\pm$ 8.0*
Left atrium, mm	45.5 $\pm$ 7.1	47.4 $\pm$ 7.1	43.8 $\pm$ 8.3	45.0 $\pm$ 6.8**
IVSD, mm	9.8 $\pm$ 1.5	10.1 $\pm$ 1.9	10.3 $\pm$ 1.8	10.6 $\pm$ 2.0
SET, ms	248 $\pm$ 33	253 $\pm$ 44	265 $\pm$ 27**	256 $\pm$ 35
DFI, ms	398 $\pm$ 165	424 $\pm$ 113	438 $\pm$ 113	438 $\pm$ 100
EDV, ml	241 $\pm$ 75	257 $\pm$ 101	256 $\pm$ 70	237 $\pm$ 91
ESV, ml	190 $\pm$ 66	203 $\pm$ 92	190 $\pm$ 55	178 $\pm$ 75*
LVEF, %	21.8 $\pm$ 6.0	22.2 $\pm$ 7.3	25.8 $\pm$ 5.8**	25.7 $\pm$ 6.8*
Tei index	0.98 $\pm$ 0.41	1.05 $\pm$ 0.58	0.78 $\pm$ 0.28*	0.76 $\pm$ 0.31*

Values are mean $\pm$ SD; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$; **** $P < 0.001$; # $P < 0.001$. All P-values are vs baseline or corresponding group. All differences between SIM and OPT at 6 months are non-significant.

Conclusions: CRT-D therapy for 6 months was associated with significant improvements in several indices of cardiac function. There was no advantage conferred by OPT of V-V compared with SIM stimulation at 6 months.

367 Comparison between long-term outcome of biventricular and left ventricular pacing mode in cardiac resynchronization therapy

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Purpose: In randomized trials of cardiac resynchronization therapy (CRT), all patients (P) were routinely paced in the biventricular mode. However, up to 30% do not improve during long-term follow-up. The aim of this study is to compare long-

term outcome of P with atrio-left ventricular pacing only versus P with biventricular mode.

Methods: All P underwent preoperative hemodynamic testing with respect to pacing mode, AV delay and optimal pacing site. Response was defined as $\geq 10\%$ pulse pressure (PP) increase. A difference of more than 3% PP increase between pacing modes discriminated the best pacing mode. After device implantation, the best pacing mode and AV delay were programmed during follow-up of CRT.

Results: Between 1999 and 2004, 399 P with sinus rhythm, QRS >150 ms, NYHA class $\geq$ III received a CRT device. 100 P were on LV pacing only, 299 P on biventricular pacing in accordance with the test procedure. We found no significant difference between the two cohorts concerning gender, underlying disease and LV ejection fraction (24 ± 7 and $23.8 \pm 5\%$). During long-term follow-up, both cohorts improved significantly in the prognostically important functional parameters of heart failure (Table). However, the analysis of serious adverse events, i.e. cardiac death, heart transplantation, or LV assist device, showed no significant difference between biventricular and left ventricular pacing (17% (50P) versus 14% (14 P)). Mean follow-up was 25 ± 19 versus 26 ± 18 months.

	LV only		biventricular	
	baseline	12 months	baseline	12 months
Patients (n)	100	59	299	174
Quality of life (score)	46 $\pm$ 17	26 $\pm$ 23*	43.5 $\pm$ 21.3	26 $\pm$ 17.5*
VO2peak (ml/min/kg)	12.6 $\pm$ 2.8	14.9 $\pm$ 2.9*	13.1 $\pm$ 3.3	15.7 $\pm$ 4.0*
LV EDD (mm)	79 $\pm$ 10	73 $\pm$ 14*	77 $\pm$ 11	70 $\pm$ 13.1*

*paired t-test $p < 0.0005$

Conclusion: Tailored left ventricular only pacing is not functionally inferior to the tailored biventricular mode. Untailored biventricular pacing may produce clinical nonresponders, especially due to asynchronous right ventricular apical stimulation in a marked amount of patients.

EXPANDING INDICATIONS AND INSIGHTS IN RESYNCHRONISATION THERAPY. WE ARE BEGINNING TO SEE THE LIGHT

368 Four year survival in 1285 patients undergoing cardiac resynchronization therapy (CRT): The importance of atrioventricular junction ablation in patients with

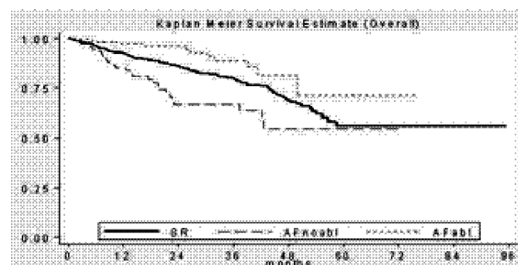
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Background: Permanent atrial fibrillation (AF) is common in heart failure (HF) and worsens prognosis both in terms of morbidity and mortality, especially when associated with ventricular conduction delay. Little is known however, on the long-term effects of CRT on all-cause survival of heart failure (HF) patients with AF.

Methods: From the experience of 4 Centers, 1285 patients were implanted with CRT devices from August 1995 to August 2005: 1042 pts were in sinus rhythm (SR) and 243 (19%) patients AF. Rate control in AF patients was achieved either by ablating the atrioventricular junction (AVJ) in 118 patients (AFabl group), or by prescribing chronotropic-negative drugs (125 patients, AFnoabl). Clinical, demographic, and cumulative survival data were prospectively collected for the 3 separate groups.

Results: Median follow-up was 24 months (IQR: 10-40 months). At baseline, AFabl patients were older ($p < .001$), less frequently implanted with a CRT-D device ($p < .002$), more often had CAD etiology, while AFnoabl patients had lower EF ($p < .001$) and longer QRS ($p < .001$). During follow up, 170 deaths occurred for SR, 28 for AFnoabl, and 11 for AFabl, with a mortality rate of 8.4%/yr, 15.2%/yr, and 4.3%/yr respectively. Kaplan-Meier estimates (see Figure) and Cox hazard's ratio (HR) analysis showed that AFnoabl patients presented a significantly worse outcome (HR AFabl vs AFnoabl: 0.32 [0.15-0.66], $p = .002$; AFnoabl vs SR 1.78 (1.18-2.69), $p = .006$) compared to the other 2 groups; results remained unchanged after adjusting for center, baseline age, gender, EF, and QRS duration (HR AFabl vs AFnoabl: 0.15 [0.05-0.43], $p < .001$; AFnoabl vs SR 1.85 (1.11-3.08), $p = 0.018$).

Conclusions: In patients with AF undergoing CRT, AVJ ablation significantly reduces long-term all-cause mortality rate.



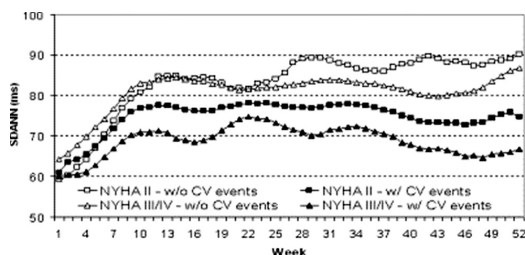
369 Heart rate variability monitored by an implanted cardiac resynchronization device predicts cardiovascular events in patients with NYHA Class II and III/IV heart failure

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There are initial evidences that cardiac resynchronization (CRT) increases parameters of heart rate variability (HRV). However, data on long-term changes of HRV in heart failure pts treated with CRT are still lacking. We analyzed the long-term changes of HRV, monitored by CRT devices, to assess the role of such changes in predicting CRT efficacy and cardiovascular events (CVE).

Methods: The study included 532 pts, 103 in NYHA class II and 429 in NYHA class III/IV, enrolled in the InSync/InSync ICD Italian Registry and implanted with CRT devices capable of continuous assessment of a time-domain parameter of HRV (SDANN). Baseline value of SDANN was considered the average of the first week after implantation.

Results: NYHA II and III/IV pts had similar LVEDD, LVESD, QRS width but different LVEF (29 ± 7 Vs $27 \pm 8\%$, $p=0.001$). At baseline, SDANN was comparable in NYHA II and III/IV pts (59 ± 3 and 63 ± 5 ms), it increased significantly in both groups after 24 weeks (83 ± 8 and 80 ± 2 ms, $p<0.05$ Vs baseline) and the improvement persisted until 52 weeks (90 ± 7 and 80 ± 4 ms). SDANN values were significantly higher in NYHA II than in III/IV pts at 24 and 52 weeks ($p<0.05$). During follow-up (median 16 months), 190/532 (36%) pts, 23 (22%) in NYHA II and 167 (39%) in NYHA III/IV, had a CVE (death, heart transplantation or HF hospitalization). The increase of SDANN measured after 4 weeks was significantly lower in pts experiencing CVE (4.3 ± 3.2 Vs 15.9 ± 2.4 ms, $p<0.01$). The figure shows the trends of SDANN for NYHA II and III/IV pts with and without CVE.



Conclusions: CRT determines long-term sustained changes of HRV profile. The greater improvement of HRV in NYHA II pts suggests that even pts with mild HF may benefit from CRT. A small increase of SDANN after CRT identifies pts at higher risk for CVE.

370 Long term outcome of cardiac resynchronization therapy in patients with atrial fibrillation without AV-nodal ablation compared to sinus rhythm

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Purpose: Cardiac resynchronization therapy (CRT) and optimized medical therapy are the treatment of first choice for patients (pts.) with congestive heart failure (CHF), NYHA>II-III, EF=150 ms. There are only few data about the outcome of patients with CHF and atrial fibrillation (AF) receiving CRT. The aim of our study was to compare CRT-pts. with AF to pts. with sinus rhythm (SR) during a follow up (FU) period of 1 year. AV-nodal ablation was not performed on AF-pts. but they received optimized rate controlled medication to avoid intrinsic conduction.

Methods: 519 pts. (SR 450, AF 69) received CRT following acute testing prior implant. FU was 23 ± 19.5 months. Epidemiologic data at baseline showed no significant differences between pts. with SR vs. AF: age: 62 ± 11 , 62 ± 10 , female 107 vs. 15, dilated cardiomyopathy 56 vs. 43%, CAD 36 vs. 33%, other cardiac disease 24 vs. 8%, EF 24 ± 7 vs. $25 \pm 8\%$, QRS-width 183 ± 29 vs. 181 ± 37 ms. NYHA, VO2 peak and 6 minute walk improved significantly in both groups without significant difference between them. Left ventricular enddiastolic diameter (LVEDD) showed a significant decrease only in SR-pts. No significant difference was observed for severe cardiac events, i.e. death, transplant (SR 15.3 vs. AF 20%).

Conclusion: Long term outcome of CRT-pts. with AF on rate controlled medication demonstrates similar improvement in functional tests and no significant

	baseline		1-year FU	
	AF	SR	AF	SR
n	69	450	29	236
NYHA	3.1 ± 0.4	$3.0 \pm 0.4^*$	2.4 ± 0.8	$2.1 \pm 0.6^*$
VO2 p (ml/kgBW/min)	12.3 ± 2.4	$13.0 \pm 3.2^*$	13.9 ± 5.1	$15.5 \pm 3.8^*$
6-min walk (min)	341 ± 139	$325 \pm 107^*$	406 ± 91	$424 \pm 96^*$
LVEDD (mm)	76 ± 9	$78 \pm 11^*$	76 ± 9	$71 \pm 14^*$

* $p<0.05$, *non-significant: SR vs. AF

difference in severe cardiac events. CRT-pts. with AF improve without AV-nodal ablation, which appears to be avoidable and the best region(s) of ventricular stimulation after AV-nodal ablation have still to be determined.

371 Continuous ambulatory hemodynamic response to cardiac resynchronization therapy in patients with heart failure

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Objective: Acute studies in the resting condition have demonstrated that cardiac resynchronization therapy (CRT) improves central hemodynamics in patients with heart failure and ventricular asynchrony. However, the chronic hemodynamic effect of CRT in ambulatory patients during daily living conditions has not been assessed.

Methods: Ten patients were implanted with both a CRT pacemaker and an implantable hemodynamic monitor (IHM, Chronicle, Medtronic), consisting of a pacemaker-like memory device and a right ventricular (RV) pressure lead. During 2-week periods of CRT "OFF" and "ON" the IHM continuously recorded RV systolic (RVSP) and diastolic pressure (RVDP), pulse pressure (RVPP), estimated pulmonary artery diastolic pressure (ePAD), diastolic filling time (DFT) and heart rate (HR). Median values of hemodynamic data were calculated for each 2-week period. In addition, patients' were evaluated by NYHA class, echocardiography, BNP, Quality of life and 6' walk test.

Results: CRT "ON" was associated with a significant decrease of ambulatory LV filling pressures (ePAD) and a trend towards lower RVDP (table). The median HR also decreased significantly during "ON" indicating a decreased autonomic tone particularly during night time. CRT "ON" was also associated with a trend towards an improved clinical status of the patients.

Hemodynamic monitoring CRT ON vs. OFF

	CRT OFF	CRT ON	p-value
ePAD [mmHg]	24.6 ± 8.0	23.9 ± 8.1	<0.001
RVPP [mmHg]	18.1 ± 7.1	18.3 ± 8.0	0.004
RVSP [mmHg]	42.7 ± 13.9	42.2 ± 14.3	0.038
RVDP [mmHg]	11.8 ± 5.7	11.8 ± 6.3	0.149
DFT [ms]	502 ± 54	530 ± 80	<0.001
HR [bpm]	76.1 ± 7.8	73.7 ± 9.8	<0.001

ePAD: estimated diastolic PA pressure, RVPP: RV pulse pressure, RVSP: RV systolic pressure, RVDP: RV diastolic pressure, DFT: diastolic filling time, HR: heart rate

Conclusions: CRT improves ambulatory central hemodynamics measured by an implanted hemodynamic monitor in patients with heart failure. These findings extend previous results from acute hemodynamic measurements to the daily living environment of heart failure patients and provides a link between chronic hemodynamic and clinical improvement by CRT.

372 Predictors of arrhythmic sudden cardiac death in heart failure patients in the CARE-HF study

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Cardiac resynchronization therapy (CRT) has become an important modality to improve symptoms, exercise performance, and survival in patients with severe heart failure and left ventricular dyssynchrony. The CARE-HF study showed that CRT reduced mortality in systolic heart failure (HF) patients with ventricular dyssynchrony by 10% (relative reduction 36%) during a mean follow-up of 29.4 months, primarily because of fewer heart failure deaths but without a significant decrease in presumed arrhythmic sudden cardiac deaths (SCD). In the pre-planned extension phase (mean follow-up 36.4 months), SCDs were significantly reduced in the CRT group.

Methods: We performed an analysis on 813 patients to determine factors predicting SCD during long-term follow-up using parameters at baseline and at the prespecified 3 month examination.

Results: Of 255 deaths, 89% occurred after 3 months. Univariate SCD predictors [hazard ratio (HR), 95% confidence interval (CI)] included randomization to CRT HR 0.47 (CI 0.29 to 0.76) and 3 month level of mitral regurgitation (MR) 1.89 (1.32 to 2.70), BNP 1.38 (1.14 to 1.66), and echo EDVI 1.002 (1.001 to 1.004). The only predictors of SCD on multivariable analysis were the severity of MR at 3 months 1.85 (1.77 to 2.60) and randomization to CRT 0.56 (0.53 to 0.96).

Conclusions: Compared with best medical therapy, CRT significantly decreases, but does not abolish, long-term risk of SCD in patients with severe heart failure. The analysis supports the concept that it is the improvement in cardiac function with CRT that leads to the reduction in lethal arrhythmias and SCD.

CONTRAST-ENHANCED MRI IN ISCHEMIC AND NON-ISCHEMIC HEART DISEASE

374 Mn2+-Enhanced MRI of acute ischemia and chronic infarction in pig hearts



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Purpose: To test intracellular type contrast agent, MnCl₂, for detection of acute cardiac ischemia and infarction of increasing duration in a large animal model.

Methods: 1. Animal model. Domestic pigs weighing 25-30 kg (n=15) were used under general anesthesia. First and 2nd diagonal branches of the left anterior descending coronary artery (LAD) were ligated through the intercostal incision after which the chest was closed. Three (n=4), 7 (n=5) and 14 (n=3) days after ligation, median sternotomy was performed and hearts were excised and perfused ex vivo with a 50:50 mixture of blood and Krebs-Henseleit buffer containing 1 μM S-propranolol and 15 μM lidocaine. Acute ischemia (n=3) was produced by permanent ligation of the same branches in vivo with subsequent excision of the hearts 30 min thereafter. Cardiac function was continuously recorded via the LV balloon connected to a pressure transducer and differentiator. At the end of each experiment hearts were sliced along the short axis and stained with 2% triphenyltetrazolium chloride (TTC) to identify infarcted areas.

2. MRI. Ex vivo experiments on beating pig hearts were performed on a 7T magnet, interfaced to a Bruker Biospec console, equipped with a 305 mm SGRAD MKII 35/305/S gradient set. Spin-echo experiments were performed with 2.0 ms SINC3 pulses, a FOV of 16x16 cm², TE = 8 ms and a data matrix at 128x128 points. The heart and 2 reference test tubes containing H₂O and H₂O + 10 mM CuSO₄ were placed into the perfusion chamber within the birdcage coil. The signal acquisition was gated by the LV dP/dt and it was collected every 2nd heartbeat in diastole (TR of 800-1000 ms). Six slices with a thickness of 8 mm and inter-slice distance of 2 mm were obtained. Following the baseline image, 0.2 mM MnCl₂ was added and serial images were acquired every 5 min over a 25-min period. Signal intensities for each slice were normalized to those of the H₂O reference.

Results: Areas of acute ischemia and chronic infarcts had 34-39% lower intensities relative to the remote areas. In all groups, addition of MnCl₂ doubled intensities of remote areas and only slightly increased intensities of ischemic and infarcted areas (18-53%) enhancing contrast between damaged and normal tissues (85-130% difference). TTC staining showed necrotic areas after all infarctions (3-14 days) and no necrosis after acute ischemia.

Conclusions: MnCl₂ helps visualize poorly perfused ischemic areas and infarct areas, in which perfusion is substantial but myocytes are irreversibly damaged.

375 Serial cardiac magnetic resonance imaging at 3 and 12 months after application of blood-derived progenitor cells in recanalized chronic coronary total occlusions



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MRI is an excellent diagnostic tool for serial assessment of changes in left ventricular function, infarct size and myocardial perfusion. Circulating progenitor cells (CPC) injected intracoronary improve myocardial perfusion and function after acute myocardial infarction as shown by MRI. In chronic total occlusions (CTO), similar effects could be observed at 3 months follow-up in our randomized, placebo-controlled, double-blind study, which evaluates the impact of CPC's on myocardial perfusion, infarct size and left ventricular function after successful recanalization of a CTO. If these effects are persistent at longer follow-up, has not been evaluated. Twenty-six patients with reperfused CTO were randomized to either CPC's or inactive serum (control), which were infused into the target vessel. Serial contrast enhanced MRI performed initially, after 3 and 12 months revealed a significant increase in left ventricular ejection fraction in the CPC group (from 51±14 to 58±13% and 60±10%; p<0.01 versus baseline), a decrease in endsystolic volume (from 68±33 to 60±33 ml and 60±31 ml; p<0.05 versus baseline) and unchanged enddiastolic volumes (136±37 vs. 133±33 and 147±45, p=n.s. vs. baseline). Infarct size in percent of left ventricular mass, measured as delayed enhancement MRI, decreased significantly from 10.3±7.7 to 9.0±7.2 and 9.5±8.5%, p<0.05 vs. baseline. First-pass myocardial perfusion MRI at rest and stress using adenosine at standard dose revealed a significant improvement of the myocardial perfusion reserve index in the affected segments by 1.1±0.8 to 1.3±0.9 and 1.3±1.0, p<0.05. In the control group ejection fraction, left ventricular volumes, infarct size and myocardial perfusion reserve index remained unchanged. Analysis of serial contrast-enhanced MRI suggests that intracoronary application of CPC post recanalization of CTO is associated with improved myocardial perfusion and subsequent improved recovery of left ventricular function as compared to a control group at mid-term and long-term follow-up. Further investigations of the pathophysiological CPC effects on macro- and microvascular function are required.

376 MRI study of contractile function, perfusion and delayed contrast enhancement in 15 patients with left ventricular apical ballooning syndrome



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Purpose: left ventricular apical ballooning syndrome (LVABS), so far observed mainly in Japan, is an acute coronary syndrome mimicking acute myocardial infarction (AMI), and characterized by reversible apical akinesia and dilation in the absence of significant coronary artery disease. MRI can provide detailed information about morphology and function in LVABS, including myocardial perfusion.

Methods: between November 2003 and October 2005 in a series of 654 consecutive pts with ST elevation-AMI undergoing coronary angiography within 24 hours from symptom onset 15 pts (2.3%), all women, aged 75±8 yrs, fulfilled the diagnostic criteria for LVABS. Each patient was assessed with cardiac MRI performed 24 hours and 2 months after admission.

Results: in the acute phase LV ejection fraction was 0.48±0.16 and improved to 0.77±0.05 at 2 months; apical wall motion abnormalities returned to normal in 15/15 of patients. LV wall-motion abnormalities as assessed by MRI were confined to the midventricular and distal segments of the LV. In 13 of the 15 patients (87%) with early post-event MRI, abnormal regional wall motion involved areas of the LV beyond the vascular distribution of a single artery, ie, 2 vascular territories in 4 patients (27%) and 3 territories in the other 9 patients (60%). In all patients, we did not observe hypoenhancement during the first pass of gadolinium. Delayed gadolinium hyperenhancement was not present, consistent with viable myocardium and the absence of myocardial scar and infarction.

Conclusions: 1) MRI frequently identifies diffusely distributed segmental wall-motion abnormalities that encompass LV myocardium in multiple coronary arterial vascular territories in the LVABS; 2) MRI studies performed during hospital admission were uniformly consistent with preserved microvascular integrity without evidence of no-reflow zone; 3) given the absence of delayed hyperenhancement on MRI studies, it is highly unlikely that erosion or rupture of an otherwise nonobstructive plaque play a role in the LVABS; 4) MRI may be used for differentiation between LVABS and myocardial infarction or myocarditis.

377 Role of cardiac magnetic resonance imaging in patients with myocarditis: do the findings in the acute phase have prognostic value?



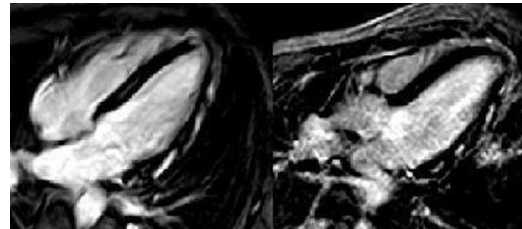
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Background: Contrast enhanced CMR shows a growing value in the investigation of myocarditis, but, information regarding evolution of CMR findings during follow-up is lacking. The aim of our study is to analyse changes in MRI findings 6 months after the acute phase and to evaluate its prognostic value.

Methods: We analysed 26 consecutive patients diagnosed of myocarditis in our institutions. MR examinations were performed with a 1.5-T unit (Intera 9.0; Philips®), including cine image acquisition and delayed enhancement (DE) imaging. A total dose of 0.2 mmol/kg of Gd-DTPA was administered and DE-enhancement image acquisition was performed 10 minutes later in short and long axis views (3D-T1-TFE sequence with a specific inversion prepulse). Patients underwent clinical follow-up and MR examinations 6 months later.

Results: Mean age was 34±15 years old and 23 patients (89%) were male. 18 patients (69%) showed segmental contractile dysfunction in the acute phase; mean ejection fraction was 52±6%. Areas of DE were detected in all patients; all patients but 3 showed multifocal pattern. Myocardial involvement was most frequent in the lateral wall (68%), followed by the inferior wall (32%). 6 months' follow-up was completed in 17 patients (65%). Mean change in ejection fraction 6 months later was 10±9%. Significant reduction of extension of DE foci was observed in 10 cases (58%) but only in one case they completely disappeared. However, patients with LE reduction did not show higher LV function recovery (8% vs 7%, p=0.9). No adverse events were reported at follow-up.



Myocarditis: acute phase, 6 months later

Conclusions: Persistence of contrast enhancement in CMR during follow-up is a frequent finding in myocarditis. However, it does not seem related to mid-term clinical evolution nor to absence of left ventricular function recovery.

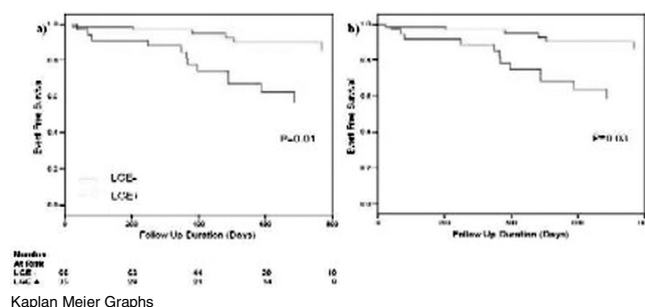
378 Cardiovascular magnetic resonance, fibrosis and prognosis in dilated cardiomyopathy



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Background: Risk stratification of patients with non-ischemic dilated cardiomyopathy (DCM) in the era of device implantation is problematic. Approximately 30% of patients with DCM have mid-wall fibrosis as detected by late gadolinium-enhancement (LGE) cardiovascular magnetic resonance (CMR) which may increase susceptibility to arrhythmia and progression of heart-failure.

Methods and Results: Consecutive DCM patients (N =101) with the presence or absence of mid-wall fibrosis were followed prospectively for 658 +355 days for events. Mid-wall fibrosis was present in 35% of patients, and was associated with a higher rate of the pre-defined primary end-point of all-cause death and hospitalization for a cardiovascular event (hazard ratio 3.4, $p=0.01$, see figure 1a). Multivariate analysis demonstrated mid-wall fibrosis as the sole significant predictor of death/hospitalization (see figure 1b). Mid-wall fibrosis also predicted secondary outcome measures of sudden cardiac death/ventricular tachycardia (SCD/VT, hazard ratio 5.2, $p=0.03$). Mid-wall fibrosis remained predictive of SCD/VT following correction for baseline differences in left ventricular ejection fraction between the two groups. (see figure)



Conclusions: In DCM, mid-wall fibrosis determined by CMR is a predictor of all cause mortality and cardiovascular hospitalization independent of ventricular remodeling. In addition, LGE-CMR predicts SCD/VT. This suggests a potential role for CMR in the risk stratification of patients with DCM, which may have value in guiding the need for device therapy.

379 Prognostic Value of Cardiovascular Magnetic Resonance Assessment of LV Function and Scar - a Multicenter Study



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Background: Cardiovascular Magnetic Resonance (CMR) is the gold-standard for assessment of cardiac function and myocardial scar (delayed-enhancement CMR, DE-CMR). Despite excellent diagnostic accuracy of both techniques, the prognostic significance is unknown.

Aim: To determine if CMR assessment of left ventricular ejection fraction (LV-EF) and presence and/or extent of enhanced myocardium representing myocardial scar (DE) can predict all cause mortality.

Methods: Consecutive patients who have undergone a complete CMR assessment of LV function and scar on a clinical scanner between September 9th, 2002 and January 22nd, 2004 were enrolled from ten sites in the US, Europe and Brazil. Only patients with at least 1 year of follow-up were enrolled. The primary endpoint was all cause mortality. DE was assessed visually (17 segments) by experienced CMR readers at each site blinded to follow-up data. EF was determined by planimetry or visually.

Results: A total of 1493 pts (69% male, age 58.9 ± 14.3 years) were enrolled of which 167 pts (11.2%) died during follow-up. From each site 149 ± 104 pts (range 50-345 pts) were enrolled. 949 pts (65%) had a history of known or suspected coronary artery disease (CAD). Mean EF was $46 \pm 18.2\%$ (range 7-88%), 64% of EF-values were assessed by planimetry. In 983 pts (66%) there was at least one segment with DE present, the mean percentage of segments with DE (% segs w DE) was $30.4 \pm 31.6\%$. The median follow-up time was 2.4 years (25th, 75th percentiles: 1.2, 2.9 years). On univariate analysis the only clinical parameters predictive of all cause mortality were older age (hazard ratio[HR] 1.04; $p<0.0001$) and history of CAD (HR 2.13; $p=0.0003$). CMR predictors of mortality on univariate

analysis were EF (HR 0.96; $p<0.0001$) the presence of DE (HR 1.69; $p=0.007$) and extent of DE (% segs w DE; HR 1.02; $p<0.0001$). On multivariate analysis age, EF, and extent of DE were independent predictors of all cause mortality (chi squared=96.62; $p<0.0001$). (Table)

Multivariate Analysis (N=1493)

Variable	Hazard Ratio	95% CI Hazard Ratio	P Value
EF	0.972	0.961, 0.983	<0.0001
Age	1.029	1.015, 1.042	<0.0001
% segs w DE	1.007	1.001, 1.012	0.02

Conclusion: CMR determined EF and extent of myocardial scar independently predict all cause mortality.

MULTIMODALITY IMAGING: CHALLENGES IN ISCHEMIC SYNDROMES

380 Coronary artery lesions with Intra-plaque Enhancement in Multislice Computed Tomography in Acute Coronary Syndrome



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Background: Multislice Computed Tomography permits non-invasive visualization of coronary arteries and atherosclerotic plaque. In the MSCT images of lesions in acute coronary syndrome (ACS), unique appearance of intra-plaque enhancement (IPE) is sometimes observed. However, clinical significance of this appearance has not been reported. We investigated the clinical and angiographic features of IPE and its impact on coronary flow after PCI in the setting of ACS.

Methods: We investigated 169 stenotic lesions from 129 patients planned for percutaneous coronary intervention (PCI), who underwent MSCT before PCI. One hundred and fifty one lesions were evaluable by MSCT, and 38 lesions (25.2%) were culprit lesions of ACS. IPE was defined as an enhancement at outer side of coronary plaque with hypodense defect at luminal side in cross-sectional images of MSCT. Angiographic data was evaluated by QCA, and TIMI flow grade and corrected TIMI frame count (CTFC) were also examined. Frequency of IPE and immediate outcomes of PCI were compared between culprit lesions of ACS (ACS group) and lesions of stable angina (non-ACS group).

Results: IPE was observed in 57 lesions by MSCT (37.7%), and was more frequently observed in ACS group than in non-ACS group (63.2% vs 29.2%, $p<0.05$). Angiographic data showed that pre-procedural mean reference diameter (RD) and mean diameter stenosis rate (%DS) were both significantly greater in IPE lesions than in the lesions without IPE (RD; 3.02 ± 0.67 mm vs 2.73 ± 0.67 mm, %DS; $65.0 \pm 14.8\%$ vs $58.0 \pm 12.4\%$, $p<0.05$). Mean lesion length and lesion calcification were not significantly different between two groups with and without IPE. After PCI procedures, TIMI 1 or 2 grade flow was more frequently observed in lesions with IPE (15.8% vs 2.1%, $p<0.05$), and CTFC was also significantly greater in IPE lesions (24.0 ± 10.9 vs 18.1 ± 8.2 , $p<0.05$). Lesions with IPE in ACS tended to be more susceptible to slow flow (25.0%), and CTFC was greatest (27.7 ± 13.5) in these lesions.

Conclusion: Lesions with IPE in MSCT was suggested to be relevant to acute coronary syndrome, and acute coronary lesions with IPE indicate propensity to immediate adverse outcomes after PCI.

381 Sustained effect of autologous bone marrow cell transplantation in no-option patients with chronic angina pectoris and myocardial ischemia: final 12 months results



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Background: Cell transplantation is proposed as a novel therapeutic option for patients with coronary artery disease. This study investigated whether autologous bone marrow-derived mononuclear cell injection into ischemic myocardium of patients with severe angina pectoris could safely reduce anginal symptoms, improve myocardial perfusion and increase left ventricular (LV) function.

Methods: In 25 patients (64 ± 10 yrs, 21 male) with drug-refractory angina pectoris (Canadian Cardiovascular Society class III-IV) despite optimized medical therapy and without options for conventional revascularization, bone marrow was aspirated from the iliac crest. Mononuclear cells ($84 \pm 29 \times 10^6$) were injected intramyocardially (using the NOGA system) in regions with stress-induced ischemia on Tc-99m tetrofosmin gated single-photon emission computed tomography (SPECT). Anginal symptoms and quality of life (Seattle Angina Questionnaire) were reassessed at 3, 6 and 12 months follow-up. At baseline, 3 and 12 months follow-up, gated SPECT imaging was performed to assess LV function and myocardial perfusion.

Results: Intramyocardial injection of bone marrow cells was safe: laboratory measures did not reveal infarction, echocardiography showed no pericardial effusion, and sustained ventricular tachycardias were not observed. One patient died at 7

months follow-up, presumably of intracranial haemorrhage. CCS class improved from 3.4 ± 0.6 at baseline to 2.3 ± 0.6 after 3 months, 2.3 ± 0.6 after 6 months and 2.6 ± 0.7 after 12 months (all $P < 0.01$ vs. baseline). Quality of life improved from $53 \pm 10\%$ to $71 \pm 11\%$ at 3 months, to $72 \pm 14\%$ at 6 months, and 68 ± 14 at 12 months follow-up (all $P < 0.01$ vs. baseline). Gated SPECT revealed an increased LV ejection fraction from $48 \pm 13\%$ to $54 \pm 17\%$ at 3 months follow-up ($P < 0.01$) and $53 \pm 16\%$ at 12 months follow-up ($P < 0.05$ vs. baseline). Regional wall motion at rest improved from 5.9 ± 1.7 mm to 6.7 ± 2.2 mm at 3 months ($P < 0.01$) and 6.6 ± 1.7 mm at 12 months follow-up ($P < 0.05$). The number of segments with stress-inducible ischemia per patient decreased from 4.6 ± 3.2 to 2.0 ± 2.6 ($P < 0.01$) and remained unchanged at 12 months follow-up.

Conclusion: Autologous bone marrow-derived mononuclear cell injection in patients with ischemia is safe and produces a durable beneficial effect on anginal symptoms, myocardial function and myocardial perfusion.

382 Left ventricular function after intracoronary infusion of bone-marrow derived progenitor cells after acute STEMI: MRI substudy of the double-blind, placebo-controlled, multicenter REPAIR AMI trial



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The "Reinfusion of Enriched Progenitor Cells And Infarct Remodeling in Acute Myocardial Infarction" trial (REPAIR-AMI) has established a beneficial effect of intracoronary infusion of bone-marrow-derived progenitor cells (BMC) on left ventricular function, assessed by quantitative left ventricular angiography. A prespecified analysis revealed, that especially patients with large infarcts (below the median ejection fraction) derived the most benefit from therapy. The goal of the present substudy is to scrutinize these findings by MRI as the gold standard technique to assess myocardial function and geometry.

Methods: In this double-blind, randomized, placebo-controlled multicenter trial, patients with successful reperfusion therapy of a STEMI were randomized into intracoronary infusion of bone marrow-derived progenitor cells or placebo medium. Sixty of the randomized 204 patients participated in the MRI substudy ($n = 30$ BMC, $n = 30$ Placebo). Left ventricular function and dimensions were quantitated using SSFP-cine sequences and multi-slice volumetry at the index hospitalization and after 4 months.

Results: Baseline ejection fraction (EF) was similar in the BMC and Placebo group in patients with an EF below the median of 48.9% (BMC = $38.7 \pm 8.1\%$, Placebo = $40.5 \pm 8.0\%$, $p = 0.54$) and those above the median (BMC = $56.5 \pm 4.1\%$, Placebo = $55.1 \pm 6.2\%$, $p = 0.45$). In patients with baseline EF below the median, ejection fraction increased by $5.0 \pm 5.7\%$ ($p = 0.014$), whereas there was no change in ejection fraction in the placebo group ($-0.82 \pm 7.8\%$, $p = 0.68$). Thus, BMC treatment effect on EF was 5.8 absolute % increase in EF (95%CI 0.5 to 11% , $p = 0.034$). In contrast, patients with smaller infarcts ($>$ median of baseline EF), derived no benefit from the therapy (treatment effect -0.9% , 95%CI -6.4 to 4.5%). Likewise, BMC therapy was associated with a significant decline of enddiastolic volumes (treatment effect -29 ml, 95%CI -0.7 to -53 ml, $p = 0.045$) and endsystolic volumes (treatment effect -28 ml, 95%CI -2.1 to -53 ml, $p = 0.035$) in patients with baseline EF $<$ median.

Conclusions: In patients with a large ST elevation myocardial infarction, intracoronary infusion of bone marrow-derived progenitor cells significantly enhances recovery of left ventricular contractile function and beneficially interferes with left ventricular remodeling processes in the 4 months follow-up. Therefore, MRI findings confirm that bone marrow - derived progenitor cell therapy holds great promise to limit post infarction heart failure.

383 Usefulness of strain rate imaging to determine the transmural of anterior wall myocardial infarction. Correlation with contrast-enhanced magnetic resonance



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Purpose: The assessment of necrosis transmural after acute myocardial infarction brings important prognostic implications. The aim of this study was to evaluate the usefulness of Strain Rate Imaging (SRI) to discriminate different degrees of myocardial necrosis and to identify segments with potential functional recovery in correlation with Contrast-enhanced Magnetic Resonance (Ce-MR).

Methods: 18 patients (median age 60.28 y) with acute anterior wall myocardial infarction underwent tissue doppler echocardiography with SRI (median 6 days) and Ce-MR (median 13 days between both techniques). 88.8% of patients were revascularized with thrombolysis (50%) or primary angioplasty (50%). Longitudinal peak systolic strain rate (SRs) was measured in a 12 segment model (total: 126 segments) and compared with the extension of hyperenhancement graded in three groups (Table 1).

Results: Negative SRs was significantly higher in normal segments compared with transmural ($p = 0.0005$). There was significant difference between segments

Table 1

Delayed enhancement	0 Normal	<90% Non-transmural	>90% Transmural
Segments analyzed (n%)	130/60.2%	27/12.5%	59/27.3%
SRs (s^{-1}) mean $\pm$ ED	-0.92 ± 0.53	-0.85 ± 0.53	-0.40 ± 0.29

with non-transmural and transmural necrosis ($p = 0.0001$). The sensitivity, specificity and area under the ROC curve to identify those segments with potential functional recovery ($<50\%$ of delayed enhancement) was 73.7% , 70.8% and 0.76 using a cutoff of $-0.60s^{-1}$.

Conclusions: SRI is useful to evaluate the transmural of the necrosis and thereby to identify the presence of non viable myocardium after an acute myocardial infarction.

384 Extent of myocardial viability detected by myocardial contrast echocardiography early after acute myocardial infarction is an independent predictor of mortality and reinfarction



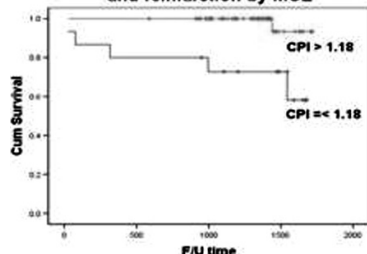
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Background: Myocardial viability detected by myocardial contrast echocardiography (MCE) has been shown to predict recovery of left ventricular (LV) function in patients with acute myocardial infarction (AMI). However, to date no study has shown its value to predict outcome in such patients.

Method: Accordingly, 76 stable AMI patients underwent vasodilator low power MCE at 7 ± 2 days after thrombolysis. Contrast perfusion index (CPI), a measure of residual myocardial viability, was obtained by adding contrast scores ($2 = \text{homogenous}; 1 = \text{reduced}; 0 = \text{minimal/absent opacification}$) in all 16 LV segments divided by 16. Ischaemia was diagnosed when myocardial replenishment was incomplete 1 second after the destructive imaging following vasodilator stress. At discharge 55 (72%) patients, had either undergone or were scheduled for revascularisation independent of the MCE result. The patients were subsequently followed up for death and reinfarction.

Results: During the mean follow up time of 42 ± 11 months, there were 9 (12%) major cardiac events (6 cardiac deaths and 3 AMI). Amongst the clinical, biochemical and echocardiographic markers of prognosis, both the extent of residual viability and the presence of ischaemia or viability were univariate predictors of mortality ($P = 0.01$ & $P = 0.03$ respectively) and the combined end point of mortality or reinfarction ($P = 0.04$ & $P = 0.04$ respectively). However, only the extent of myocardial viability was an independent predictor of both mortality ($P = 0.01$) and the combined endpoint of mortality or reinfarction ($P = 0.04$) in this group of patients. (Figure)

Kaplan Meier curve for prediction of death and reinfarction by MCE



Conclusion: The extent of residual myocardial viability predicted by MCE was the only independent predictor of mortality and reinfarction in patients following AMI and thrombolysis.

ION CHANNELS AND ARRHYTHMOGENESIS IN NATIVE AND ENGINEERED CARDIAC CELLS

386 Ongoing functional integration of transplanted human mesenchymal stem cells in an electrical syncytium of cardiomyocytes during long-term incubation



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Background: Cardiac cell therapy using certain cell types carries the risk of ventricular arrhythmias, associated with electrical isolation of transplanted cells from host myocardium. Therefore, we assessed whether bone-marrow derived human adult mesenchymal stem cells (hMSCs) are able to electrically integrate in an electrical syncytium of cardiomyocytes (CMCs) for longer periods. Furthermore, we studied the role of connexin43 (Cx43) in this process using RNA interference (RNAi) technique and immunohistochemistry.

Methods: Neonatal rat CMCs were cultured in multi electrode mapping array (MEA, Multichannel Systems, Germany) culture dishes. After 2 days, a central a-

cellular channel was made, dividing the spontaneously and synchronously beating monolayer in two asynchronously beating CMC fields. hMSCs were transfected by adeno-viral constructs knocking down connexin43 (hMSCs-Cx43↓) or Firefly luciferase (pLuc) (hMSCs-pLuc↓) as control. Efficiency of knock down was assessed by western blot analysis. Then, 5x10E4 hMSCs-Cx43↓ or hMSCs-pLuc↓ were applied in the channel. Electrical conduction velocity (CV) across the channel with hMSCs was measured for up to 14 days and compared with CV across CMCs. Immunostaining of Cx43 was performed at day 1, 7, and 14 of co-culture.

Results: In the control group, hMSCs-pLuc↓ (n=8) restored electrical conduction between two CMCs fields within 24 h, which sustained for at least 14 days. CV across hMSCs-pLuc↓ was constant during the first 7 days (1.4 ± 0.3 cm/s), but increased significantly to 3.5 ± 0.5 cm/s at day 14 ($p < 0.05$). This was associated with a concomitant increase in Cx43 expression in-between adjacent CMCs, adjacent hMSCs, and CMCs adjacent with hMSCs from day 7 onward, as assessed by immunostaining. In contrast, hMSCs-Cx43↓ (n=8) did not restore electrical conduction between two CMC fields. CV across CMCs (n=6) did not change significantly during 14 days of measurement (16.8 ± 0.2 cm/s). Western blot analysis showed a >70% decrease in Cx43 expression in hMSCs-Cx43↓ compared to hMSCs-pLuc↓.

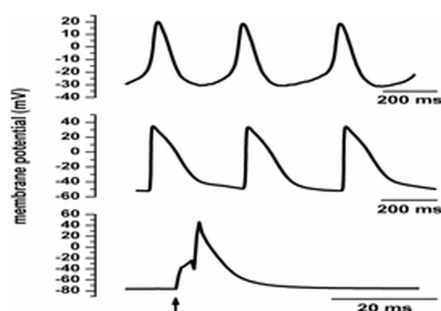
Conclusions: Transplanted bone-marrow derived human adult mesenchymal stem cells (hMSCs) are electrically coupled with host cardiomyocytes (CMCs) in a connexin43-dependent process. During 14 days in co-culture, ongoing electrical integration of the transplanted hMSCs occurs in the syncytium of CMCs. This is reflected by a steadily rising electrical conduction velocity across hMSCs, accompanied by increased Cx43 expression.

387 Functional differentiation of CD34+ human stem cells cocultured with mouse neonatal myocytes



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CD34+ cells, isolated from human cord blood, are endothelial progenitors expressing CD34, CD133 and VEGFR2. We cocultured CD34+-derived cells (SC) onto mouse neonatal cardiac myocytes (Pesce et al., 2005) and tested development of a functional phenotype. SC were labelled by a GFP vector. After 4-7 days in coculture GFP+ cells laid either in contact with neonatal myocytes or in isolation. Intrinsic contractile activity could be identified visually in cells attached to myocytes and only occasionally in isolated ones. Quiescent GFP+ cells were mostly round-shaped, contracting ones were flat and branched. Whole-cell patch-clamp recordings were obtained from both types of GFP+ cells and from neighbouring neonatal myocytes. Most quiescent GFP+ cells had stable resting potentials (-24.2 ± 4 mV, n=11) and were non-excitable; total membrane current was either instantaneous or time-dependent, had a negative apparent reversal potential (-33.8 ± 5.6 mV, n=7) and displayed outward rectification. In a single instance a quiescent GFP+ cell with a negative resting potential (-77 mV) could be excited (bottom panel). Contracting GFP+ cells always displayed electrical activity, either of pacemaker (upper panel), or follower type (middle panel).



Electrical activity in SC-derived cells

Their total current included inward transient components, suggesting expression of I_{Na} and/or I_{Ca} . The electrical activity of GFP+ contracting cells was similar to that of neonatal myocytes. Thus, cardiac-type functional phenotype can be induced in human CD34+-derived cells by coculture onto mouse neonatal myocytes. Contact between cells seems to be required and further experiments are necessary to discriminate between cell fusion and gap-junctional coupling.

388 Cytoskeletal structure and Ca2+ spark localization in engineered cardiac myocytes



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We have used microcontact printing techniques in order to discover whether extracellular matrix geometry influences the cytoskeletal architecture and the spatiotemporal dynamics of the Ca2+ signaling machinery in cardiac myocytes. It

has long been known that the extracellular matrix (ECM) can regulate both the structure and the function of the heart and that aberrant ECM geometry can lead to heart damage and failure. However, the molecular basis of the transduction of these mechanical stimuli into physiological responses is poorly understood, though recent data suggest that a regulatory relationship may exist between the extracellular matrix (ECM), the cytoskeleton, and ion channels. Here, we asked whether the geometry of the ECM can control the cytoskeletal architecture in cardiac myocytes, and whether this has an effect on ion channel physiology. We have controlled the structure of the cytoskeleton and the distribution of cellular components involved in cell-ECM contacts in single cardiac myocytes. Further, we have used optical microscopy and image processing techniques to investigate the spatiotemporal localization of Ca2+ sparks and the spark-to-wave transition in patterned cardiac myocytes.

389 Pharmacological remodelling of human atrial K+ currents by chronic beta-blockade



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Purpose: The chronic treatment of patients with a beta-blocker is associated with prolongation of the atrial action potential duration (APD), potentially contributing to its ability to prevent atrial fibrillation (AF). This may involve pharmacological remodelling of atrial K+ currents which affect APD. This project aimed to test the hypothesis that various characteristics of human atrial K+ currents, including voltage, time and rate dependency, differ between patients treated and not treated with a beta-blocker.

Methods: Myocytes were isolated enzymatically from right atrial appendage tissue obtained from consenting patients, in sinus rhythm, undergoing cardiac surgery. Currents were recorded by whole cell patch clamp at 35-37°C.

Results: Patients who received a beta1-selective blocker for at least 4 weeks immediately before surgery (n=13) had a significantly lower heart rate than non beta-blocked patients (54 ± 1 vs 75 ± 4 beats/min, $p < 0.05$, n=15). Chronic beta-blockade was associated with a 41% reduction in the transient outward potassium current (ITO) density (9.3 ± 0.8 vs 15.7 ± 1.1 pA/pF, $p < 0.05$) and a reduction in the Ba2+ (0.5 millimolar)-sensitive, inwardly rectifying potassium current, IK1, at -120 mV (-1.7 ± 0.0 vs -2.5 ± 0.2 pA/pF, $p < 0.05$; n=18-33 cells, 11-15 patients). The sustained outward current, IKs was unaffected (10 ± 0.6 vs 11.4 ± 1.1 pA/pF, $p > 0.05$). In cells from the non beta-blocked patients, the voltages for half maximal activation and inactivation of ITO were 24 ± 1 and -20 ± 1 mV, respectively, with corresponding slope factors of 9 ± 0 and 5 ± 0 mV. The decay of ITO was bi-exponential with fast and slow time constants of 6.8 ± 0.4 and 52.2 ± 6.3 ms. Reactivation was mono-exponential with a time constant of 31.4 ± 1.9 ms. None of the variables for voltage or time dependency were significantly different in cells from the beta-blocked patients. The density of ITO decreased significantly with increasing rate between 75 and 500 beats/min in both beta-blocked and non beta-blocked patient groups. Nevertheless, ITO density remained significantly reduced in beta-blocked patients at all rates studied, including 500 beats/min (3.5 ± 0.4 vs 5.5 ± 0.8 pA/pF, n=17-27 cells, 6-11 patients).

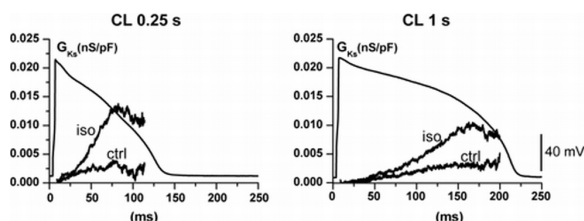
Conclusion: Chronic treatment of patients with a beta-blocker remodelled atrial K+ currents by reducing the densities of ITO and IK1, but not IKs. These changes may contribute to beta-blocker induced APD prolongation but the voltage, time and rate dependent characteristics of ITO do not. The preservation of ITO reduction at fast rates may contribute to the ability of beta-blockers to prevent AF.

390 Beta-adrenergic activation supports IKs expression during tachycardia



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During tachycardia, action potential duration may seem inadequate to allow for significant IKs activation; still, IKs deficiency causes major repolarization instability. Since tachycardia is physiologically induced by beta-adrenergic (b-AR) stimulation, we tested whether the latter may interact with pacing cycle length (CL) to explain this apparent paradox. We measured IKs during pacing at CLs of 0.25 and 1 s, reproduced in guinea-pig ventricular myocytes by the action-potential-clamp technique (HMR1556-sensitive current, at 35°C). The time course of IKs conductance (GKs) was obtained from the ratio between IKs and its driving force at each instant. The figure shows GKs course during the action potential at two CLs in control (ctrl) and with a b-AR agonist (iso, 0.1 μM). GKs increased at shorter CL mainly due to a faster onset of time-dependent GKs, reflecting increased activation rate. The instantaneous component of IKs, reflecting incomplete diastolic deactivation, was minimally affected. Iso increased IKs activation rate by 149% at CL = 1 s and 356% at CL = 0.25 s ($p < 0.05$). A two-step V-clamp protocol was used to assess IKs deactivation time constant (Tdeact at -80 mV) and pause-dependency of reactivation time constant (Tact). Consistent with the small magnitude of instantaneous IKs, Tdeact was short (43 ± 2 ms) and only slightly increased by iso (55 ± 3 ms; $p < 0.05$). Tact was pause-dependent (e.g. 433 ± 60 ms at 500 ms vs. 269 ± 23 ms at 30 ms; $p < 0.05$); iso decreased Tact and extended the range of its pause-dependency. Thus 1) IKs activation rate is pause-dependent; 2) faster activation, rather than incomplete diastolic deacti-



CL-dependency of GKs

vation, accounts for rate-dependent increase in IKs; 3) b-AR stimulation and CL shortening strongly interact to increase IKs activation rate

391 Relationship between intracellular calcium homeostasis and electrical and mechanical alternans in human atrial myocytes



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Cardiac electrical and mechanical alternans has been attributed to oscillations in calcium release from the sarcoplasmic reticulum in animal models, but information about the cellular mechanisms contributing to this phenomenon in the human heart is sparse.

Purpose: To characterize the calcium handling mechanisms associated to the generation of electrical and contractile alternans in human atrial myocytes.

Methods: Forty-two human right atrial myocytes isolated from 22 patients in sinus rhythm undergoing cardiac surgery were analyzed. Amplitude of the L-type calcium current (I_{Ca}) was determined at stimulation frequencies of 0.2, 0.5, 1 and 2 Hz. The fast, calcium release dependent, time constant for I_{Ca} inactivation (τ) was obtained using a double exponential fit. The time integrals of the tail current (Q_{tail}) and the caffeine induced Na-Ca exchange current were used as indicators of sarcolemmal calcium extrusion and sarcoplasmic reticulum calcium content respectively. The incidence of spontaneous calcium release was determined as the frequency of spontaneous Na-Ca exchange currents (I_{NCX}) at rest. Cell shortening was determined off-line from video recordings.

Results: Beat-to-beat changes (alternans) in the magnitude of I_{Ca} , τ , Q_{tail} , and cell shortening were observed in 12 cells stimulated at 1 Hz and in 10 cells stimulated at 2 Hz. On average I_{Ca} alternated between 1.9 and 2.5 pA/pF, τ alternated between 15.8 and 23.1 ms and Q_{tail} alternated between 0.21 and 1.01 amol/pF. Responses showing a larger cell shortening were associated with a smaller I_{Ca} amplitude, faster I_{Ca} inactivation, and a larger tail current. Cells displaying alternans had a larger I_{Ca} amplitude (2.27 ± 0.24 vs 1.54 ± 0.21 pA/pF, $p < 0.05$), a larger Q_{tail} (0.61 ± 0.08 vs 0.37 ± 0.04 amol/pF, $p < 0.05$), and a higher frequency of spontaneous Na-Ca exchange currents (1.58 ± 0.37 vs 0.40 ± 0.21 waves/min, $p < 0.05$) than non-alternating cells when stimulated at 0.5 Hz. The caffeine releasable sarcoplasmic reticulum calcium content was similar for the two cell populations.

Conclusions: Electrical and mechanical alternans in human atrial myocytes is linked to oscillations in the L-type calcium current and in the calcium released from the sarcoplasmic reticulum. Myocytes with larger L-type calcium current density and a higher incidence of spontaneous calcium release are more prone to develop alternation.

PROTECTIVE SIGNALING PATHWAYS IN CARDIAC REMODELLING

392 Downregulation of beta-catenin is required for physiologic cardiac hypertrophy in vivo



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β -catenin downregulation initiates heart formation in embryogenesis. Furthermore, β -catenin stabilization has been implicated in adult cardiac hypertrophy in vitro. Here we analyzed the role of β -catenin in adult cardiac hypertrophy in vivo. To avoid embryonic lethality, we employed a cardiac-specific mifepristone-inducible α MHC-Cre transgene to induce β -catenin deletion (exon3-6) or stabilization (exon 3). Heart-specific recombination of loxP sites flanking the above mentioned exons was confirmed by PCR. Decreased β -catenin expression in β -catex3-6 mice was confirmed by immunohistochemistry and Western blot. Expression of stabilized β -catenin (β -catex3) was confirmed by Western blot. Mice with cardiac specific β -catenin modulation through mifepristone injection were viable. Surprisingly, decreasing β -catenin levels resulted in a phenotype of modest cardiac hypertrophy at baseline as assessed by echocardiography, histology and hypertrophic gene markers measured by real-time RT-PCR. Infusion of Ang II by osmotic minipumps induced cardiac hypertrophy both in wild type mice as well as in β -catex3-6 (echo, histology, hypertrophic gene markers). In contrast, sta-

bilizing β -catenin resulted in decreased cross sectional area at baseline and an abrogated hypertrophic response to AngII infusion (echo, histology, hypertrophy gene markers). However, decreased hypertrophy in β -cat ex3 mice was accompanied by a significant reduction in fractional shortening after 2 weeks (30 ± 2 vs. $21 \pm 3\%$).

In conclusion, β -catenin deletion in adult heart leads to a modest cardiac hypertrophy at baseline without affecting Ang II-induced cardiac hypertrophy. Stabilizing β -catenin abrogates AngII-induced cardiac hypertrophy at the price of reduced cardiac function. β -catenin seems to be involved in adaptive (physiologic) hypertrophy possibly reactivating the genetic program executed in cardiac embryogenesis.

393 Pharmacological inhibition of Akt signaling reduces LV-dilation and improves contractile function after TAC-induced LV pressure overload in mice



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Akt signaling is a crucial pathway leading to cardiac hypertrophy. However, it is still an open question whether activation of Akt causes a beneficial or maladaptive form of hypertrophy. Transgenic overexpression studies recently have provided evidence that Akt signaling is not beneficial or maladaptive in principle. Instead, the character of the hypertrophy is determined by the degree of Akt overexpression. Therefore, we were looking for a pharmacological tool to titrate Akt activity. In non-myocardial tissue, the cyclooxygenase (COX)-2 inhibitor celecoxib (CEL) has been shown to inhibit the Akt pathway in a COX-independent manner. Thus, we investigated the effects of CEL on cardiac hypertrophic signaling and response in vitro and in vivo.

Adult rabbit cardiac myocytes were treated with insulin, a stimulator of the Akt pathway. After 1 h of incubation, insulin ($10 \mu\text{M}$) significantly increased phosphorylation of Akt and its downstream targets GSK-3 β and p70 S6 kinase by 248% ($n=8$, $P < 0.05$), 171% ($n=8$, $P < 0.05$) and 50% ($n=4$, $P < 0.05$), respectively. $50 \mu\text{M}$ CEL (for 1 h) attenuated the insulin-induced increase in Akt-, GSK-3 β - and p70 S6 kinase-phosphorylation by 63% ($n=8$, $P < 0.05$), 71% ($n=8$, $P < 0.05$) and 100% ($n=4$, $P < 0.05$), respectively. Inhibition of the Akt-pathway by CEL was accompanied by a significant suppression of characteristic features of cardiac hypertrophy: CEL (10 and $25 \mu\text{M}$) inhibited the agonist-induced enhancement of total protein synthesis ($n=11$, $P < 0.05$) and BNP mRNA expression ($n=6$, $P < 0.05$) in a concentration dependent manner.

In mice subjected to LV pressure overload by transversal aortic constriction (TAC), oral treatment with CEL (50 mg/kg/d) significantly attenuated LV-Dilation 14 d after TAC compared with placebo-treated mice (LVEDD $3.95 \pm 0.08 \text{ mm}$ [$n=7$] vs. $4.50 \pm 0.09 \text{ mm}$ [$n=5$], $p < 0.05$). Furthermore, 14 d after TAC contractile function was significantly improved in CEL-treated mice compared with placebo-treated animals (FS $27.4 \pm 1.9\%$ [$n=7$] vs. $18.8 \pm 0.47\%$ [$n=5$], $p < 0.05$).

In summary, CEL can be used to titrate Akt activity and thereby control the extent of the hypertrophic response in cardiac myocytes subjected to a hypertrophic stimulus.

Pharmacologically controlled inhibition of Akt signaling by CEL reduces pressure overload induced LV-Dilation and it improves contractile function in vivo. Thus, it attenuates two important features of maladaptive hypertrophy.

394 Heart-restricted NF-kappaB inhibition abrogates left ventricular remodeling after trans-aortic banding



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Recently we reported that cardiomyocyte-restricted inhibition of NF- κ B in vivo attenuated hypertrophy induced by short term stimulation with β -adrenergic agonists or angiotensin II. Here we tested whether heart-restricted inhibition of NF- κ B attenuates hypertrophy and left ventricular dilation induced by trans-aortic ligation (TAC). IkappaBDeltaN is a non-degradable inhibitor of NF- κ B which was expressed cardiomyocyte-specifically in mice employing the Cre/lox system (DeltaNMHC mice). In control mice (CT) 4 weeks of TAC increased dimensions of intraventricular septum (IVS) and LV posterior wall (LVPW) as determined by echocardiography ($n=4$ for each group). By contrast 4 weeks of TAC did not induce hypertrophy in DeltaNMHC mice. After 8 weeks of TAC heart weight/tibia length (HW/TL) of CT was significantly increased, whereas elevation of HW/TL was absent in TAC-treated DeltaNMHC mice. As expected LV dilation occurred in CT+TAC but was completely absent in DeltaNMHC+TAC. In conclu-

	Stream	Control + TAC	Delta NMHC + TAC
Septum diastolic diameter 1 wk (mm)	0.63 ± 0.04	1.0 ± 0.002	11.73 ± 0.009
Posterior wall diameter 4 wk (mm)	0.66 ± 0.03	1.1 ± 0.01	0.8 ± 0.06
LV end-diastolic diameter 8 wk (mm)	39.7 ± 4.1	52.3 ± 5.7	40.3 ± 2.3
Heart weight/tibia length 8 wk	5.8 ± 0.1	7.6 ± 0.8	6.5 ± 0.4

sion, cardiomyocyte-specific inhibition of NF- κ B protects from cardiac hypertrophy and subsequent left ventricular dilatation after TAC. Targeting NF- κ B might be a new therapeutic strategy to prevent end-organ damage in hypertension.

395 Diacylglycerol kinase zeta prevents cardiac remodeling by mechanical overload



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Background: Gq protein-coupled receptor (GPCR) signaling pathway including diacylglycerol (DAG) and protein kinase C (PKC) plays a critical role in the development of cardiac hypertrophy and heart failure. DAG kinase (DGK) phosphorylates DAG and controls cellular DAG levels, thus acting as a regulator of GPCR signaling. We previously reported that DGK inhibited GPCR agonists-induced activation of the DAG-PKC signaling and subsequent cardiomyocyte hypertrophy. In this study, we examined whether DGK modifies cardiac remodeling by mechanical stresses.

Methods and Results: We used two different models of mechanical overload, pressure overload by aortic constriction and myocardial infarction by coronary artery ligation, in mice. Thoracic transverse aortic constriction (TAC) was created in transgenic mice with cardiac-specific overexpression of DGKzeta (DGK-TG) and wild-type (WT) mice. Increases in heart weight at 4 weeks after TAC were attenuated in DGK-TG mice compared to WT mice. Increases in inter-ventricular septal thickness, dilatation of the left ventricular cavity, and decreases in left ventricular systolic function were observed with echocardiography in WT mice at 4 weeks after TAC surgery. However, these structural and functional changes after TAC were attenuated in DGK-TG mice. Increases in cardiomyocyte cross-sectional area after TAC were also attenuated in DGK-TG mice compared to WT mice. Up-regulation of atrial natriuretic factor and beta-myosin heavy chain mRNA was observed after TAC in WT mice, but not in DGK-TG mice. Next, left anterior descending coronary artery was ligated in DGK-TG and WT mice. Left ventricular chamber dilatation, left ventricular systolic dysfunction, and increases in left ventricular weight and lung weight at 4 weeks after myocardial infarction were attenuated in DGK-TG mice compared to WT mice. In the non-infarct area, cardiac fibrosis and up-regulation of profibrotic genes such as transforming growth factor-beta 1, collagen type I, and collagen type III were observed at 4 weeks after myocardial infarction in WT mice. However in DGK-TG mice, cardiac fibrosis and profibrotic gene induction were blocked. The survival rate after myocardial infarction was higher in DGK-TG mice than in WT mice.

Conclusion: These results demonstrate the first evidence that DGKzeta suppresses cardiac structural remodeling after TAC and myocardial infarction. DGKzeta may be a potential novel therapeutic target to prevent cardiac remodeling in response to mechanical overload.

396 Microsomal Prostaglandin E Synthase-1 (mPGES-1) plays a role in cellular remodeling and preservation of left ventricular geometry and function after myocardial infarction



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Inducible PGE2 biosynthesis is under the regulation of microsomal prostaglandin E2 synthase-1 (mPGES-1), encoded by the Ptges gene. mPGES-1 is directly downstream from COX-2 in the inducible PGE2 biosynthetic cascade. The purpose of this study was to evaluate the effect of targeted deletion of Ptges on myocardial ischemic injury. Eight to 12 weeks old Ptges^{+/+} and Ptges^{-/-} mice were subjected to myocardial infarction (MI) through permanent left coronary artery ligation. Left ventricular (LV) function was assessed in vivo by echocardiography at day 0, 7 and 28 and by LV pressure conductance catheterization. Histological and morphological analyses were performed at day 28 after perfusion fixation of the hearts in situ. The area of infarcted myocardium was similar in Ptges^{+/+} and Ptges^{-/-} mice. Analysis of LV geometrical remodeling 28 days after MI showed that Ptges^{-/-} mice exhibited increased LV dilatation when compared to Ptges^{+/+} (LV End Diastolic Volume = 45.4 μ L vs 33.8 μ L, $p < 0.05$). LV functional analysis showed that Ptges^{-/-} mice displayed a worsened systolic (LV Ejection Fraction = 18.6% vs 24.6%, $p < 0.05$) and diastolic (LV relaxation time = 23.8 msec vs 16.6 msec, $p < 0.05$) function than Ptges^{+/+} mice. Cardiomyocytes remote from the infarcted zone underwent hypertrophy in both Ptges^{+/+} and Ptges^{-/-} mice, but the degree of hypertrophy was significantly less in Ptges^{-/-} mice. Cardiac mass and extracellular matrix degradation were similar in both groups. Ex vivo analysis of cardiomyocytes isolated from Ptges^{+/+} and Ptges^{-/-} hearts 28 days after MI showed less adaptive hypertrophy, with decreased width and a greater length/width ratio in Ptges^{-/-} mice. Our data demonstrate that mPGES-1 regulates post MI left ventricular remodeling and adaptive cardiomyocytes hypertrophy. In our model, mPGES-1 controlled cellular remodeling was associated with better preservation of left ventricular geometry and function after acute MI.

397 Modulation of diastolic function in cardiac hypertrophy by a novel pathway involving the sarcolemmal calcium pump



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Diastolic dysfunction in cardiac hypertrophy is a major contributor to heart failure, but little is known about the molecular mechanisms involved. Previously we have demonstrated that an isoform of the sarcolemmal calcium pump (PMCA4b) interacts and down-regulates neuronal nitric oxide synthase (nNOS) activity in non-cardiac cells. It has been demonstrated by others that mice lacking nNOS develop age-related left ventricular hypertrophy and suppressed beta-adrenergic inotropic responses. We therefore investigated the role of PMCA4 and the involvement of the nNOS signalling pathway in isoproterenol-induced hypertrophy.

Cardiac hypertrophy was induced in 3 month old PMCA4^{-/-} mice and wild type control mice by treatment with isoproterenol (10mg/kg body weight/day) for 7 days. One group of PMCA4^{-/-} mice and wild type littermates were pre-treated with the specific nNOS inhibitor, Nw-propyl-L-arginine (L-NPA; 10 mg/kg body weight), prior to each isoproterenol injection. Cardiac function was assessed using echocardiography and the pressure-volume catheter system.

Hypertrophy was induced in PMCA4^{-/-} mice and wild type littermates; there was no difference in the hypertrophic response (heart weight to body weight) between the two groups. However, diastolic function was preserved in PMCA4^{-/-} mice (Tau: 8.80 second $\pm$ 3.69 vs 10.16 $\pm$ 2.18, saline vs isoproterenol treatment respectively, $p = NS$) but deteriorated in wild type mice as indicated by a significantly increased relaxation time constant (Tau: 8.19 second $\pm$ 1.98 vs 13.48 $\pm$ 6.85, saline vs isoproterenol treatment respectively, $p < 0.05$). Expression of nNOS was up-regulated in hypertrophic wild type mice, conversely in PMCA4^{-/-} mice nNOS expression was downregulated following hypertrophy (both $p < 0.05$). When pre-treated with L-NPA, the hypertrophic response was significantly increased in wild type mice ($p < 0.05$) but not in PMCA4^{-/-} mice.

Our data suggest that PMCA4 is a major and previously unknown regulator of diastolic function in cardiac hypertrophy through the modulation of nNOS activity, making this pathway a novel target for pharmacological intervention.

POSTER SESSION 1

MODERATED POSTERS DRUGS, ABLATION AND ELECTRICAL THERAPY OF ARRHYTHMIAS

P439 Combined treatment with hypothermia and atrial pacing for postoperative junctional ectopic tachycardia



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Background: Junctional ectopic tachycardia (JET) after surgical repair of congenital heart defects is a potentially life-threatening condition. The efficacy of pharmacological treatment is usually poor and it can entail serious side effects.

Objective: We sought to assess the efficacy and safety of an initial strategy of early combined treatment with hypothermia and atrial pacing in patients with post-operative JET.

Methods: Between September 1998 and December 2005, 21 infants with post-operative JET (mean age 2.7 $\pm$ 2.3 months) underwent a combined treatment of early moderate hypothermia (33-35°C) and atrial pacing. 8 patients received additional treatment with amiodarone after establishment of hypothermia.

Results: Mean interval between diagnosis of JET and initiation of hypothermia was 1.38 $\pm$ 1.8 hours. After 2 hours, heart rate decreased from 181.8 $\pm$ 17 to 169.4 $\pm$ 21 beats per minute ($p = 0.019$). After 4 hours, systolic blood pressure rose from 73.8 $\pm$ 12 to 83.8 $\pm$ 16 mmHg ($p = 0.018$), hourly urine output increased from 3.4 $\pm$ 2.1 to 5 $\pm$ 3.1 ml/kg/h ($p = 0.029$) and central venous pressure decreased from 14.4 $\pm$ 4.5 to 11.6 $\pm$ 3.2 mmHg ($p = 0.002$). No side effects directly attributable to hypothermia or atrial pacing were observed. One patient died as a direct consequence of the arrhythmia, after having received amiodarone. 2 additional patients died during the postoperative course due to other associated cardiovascular causes. Stable sinus rhythm was restored after 72 $\pm$ 38.8 h in the remaining patients. After a mean follow-up of 3.2 $\pm$ 2.8 years, sinus rhythm has been maintained in all these patients except one, who has exhibited episodes of nodal rhythm.

Conclusion: Aggressive treatment with early moderate hypothermia and atrial pacing is an effective and safe therapeutic option for postoperative JET.

P440 Dronedronarone: rhythm and rate control in management of atrial fibrillation. Focus on symptomatic arrhythmia



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Background: Atrial fibrillation/flutter (AF) is the most common cardiac arrhythmia. Conversion to sinus rhythm (SR) and maintenance is still the key factor in management. However, the optimal approach to maintaining SR remains a major challenge. In the EURIDIS* (E) and ADONIS** (A) studies, dronedarone (D) significantly increased the time to first AF recurrence compared to placebo (P). This analysis focused on the effect of D on the incidence of symptomatic first AF recurrence and on ventricular rate and in patients of the E/A trials.

Methods: Patients with a documented history of AF were randomized to receive 400 mg D bid (n=411 E/417 A) or P (n=201 E/208 A) for one year. Patients transmitted ECG via a transtelephonic monitor at standard timepoints during the study or if symptomatic. The presence or absence of symptoms (palpitations, dizziness, fatigue, chest pain, dyspnea) was noted at each transmission. Two-sided Fisher's exact test was used for all qualitative parameters and log-rank technique to test null hypothesis of identical Kaplan-Meier curves in the two trials.

Results: D significantly lowered the incidence of symptomatic first AF recurrence at 12 months (37% D vs. 47.5% P in E, $p=0.0055$; 38.3% D vs. 44.5% P in A, $p=0.021$). The mean ventricular rate during the first AF recurrence was 13% lower in the E trial (102.3 ± 24.7 bpm D vs. 117.5 ± 29.1 bpm P, $p<0.001$) and 10% lower in the A trial (104.6 ± 27.1 D vs. 116.6 ± 31.9 bpm P, $p<0.0009$). D was well tolerated in both trials with no incidences of torsades de pointes or organ toxicity.

Conclusion: Dronedronarone was effective in reducing symptomatic AF recurrences and ventricular response during AF recurrence.

*EUROPEAN trial in atrial fibrillation or flutter patients receiving Dronedronarone for the maintenance of Sinus rhythm

**American-Australian-African trial with Dronedronarone in atrial fibrillation or flutter patients for the maintenance of Sinus rhythm

P441 How long should be the waiting time following radiofrequency abolition of AV accessory pathway conduction?



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Radiofrequency (RF) application can transiently or permanently abolish conduction through the AV accessory pathway (AP). A 30 minutes waiting time following successful RF application is a widespread practice to monitor AP conduction recovery. However, this practice has never been scientifically validated and the predictors for late AP recurrence are unknown.

Methods: The intracardiac recordings of 419 consecutive patients who underwent ablation of 439 APs (261 left-sided, 178 right-sided) were retrospectively reviewed. All patients had undergone ECG monitoring and pacing for at least 30 minutes following bidirectional AP conduction block by RF application.

Results: Transient conduction abolition of AP conduction was observed in 295 RF applications of 108 patients. Mean time to AP conduction recovery was 121 ± 306 sec. The risk for AP conduction recurrence after 10 minutes conduction abolition by RF application was 0.9%. There was a non-significant trend to a later recurrence for right-sided APs than for left-sided APs (149 ± 375 vs 84 ± 172 sec, $P=0.07$), despite similar RF application time in the two groups (59.3 vs 62.2 sec, $P=0.37$). The recurrence risk for AP conduction recurrence after 10 minutes conduction abolition by RF application was negligible (0.4%) for left-sided APs, in contrast with right-sided APs (1.4%), especially when they had a superior or perihisian/medioseptal location (3.8%). No apparent relation was found between the AP recurrence time and the presence of previous RF applications leading to transient AP conduction abolition.

Conclusions: It appears unnecessary to prolong the waiting time beyond 10 minutes following AP conduction abolition by RF application, except if the AP has a superior or perihisian/medioseptal location.

P442 Antiarhythmic effects of intracoronary low-dose enalaprilat after direct coronary intervention for acute myocardial infarction

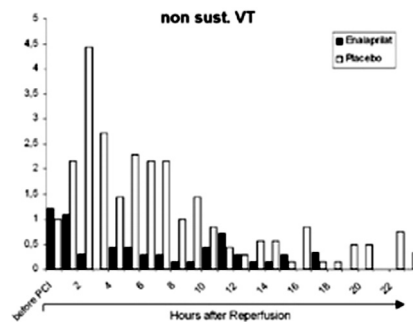


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In the era of early reperfusion therapy life-threatening ventricular arrhythmias (VA) are still frequently observed after recanalization of an occluded coronary artery. Experimental studies reported that angiotensin converting inhibitors (ACEI) sup-

press reperfusion VA, however, whether ACEI reduce reperfusion VA in the clinical setting is thus far unknown. We sought to determine the impact of low-dose intracoronary (ic.) application of enalaprilat (EN) as an adjunct to direct PCI on reperfusion VA in the acute phase of myocardial infarction (MI).

Methods and Results: Twenty-two patients with a first acute MI who underwent successful direct PCI were randomized to ic. EN (50µg) or placebo (PL), given immediately after reperfusion. VA were manually edited and counted from 24-hour-Holter-ECGs initiated on hospital admission. There were no significant differences between groups regarding clinical characteristics. Mean RR interval was not significantly different between the EN and the PL groups before and after PCI. There were also no significant differences regarding VA before PCI. After PCI the incidence of reperfusion VA was significantly lower in the EN group (VPB/hour: PL 28 ± 17 vs. EN 42 ± 21 , $p<0.01$; Couplets: EN 21 ± 17 vs. PL 96 ± 81 , $p<0.05$; Triplets: EN 21 ± 17 vs. PL 96 ± 81 , $p<0.05$; non sust. VT: EN 7 ± 3 v. 15 ± 14 , $p<0.01$).



Conclusion: Intracoronary EN, in contrast to placebo, significantly reduces the susceptibility to reperfusion associated VA. This antiarrhythmic cardioprotective effect after reperfusion has so far not been recognized and may be a major determinant for the established therapeutic benefits of ACEI therapy, beyond limitation of infarct size.

P443 Single-step atrial thrombus exclusion and cardioversion of atrial fibrillation via a transesophageal echocardiography probe



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Purpose: Transesophageal echocardiography (TEE) is routinely used for atrial thrombus exclusion prior to cardioversion (CV) of atrial fibrillation. As the TEE probe lies adjacent to the atria CV using an electrode attached to the TEE probe should allow low energy TEE-CV. We developed and evaluated a disposable cardioversion electrode sheath that can be affixed to conventional transesophageal echocardiography probes for thrombus exclusion and transesophageal CV (TEE-CV) of atrial fibrillation in one procedure.

Methods: TEE-CV electrodes with a surface area of 15.15 cm^2 were integrated into a latex or polyurethane sheath covering a conventional TEE-probe. A cutaneous patch electrode is attached to the sternum. Simultaneous echocardiographic thrombus exclusion and biphasic transesophageal cardioversion was performed in deep sedation. A step-up protocol was used to determine the atrial cardioversion threshold. Pain due to shock delivery was assessed with a visual analogous scale (0-10).

Results: TEE was performed in 27 patients (age 63 ± 10 years) for thrombus exclusion. One patient showed left atrial thrombi. TEE-CV was successful in 25 of the remaining 26 patients with a mean atrial cardioversion threshold of $63 \pm 48 \text{ J}$. The average procedure time for TEE-CV was $27 \pm 11 \text{ min}$. Pain attributable to shock delivery was little (0.3 ± 1.1 on the visual analogous scale). All patients agreed in general to undergo TEE-CV a second time if necessary.

Conclusions: Atrial thrombus exclusion and TEE-CV of atrial fibrillation via a disposable cardioversion sheath is an effective and safe alternative to external transthoracic cardioversion. It offers the opportunity to perform TEE-CV and TEE thrombus exclusion during one sedation.

P444 Incorporation of dietary N-3 polyunsaturated fatty acid supplements into erythrocytes and cardiac tissue



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Background: Substantial evidence relates an association between increased fish

oil (n-3 fatty acid) consumption and reduced risk of cardiac arrhythmia. The relationship between fish oil consumption and the level of incorporation of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into human cardiomyocytes is unknown.

Methods: 40 patients scheduled to undergo elective cardiac surgery were randomly allocated to receive fish oil (3g/day EPA + 3g/day DHA) for 7, 14 or 21 days prior to surgery or to no treatment. At baseline and immediately prior to surgery blood was drawn to assess erythrocyte fatty acid composition. At surgery atrial tissue was obtained to measure cardiomyocyte fatty acid composition.

Results: Rescheduling of surgery resulted in a continuum of treatment time from 7 to 63 days. EPA and DHA in right atrial appendage and erythrocytes increased in a curvilinear relationship with days of fish oil consumption (Figure 1) displacing mainly arachidonic acid (n-6 fatty acid). Atrial and erythrocyte n-3 fatty acids were highly correlated and regression analysis revealed approximate 1:1 relationships; EPA($r=0.97$, slope=0.92), DHA($r=0.77$, slope=0.99) and EPA+DHA($r=0.92$, slope=1.08).

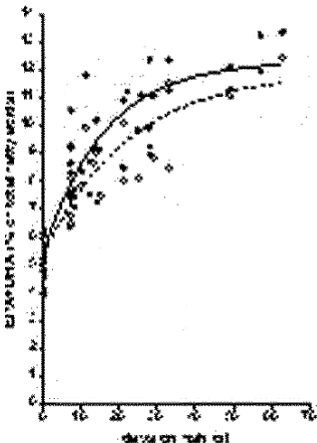


Fig. 1. %N-3 FA and time on supplement. Incorporation of EPA+DHA into atria (closed symbol and solid line) and erythrocyte (open symbol and dashed line) phospholipids for the fish oil supplemented group as a function of time on the supplement compared with the control group; atrium, $r^2=0.86$; erythrocyte, $r^2=0.86$.

Conclusion: EPA and DHA accumulate rapidly into atrial phospholipids, and exchange directly with long chain n-6 fatty acids. There is high correlation between erythrocyte and myocardial n-3 fatty acids over a wide range of values confirming the validity of erythrocyte levels of n-3 fatty acids as a suitable surrogate for cardiac myocyte n-3 fatty acid levels.

P445 Differential effect of biphasic and monophasic electrical cardioversion of atrial fibrillation on the early time course of cardiac autonomic modulation

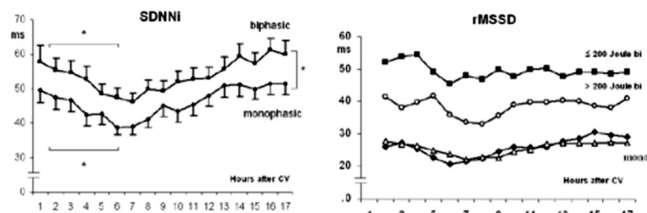


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Early recurrence of atrial fibrillation (AF) after electrical cardioversion (CV) is associated with cardiac autonomic nervous imbalance. The biphasic waveform has been shown to be superior in efficacy to the monophasic waveform in CV of AF. Whether biphasic CV has an impact on autonomic modulation after CV of AF is unclear.

Methods: We investigated 171 consecutive patients (mean age 65.4 years, 70% male, 80% structural heart disease) undergoing successful external electrical CV for AF. Biphasic CV (Bi) was performed in 82 and monophasic CV (Mo) in 89 patients. Both groups did not differ regarding age, gender, body mass index, underlying cardiovascular disease, left atrial diameter, ejection fraction, mean duration of AF, and concomitant drug therapy. Heart rate variability (HRV) was analysed from Holter ECG recordings, started directly after CV.

Results: Mean delivered total energy was significantly lower in the Bi group (Bi: 223 ± 163 Joule, Mo: 355 ± 211 Joule; $p < 0.001$). Mean RR-interval decreased within 5 hours after CV and consecutively increased within the remaining hours, without significant differences between Bi and Mo groups. The time course HRV parameters revealed biphasic profiles with the lowest levels 6 hours after CV



in both groups, however, hourly values of HRV were significantly higher in the Bi group ($p < 0.05$). Subgroup analysis within the Bi group showed significantly higher HRV values in patients after CV with energy levels lower than 200 Joule.

Conclusion: Both, waveform and delivered energy significantly influence autonomic modulation of the sinus node after successful CV of AF. Bi CV prevents an early reduction of cardiac vagal modulation, which may have an antiarrhythmic effect by reducing early electrical remodeling after CV of AF.

P446 Role of coronary angiography before radiofrequency ablation in patients presenting with paroxysmal supraventricular tachycardia



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Background: During episodes of paroxysmal supraventricular tachycardia (PSVT), electrocardiograms (ECGs) frequently show ST-segment depressions. Since many individuals also experience typical chest pain and develop elevated troponin levels, many institutions routinely perform coronary angiography (CA) prior to the ablation procedure. The aim of this study was to assess the diagnostic yield of CA in this population.

Methods: One hundred and fourteen consecutive patients undergoing radiofrequency ablation for AV-nodal reentrant tachycardia (AVNRT) or AV reentry tachycardia (AVRT) between 2000 and 2004 were reviewed. Patients were classified as to the type of PSVT, symptoms during PSVT, and cardiovascular risk factors. Maximum heart rate during PSVT, extent of ST-segment depression in 12-lead ECGs, and elevation of cardiac troponin levels were recorded. Patients with suspected coronary artery disease (CAD) were subjected to exercise testing and/or coronary angiography.

Results: Of a total of 114 patients presenting with PSVT, 35 (31%) complained of chest pain, 70 (61%) had significant ST-segment depression (>0.1 mV), and 14 (12%) had elevated troponin levels. Sixty-seven patients (59%) underwent coronary angiography. The prevalence of CAD was found to be 7% (9/114 pts) and the necessity for subsequent coronary revascularization was only 4% (5/114 pts). The amount of ST-segment depression did not differ between patients with and without CAD and showed no correlation to the heart rate ($r=0.21$, $p=0.13$). Neither the presence of chest pain, nor elevated troponin T/I levels during or after PSVT predicted the presence of a significant CAD. Only a positive exercise stress test was of predictive value.

Conclusions: Symptoms suggestive of myocardial ischemia are common in patients presenting with PSVT but have no predictive value for the presence of significant CAD. As in the general population, the pre-test probability for CAD should be assessed and non-invasive exercise testing carried out if myocardial ischemia is suspected. Although performed in many institutions, routine coronary angiography cannot be recommended in these patients prior to ablation.

ATRIAL FIBRILLATION: THROMBOEMBOLIC RISK

P447 Left atrial appendage occlusion by the transcatheter patch: experimental work and early clinical experience



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Purpose: The left atrial appendage (LAA) is the most common site of thrombus formation in patients with atrial fibrillation (AF). Left atrial appendage obliteration could prevent embolic strokes in patients unable to take adequate anticoagulation. The transcatheter patch (TP) is a balloon deliverable device, adjustable for the size and shape of the appendage with simple balloon volume changes and unable to perforate since it is wireless.

Methods: The LAA appendage was obliterated by a transcatheter patch in 12 piglets, 12-15 kg. The TP was placed in the LAA appendage through the foramen ovale using a long sheath. Single balloon/patches without retention disk were used, inflated to 10-15 mm. Preformed clot (PC) was placed on the patch in 6 animals, with the patch released in 6 hours and surgical adhesive (SA) on the apical portion of the patch in 6, with the patch released in 30 minutes. Heparin was only given in the SA group. The procedure was performed under fluoroscopy and echocardiography. Follow-up was performed in up to 3 weeks and autopsies were obtained in all animals. In 2 animals peripheral organ histology was also performed.

Five patients with AF and contra-indication to anti-coagulation had their LAA obliterated under trans-esophageal guidance and fluoroscopy. The TPs were inflated to 18-25 mm and released in 30 minutes, using SA.

Results: The LAA was effectively occluded in all animals. All TPs were safely released. Follow-up was uneventful and in autopsy the LAA was occluded without thrombus; the patch was fully endothelialized in 2 weeks. No thromboembolism or glue material was found in the peripheral organs by histology. All patients had their atrial appendage well occluded and are doing well at the lat-

est follow-up, on antiplatelet regimen only. Conclusions: Transcatheter patch LAA obliteration is effective and safe in animals. Thirty minute patch release, using SA, appears safe. Early clinical experience is encouraging and larger feasibility studies are justified.

P448(W) Antithrombotic therapy in the elderly with atrial fibrillation. A stratified analysis of a large randomized multicentre trial



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This is a stratified analysis of the NASPEAF randomised trial on antithrombotic therapy in valvular and nonvalvular atrial fibrillation (AF) patients (pts), which showed: 1) combined antiplatelet (apt) + anticoagulant (aco) was significantly better than aco alone; 2) pts with prior embolism are not sufficiently protected with aco alone (INR 2-3); 3) valvular and nonvalvular during equal therapy had similar survival curves. It is the intention of this study to compare the effect of the different antithrombotic therapies between elderly (≥ 75 y) and younger (< 75 y) pts.

Patients and methods: We compared aco (INR 2-3) vs combined therapy (triflusal 600 mg + moderate aco (mean INR 2.17)) in 924 pts stratified by the history of prior embolism and by age (215 pts ≥ 75 y, and 709 pts < 75 y). The following parameters were analysed and compared: the prevalence of risk factors for vascular events, the aco control data's, the primary events presumably related to antithrombotic therapy (fatal and non-fatal systemic embolism, stroke/TIA and myocardial infarction; sudden death and death from bleeding) and the severe bleeding events.

Results: The elderly, compared with the younger, needed significantly lower aco dose ($p < 0.001$) to maintain equal INR levels in both aco and combined arms and remained shorter proportion of time within the preset INR range due to a significant tendency to present over-range INR levels ($p < 0.01$). The elderly treated with standard aco therapy presented excessively high primary events in pts with prior embolism (rate of 11.1%/y) and the combined therapy significantly reduced the incidence of events ($p < 0.02$). The primary event and the primary event plus severe bleeding rates were significantly greater in the elderly than in the younger group (4.58 vs 2.03 and 5.98 vs 2.87, respectively). However the severe bleeding event-rate was similar showing only a tendency to be greater (2.79 vs 1.53; $p = 0.093$). Pts treated with aco tended to present intracranial fatal bleedings (9 out of 12, 6 fatal) and those treated with combined therapy gastric non fatal bleeding (11 out of 15, only 1 fatal). Gastric endoscopy showed superficial mucosal erosions in all 11 pts.

Conclusion: In conclusion, AF elderly pts during antithrombotic therapy suffer greater events-rate than the younger, but the incidence of severe bleeding was not different. Aco (INR 2-3) does not protect AF elderly pts with prior embolism and the combined apt + moderate aco therapy offers better protection in these high risk elderly pts. All pts receiving combined therapy should receive gastric protection drugs.

P449 Costs, stroke and hospitalization rates by rate controlling medications in atrial fibrillation



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Purpose: Rate control is the preferred method of management for most patients with persistent atrial fibrillation (AF). However, outcome data for patients managed with different rate-controlling medications are lacking. We aimed to compare the risk of stroke, hospitalization and health care costs among patients with AF managed with different classes of rate controlling medications.

Methods: The study consisted of a retrospective cohort of 18,197 subjects from a large health benefits company with AF who used rate-controlling medications and were continuously enrolled for a period of 12 months. We stratified all individuals into 7 mutually exclusive cohorts based upon their use rate controlling medications (digoxin, calcium channel-blocker and/or beta-blockers). Cox proportional hazard models were used to estimate the relative hazard (RH) of stroke, hospitalization and admission to extended care facilities within 12 months of AF diagnosis. Additionally, mean unadjusted total health care costs were calculated for each cohort during the 12 month follow-up.

Results: The mean age of patients was 71 ± 13 years and 46% were female. During follow-up 6779 patients were hospitalized, 2160 were admitted to extended care facilities and 2236 had a stroke. The mean unadjusted total health care costs in United States dollars (USD) for digoxin only users was 36444 ± 74988 compared to 40453 ± 76761 for beta-blockers and 37137 ± 75016 for calcium-channel blockers. The RH of hospitalization for those using digoxin alone was 0.86; 95% CI 0.80-0.94 compared to beta-blocker (0.89; 95% CI 0.85 - 0.95) and calcium channel blocker (0.89; 95% CI 0.83 - 0.97) adjusted for demographics, congestive heart failure, myocardial infarction, hypertension, diabetes, hypercholesterolemia, peripheral vascular disease and use of warfarin. The RH of stroke for those using

digoxin alone was 0.95 (95% CI 0.8 - 1.1) compared to beta-blockers (RH 1.05; 95% CI 0.95 - 1.16) and calcium channel blockers (1.06; 95% CI 0.93 - 1.20) adjusted for the same covariates. The RH of admission to extended care facilities for warfarin users was 0.88 (95% CI 0.81 - 0.96) while for rate controlling medications was non-significant.

Conclusions: All of the rate controlling medications significantly decrease the risk of hospitalization and none increase the risk of stroke. Health care costs were lower for digoxin only users compared to other rate controlling medications.

P450 Is CHADS2-score a feasible tool for predicting stroke in real life atrial fibrillation management? Results of the prospective single center registry ANTIK



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Background: The rate of stroke in atrial fibrillation depends on the presence of comorbid conditions and the use of antithrombotic therapy. CHADS2 score as a clinical classification scheme for predicting stroke in nonvalvular atrial fibrillation (AF) helps to identify patients (pts) eligible for anticoagulation. CHADS2 is an acronym for congestive heart failure, hypertension, age > 75 years, diabetes mellitus (each factor 1 point), and prior stroke or transient ischemic attack (2 points).

Objectives: To estimate the agreement in predicting the risk of stroke expected in CHADS2 compared to "real life", and to determine the implication for thromboprophylaxis in clinical practice.

Methods: In the prospective single center registry ANTIK (ANTI-Koagulations Register) 934 consecutive pts with nonvalvular AF were registered. Three groups of pts with AF were compared: low risk pts with no risk factor for stroke or death (CHADS 0), pts with moderate risk for stroke or death (CHADS 1-2) and pts with high risk for stroke or death (CHADS ≥ 3) in accordance to CHADS2 score

Results			
Patients' characteristics:	CHADS 0 (n=318)	CHADS 1-2 (n=512)	CHADS ≥ 3 (n=104)
age (years)	59.0	65.4	71.0
men (%)	71.7	74.0	70.2
structural heart disease (%)	26.4	64.8	76.0
EF $< 40\%$ (%)	0.0	14.0	22.2
LA-thrombus (%)	1.9	5.7	12.1
anticoagulation therapy at discharge (%)	64.5	77.9	86.5
Follow up (67 months median):	CHADS 0	CHADS 1-2	CHADS ≥ 3
stroke/death (%)	11.9	26.0	43.4

Conclusions: During follow up dimension of comorbid conditions in pts with AF being reflected in rising CHADS2 score was associated with significantly higher prevalence of stroke/death ($p < 0.001$). These findings are consistent with the expected stroke rate using CHADS2 score being a practicable tool for risk stratification in real life atrial fibrillation management.

P451 Effect of underlying risk of stroke on treatment effects in the ACTIVE-W Trial



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Introduction: ACTIVE-W demonstrated that oral anticoagulation (OAC) is more effective than combined treatment with clopidogrel and aspirin (C+A), at preventing cardiovascular events in patients with atrial fibrillation. However, as OAC is associated with bleeding complications, several stratification schemes have been devised to identify patients whose risk of stroke is low, in whom the benefits of OAC do not exceed its risks.

Methods: Patients in ACTIVE-W were classified using the CHADS-2 stratification scheme (1 point for history of congestive heart failure, hypertension, age > 75 years, diabetes mellitus and 2 points for history of stroke or TIA). Rates of stroke and major bleeding were calculated for each level of CHADS-2 score. The mean age of the ACTIVE-W population is 70.2 years.

Results: The risk of stroke is greater with increasing CHADS-2 score. Of patients with a CHADS-2 = 1, 76% had hypertension, 12% were > 75 years old, 8% had heart failure and 3% had diabetes mellitus. OAC reduced their absolute rate of stroke by 0.87/100 patient-years. Patients with a prior stroke or TIA had a high

Stroke Risk: C+A vs. OAC			
CHADS-2 Score	Stroke Rate C+A (/100 pt-years)	Stroke Rate OAC (/100 pt-years)	RR of Stroke C+A vs. OAC
1 (N=2431)	1.3	0.4	3.25, (95% CI 1.31-8.11) $p = 0.01$
2 (N=2290)	1.9	1.8	1.08, (95% CI 0.63-1.85) $p = 0.77$
3 (N=1106)	2.8	1.7	1.62, (95% CI 0.79-3.34) $p = 0.18$
4 (N=487)	6.8	3.3	2.07, (95% CI 0.97-4.42) $p = 0.06$
5 (N=183)	11.7	2.7	7.27, (95% CI 1.63-32.4) $p = 0.009$
1 ⁰ prevention	2.6	1.2	2.16, (95% CI 1.31-2.72) $p = < 0.001$
2 ⁰ prevention	6.2	4.1	1.53, (95% CI 0.71-2.71) $p = 0.20$

C+A: Clopidogrel plus ASA; OAC: Oral Anticoagulation

rate of stroke (6.16/100 patient-years), and derived a large absolute benefit from OAC (2.07 strokes prevented 100 patient-years). In primary prevention the risk of stroke was lower (2.61/100 patient-year) and the absolute reduction in stroke with OAC was 1.38/100 patient-year. The risks of major bleeding with OAC and C+A were similar and were not significantly affected by CHADS-2 score or history of prior stroke.

Conclusions: In patients with AF without prior stroke and only a single risk factor (CHADS-2 = 1), the risk of stroke on C+A is low. However on OAC, the rate of stroke is 0.87 events per year lower.

P452 Does mitral regurgitation prevent from atrial thrombus formation? A TEE-study in 261 consecutive patients



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Atrial fibrillation (AF) represents a major risk factor for the development of atrial thrombi, which can be detected by transesophageal echocardiography (TEE). This study investigated the influence of various echocardiographic parameters, especially the presence of mitral regurgitation, assessed during transthoracic echocardiography (TTE) and TEE on thrombus formation.

Methods: TTE and TEE were performed in 261 consecutive patients (57.8% male, 67.5±12 years) with AF, who were planned to undergo electrical cardioversion (CV). The following parameters were included into the dataset: left atrial diameter (LA), presence and severity of mitral regurgitation (MI) or stenosis (MS), left ventricular end-systolic and end-diastolic diameter (LVes; LVed), fractional shortening (FS), diastolic LV function (LVdiast), presence of spontaneous echocontrast during TEE (SEC) and flow velocity in the left atrial appendage (LAA-flow). All variables were screened using a Chi-Square test before entering into a multivariate regression model computed with the SPSS 12.0 software.

Results: A thrombus was detected in 30 patients (11.5%) in the LA or LAA. Out of these patients, 96.3% vs. 44.9% of patients without thrombus showed SEC ($p < 0.001$) and 72.0% vs. 16.0% revealed a reduced LAA-Flow ($< 0.3 \text{ m/s}$). Moreover, thrombus formation was significantly associated with higher patient age (70.2 vs. 67.1 years, $p = 0.021$), larger LA (50.2 vs. 46.3 mm) and lower FS (26.6 vs. 30.7%, $p = 0.027$). No significant influence was found for MI irrespective of its severity ($p = 0.67$), MS ($n = 3$, $p = 0.49$), LVed ($p = 0.098$) and LVdiast ($p = 0.823$). Regression analysis calculated the greatest influence on thrombus formation for LAA-flow ($\beta = 0.322$), followed by FS ($\beta = 0.205$) and SEC ($\beta = 0.155$).

Conclusion: In contrast to the results of other studies, no significant impact of MI on atrial thrombus formation was found in this patient group. Even the presence of a moderate or severe MI does not relativize the indication for a TEE in patients considered for CV.

P453 The relationship between atrial fibrillation, neurocognitive deficits and depression



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Background: This study investigated whether the presence of atrial fibrillation (AF) in elderly subjects is accompanied by neurocognitive deficits and depression. In addition the relationship between duration of AF, hs-CRP-values and neurocognitive performance were examined. The current data are part of an ongoing pilot study that investigates the effect of aggressive cholesterol lowering by atorvastatin (40 mg) in combination with ezetimibe (10 mg) on the incidence of white matter lesions in cerebrum and neurocognitive decline.

Methods: 40 elderly subjects with AF (chronic and paroxysmal) were examined by means of an extended neuropsychological battery and the Montgomery-Asberg Depression Rating Scale (MADRS). These neuropsychological end depression data were compared to available norms. In addition MRI scans were made for 33 subjects.

Results: AF-patients performed significantly worse as opposed to available norms. Striking cognitive deficits were found in speed of information processing. Cognitive deficits were also found in visuospatial skills, and executive functioning. No deficits were found in semantic memory, attention and concentration. MRI scans showed the most prominent white matter lesions in subcortical areas (91% $< 1 \text{ mm}$, 38% $< 5 \text{ mm}$, 25% $> 5 \text{ mm}$), which is in line with the pattern of cognitive decline. There was a significant correlation between the duration of illness and neuropsychological test outcome (Spearman's $\rho = .395$, $p = .031$). Duration of illness was significantly lower for subjects with low hs-CRP (10 mg/l): $F(1,32) = 6.708$, $p = .014$. There was no significant correlation between hs-CRP and neurocognitive performance. Most subjects (28) showed no signs of depression, 11 subjects showed signs of mild and 1 of moderate depression.

Conclusions: AF-patients showed white matter lesions and cognitive deficits indicative of subcortical damage. The duration of AF correlated inversely with cognitive performance, but showed no relation to depressive symptoms.

P454 Does everybody with CHADS2-score 3 or higher and sufficient anticoagulation need a transesophageal echocardiography? Results of the prospective single center registry ANTIC



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Background: CHADS2 score as a clinical classification scheme for predicting stroke in nonvalvular atrial fibrillation (AF) helps to identify patients (pts) eligible for anticoagulation. CHADS2 is an acronym for congestive heart failure, hypertension, age > 75 years, diabetes mellitus, and prior stroke or transient ischemic attack.

Objectives: The presence of thrombus formation in the left atrium (LA) has been associated with a higher risk of thromboembolism and cerebrovascular accidents in pts with AF. Little is known about association between aortic atherosclerotic plaques and future cerebrovascular events in pts with AF. The purpose of this study was to define the prevalence and location of transesophageal echocardiographic predictors of thromboembolism for pts with nonvalvular AF in accordance to CHADS2-score as well as diagnostic implications.

Methods: In the prospective single center registry ANTIC (ANTIKoagulations Register) 541 consecutive pts with nonvalvular AF undergoing transesophageal echocardiography (TEE) were registered. Three groups of pts with AF were compared: low risk pts with no risk factor for stroke or death (CHADS 0), pts with moderate risk for stroke or death (CHADS 1-2) and pts with high risk for stroke or death (CHADS ≥ 3) in accordance to CHADS2 score

Results:

Patients' characteristics	CHADS 0 (n=159)	CHADS 1-2 (n=316)	CHADS ≥ 3 (n=66)
age (years)	60.1	65.1	71.4
men (%)	75.5	74.4	69.7
structural heart disease (%)	27.0	66.1	75.8
anticoagulation at time of TEE (%)	81.8	82.1	83.5
LA-thrombus (%)	1.9	5.7	12.1
aortic atherosclerotic plaques (%)	11.9	24.7	30.3

Conclusions: Prevalence of thrombus formation in LA as well as prevalence of aortic atherosclerotic plaques as surrogate parameter for future thromboembolic risk significantly increased with rising CHADS2-score. There was a two fold increase of thrombus formation in LA between CHADS 1-2 and CHADS ≥ 3 , nearly one third of pts with CHADS ≥ 3 showed aortic atherosclerotic plaques. Therefore especially pts with CHADS ≥ 3 should have TEE-guided cardioversion for risk stratification of thromboembolic events.

P455 Type of atrial fibrillation, concomitant diseases and stroke risk factors: chronification of atrial fibrillation is related to accumulation of stroke risk factors



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Incidence, prognosis, and complications of atrial fibrillation importantly depend on various risk factors and concomitant diseases, modification of which may provide an opportunity to alter the course of the disease. The central patient registry of the German Competence Network on Atrial Fibrillation has collected an extensive database on clinical parameters of patients with atrial fibrillation (AF) to address these issues.

Results: We performed an interim analysis based on 4372 validated data sets to assess the prevalence of risk factors and concomitant diseases and their relation to the type of atrial fibrillation (first episode, paroxysmal, persistent, permanent). By far the most prevalent concomitant disease was arterial hypertension (69.5%), followed by smoking (44.5%), hyperlipidemia (40.3%), heart failure (35.2%), diabetes (22.3%), coronary artery disease (20.8%), and BMI > 30 (20.4%). Interestingly, a family history of atrial fibrillation was present in 10% of the patients, while excessive consumption of alcoholic beverages or excessive coffee intake were reported only occasionally (6.8% and 2.2%, respectively). Of these patients, 11.1% presented with a first episode, 30.4% as paroxysmal, 19.4% as persistent, and 34.0% as permanent atrial fibrillation. However, chronification of atrial fibrillation was strongly related to the number of stroke risk factors present. While only 19.1% of patients without risk factors for stroke were in permanent atrial fibrillation, the fraction of patients in permanent atrial fibrillation increased to 59.0% in patients with 5 or more stroke risk factors. The increase in permanent atrial fibrillation with accumulation of stroke risk factors was exclusively at the cost of paroxysmal atrial fibrillation, as the fraction of patients classified as persistent atrial fibrillation remained essentially constant (range: 16.8% - 22.7%) indicating that classification of atrial fibrillation as persistent or permanent by the physician did not influence

this relation. This suggests an intrinsic connection between stroke risk factors and factors promoting permanent atrial fibrillation.

Conclusion A close correlation exists between transition from paroxysmal to permanent atrial fibrillation and accumulation of stroke risk factors, prevention of which appears essential to avoid chronification of paroxysmal atrial fibrillation.

P456 Risk of bleeding in very old Atrial Fibrillation patients on warfarin: relationship with ageing and CHADS2 score



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In atrial fibrillation (AF) patients, age ≥ 75 years is one of the major risk factors for stroke. However, it is not clear if an upper limit for the indication to OAT exists. For this reason, we performed a prospective study on 290 AF patients on OAT aged ≥ 75 years (median age 82 years, total follow-up period 814 pt-yrs) followed by our Anticoagulation Clinic. Seventeen major bleeding events were recorded (rate 2.1 x100 pt/yrs), 11 of which cerebral (1.35 x100 pt/yrs). The occurrence of major bleedings was associated with history of previous TIA or stroke [OR 3.4 (1.1-12.5), $p=0.01$] and with diabetes [4.4 (1.3-14.7) $p=0.01$]. We found a trend to a progressive increase in the rate of bleeding risk with the increase of the CHADS2 score: patients with score 4-6 showed a rate of 3.4 x100 pt/yrs with respect to 1.5 x100 pt/yrs of patients with lower score. Number Needed to Harm (NNH) was calculated for the classes of CHADS2 score and age and compared with Number Needed to Treat (NNT) obtained from a metaanalysis of clinical trials (Lip 2005). For CHADS2 score 1 and 2-3, NNHs were 51 and 68 without significant changes across the different classes of age (75-79, 80-84, >85 years). The corresponding NNTs were 58 and 32. For CHADS2 score 4-6, NNH was 29 (vs NNT of 16), but its values varied among the 3 groups of ages reaching a value of 10 in patients ≥ 85 years. Our data suggest: 1) in patients with CHADS2=1 the indication of OAT is questionable, 2) in patients >85 years with CHADS2 4-6 both NNHs and NNTs are quite low and the use of OAT should be highly individualised. In all the other patients the balance is in favour of OAT.

P457 Cardiac magnetic resonance correlations of left atrial appendage peak emptying velocities determined by transesophageal echocardiography

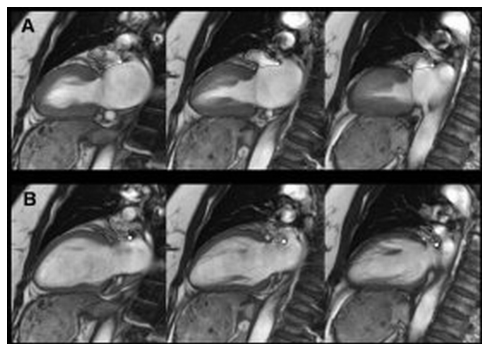


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Background: Left atrial appendage (LAA) emptying velocities (LAAv) are an important predictor for cerebral embolism in patients with atrial fibrillation (AF). Transesophageal echocardiography (TEE) is able to determine this risk factor accurately. Aims of our study were to assess LAA volumes and ejection fraction with cardiac magnetic resonance imaging (CMR) and to correlate with LAAv as quantified by TEE.

Methods: Consecutive patients with AF scheduled for TEE prior to cardioversion were included to the study. Patients with sinus rhythm and other TEE indication served as controls. All patients were scanned in a 1.5-T whole body scanner. Contiguous functional images covering the entire LAA in long axis orientations were performed (figure). LAA minimal and maximal volumes were calculated and LAA ejection fraction quantified and correlated to LAAv as determined by TEE.

Results: 32 patients (21 with AF and 11 with sinus rhythm) were included to the study. Patients with AF had a significantly larger LAA (12.8 ± 4.6 ml vs. 5.9 ± 2.5 ml, $p<0.0001$) and lower LAAv (0.3 ± 0.2 m/s vs. 0.7 ± 0.1 m/s, $p<0.0001$) compared to patients with sinus rhythm. LAAv highly correlated with LAA ejection fraction as determined by CMR in all patients ($r=0.95$, CI 0.90-0.98, $p<0.0001$). Mean LAA ejection fraction in patients with reduced LAAv (≤ 0.2 m/s) was $8.4 \pm 1.7\%$.



Conclusion: CMR is able to determine LAA ejection fraction with a high correlation to LAAv. Reduced LAA ejection fraction ($\leq 10\%$) as seen by CMR matches

with reduced LAAv (≤ 0.2 m/s) indicating an increased embolic risk in patients with AF. Thus, CMR can possibly act as a non-invasive tool to detect patients with increased embolic risk.

P458 Anticoagulation of patients with atrial fibrillation in cardiology clinics in Spain: the FAMA study



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Purpose: Primary objectives of the FAMA study included an evaluation of anticoagulation management of atrial fibrillation (AF) in cardiology out-patient clinics in Spain and hence definition of compliance levels with the Spanish Cardiology Society (SEC) treatment recommendations (grade A class I).

Methods: In this cross-sectional multicentre study, treatment decisions were made based on the history of all cases of AF detected in a sample of 50 consecutive patients over 18 years of age attending the out-patient clinic of 117 Spanish cardiologists nationwide. Information was obtained on demographic data, risk factors for systemic embolism, any prior treatment with antithrombotic agents, current INR control and contraindications to anticoagulation. The clinical judgement of the investigator was recorded for each case regarding the indication to anticoagulation and compared to the aforementioned guidelines (grade A class I; anticoagulation indicated for rheumatic AF, non-rheumatic AF with one or more risk factors for systemic embolism or previous stroke/TIA).

Results: Data were available from a total of 1173 patients with AF, 41.7% having 1-2 risk factors for embolism, 58.2% having 3-4 and 0.2% with more than 4. The proportion of patients receiving anticoagulation which was indicated as per SEC recommendations was 75%. The most common contraindications to effective anticoagulation were high risk of haemorrhage (9%), suspected poor compliance (7%), poor access to adequate medical care (3%) and poor control of INR (2%). Those receiving non-indicated anticoagulation numbered 2%. Concomitant anti-platelet medication was prescribed to 10% of anticoagulated patients. The proportion of patients whose most recent INR was outside the therapeutic range (2-3) was 21% with 11% of physicians incorrectly considering this to be good control.

Conclusions: The FAMA study reveals some underuse of anticoagulation compared to SEC recommendations in the Spanish AF population. Contraindications to effective anticoagulation were principally either haemorrhage risk or specific to the drawbacks of vitamin-K antagonists. Therapeutic INR control remains difficult to achieve in all patients.

P459 Metabolic syndrome as a predictor of atrial fibrillation and the impact on stroke



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Purpose: Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is associated with an increase risk for stroke and mortality. Recently, obesity, hypertension and diabetes were found to be predictors for the development of AF. We evaluated the association of components of the metabolic syndrome (MS) with presence of AF and the risk for stroke.

Methods: Using claims data from a large health benefits company we identified 391,134 subjects with at least one risk factor for coronary artery disease (CAD): hypertension, obesity, diabetes, and lipid abnormalities. MS equivalent was defined based on the presence of three or more of these CAD risk factors. We defined stroke using the corresponding ICD-9 code. Within this population we identified individuals with AF to determine the cross-sectional probability of having AF using logistic regression. Then in a retrospective cohort study of those with AF we evaluated the predictive value of MS to identify those that developed stroke using cox proportional hazard models. We also calculated the CHADS2 score (an acronym for congestive heart failure, hypertension, age >75 , diabetes, and stroke) and compared it with the MS for stroke prediction.

Results: We identified 15,782 individuals with AF with a mean age of 71 ± 12.6 years. The odds ratio of having AF in those with four MS components compared to those with one was 1.4; (95% CI 1.2 - 1.6), after adjusting for demographics, mitral disease, congestive heart failure and CAD. After a mean follow-up of 331 ± 155 days, 383 stroke cases were identified. The hazard ratio (HR) for stroke was 1.6; (95% CI 1.3- 2.0) in subjects with MS compared to those without MS, after adjusting for the same covariates, while the HR in those with moderate risk based on the CHADS2 score was 40; (95% CI 10 -163) compared to those with low risk.

Conclusions: Patients with MS are at higher risk for AF and stroke. The CHADS2 score is a better predictor for stroke than the addition of individual components of the MS. Whether the modification of MS risk factors reduces the rate of AF and stroke awaits further study.

P460 Atrial Fibrillation and mild cognitive impairment: what correlation?



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Background: Atrial Fibrillation (AF) is the most common cardiac arrhythmia and its prevalence increases with age. AF increases the risk of stroke or TIA due to macro-embolism. Moreover it may produce multiple cerebral ischemic areas due to micro-embolic phenomena and episodic hypoperfusion, eventually leading to a progressive cognitive impairment and even to acclaimed vascular dementia during the years.

Purpose of our study was to evaluate the prevalence of cognitive impairment in patients with AF for a two years period. The presented results concern data obtained at the moment of recruitment.

Method: we studied 42 patients with a history of non valvular AF and 40 sex and age matched controls with sinus rhythm. All subjects underwent careful anamnesis, physical examination, biochemistry tests and instrumental tests (EKG, echocardiogram and echo-Doppler duplex scanning of the epi-aortic trunks). Inclusion criteria were: age between 60 and 80 years, EF $\geq$ 45%, negative history of previous cerebrovascular diseases and a normal ecocolor Doppler duplex scanning of the epi-aortic trunks. Moreover to investigate the cognitive status all subjects underwent the following neuropsychological rating scales: Mini Mental State Examination (MMSE), Clinical Dementia Rating Scale (CDR), Global Deterioration Scale, Geriatric Depression Scale (GDS), Hachinski Ischemic Score (HIS). Patients with a diagnosis of dementia or with a score $<$ 18 at MMSE, $>$ 1 at CDR and $>$ 2 at GDS were excluded.

Results: patients with AF had a worse scores at Global Deterioration Scale (Global Deterioration Scale =2, 57.2% vs 47.5%, $p=0.0001$), HIS (1.4 ± 1.77 vs 0.30 ± 1.18 , $p=0.001$), CDR (0.13 ± 0.25 vs 0.05 ± 0.15 ; $p=0.07$), GDS (4.21 ± 3.65 vs 2.85 ± 3.26 ; $p=0.07$) vs controls; no significant differences were found for MMSE even after correction for age and education (28.48 ± 1.88 vs 28.43 ± 1.88 , $p > 0.05$). Among patients with AF those treated with warfarin as compared with those on ASA treatment, showed best scores at CDR (0.03 ± 0.1 , vs 0.3 ± 0.3 , $p=0.04$), Global Deterioration Scale (Global Deterioration Scale =2, 37.5% vs 80%) and GDS (2.4 ± 2.6 vs 6 ± 4.3 , $p=0.03$). Correct MMSE scores didn't differ.

Conclusion: Data from our preliminary study showed more frequent complaint of cognitive impairment in AF subjects, as detected by Global Deterioration Scale, CDR, HIS, especially in patients not under anticoagulation therapy and in paroxysmal, persistent or recurrent AF subjects vs permanent AF patients, probably due to micro-embolism phenomena. Further investigations and a re-evaluation after one and two years period are needed.

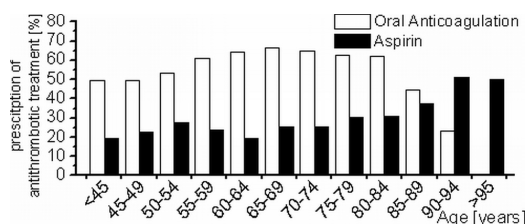
P461 Use of antithrombotic treatment in daily medical practice in patients with atrial fibrillation: data from the central patient registry of the German Competence Network on Atrial Fibrillation



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Even though oral anticoagulation is known to be highly effective in preventing embolic events in patients with atrial fibrillation (AF), reports from only a few years ago indicate that this treatment is still significantly underused in daily medical practice. Patients of the central patient registry of the German Competence Network on Atrial Fibrillation were recruited from all levels of medical care ranging from general practitioners to university hospitals to allow assessment of utilisation of antithrombotic treatment in daily medical practice.

Results Antithrombotic treatment was assessed on discharge at the time of inclusion of the patient in the registry. Patients with contraindications for anticoagulation (malignancy, previous significant bleeding) were excluded from analysis (9.8%). Overall prescription of oral anticoagulation was influenced by type of AF (first episode, paroxysmal, persistent, or permanent), with the highest anticoagulation rate present in persistent (76.3%) and permanent AF (69.3%), and lower rates for first episodes (42.9%) and paroxysmal AF (53.1%). Aspirin appeared to be used in a complementary fashion, with high rates for first episodes (37.5%) and paroxysmal AF (30.7%; persistent AF: 18.7%; permanent AF: 24.3%). Use



Graph-3c.GIF

of oral anticoagulation declined sharply in patients older than 85 years, where aspirin was increasingly used as antithrombotic treatment (Figure).

Conclusion Overall rate of antithrombotic treatment in patients with AF in this registry appears very similar to results from the Euro Heart Survey. The sharp decline of oral anticoagulation at ages older than 85 years is likely driven by individual decisions. A more detailed analysis will provide insight on the influence of the level of medical care on antithrombotic treatment.

P462 Predictors of out-of-range INR for patients with atrial fibrillation on oral anticoagulation: results from ACTIVE



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Purpose: Oral anticoagulation (OAC) has a narrow therapeutic window. Understanding factors which predict good INR control will optimize outcomes.

Methods: ACTIVE compared clopidogrel plus aspirin vs. OAC in preventing vascular events in high risk atrial fibrillation patients in 31 countries. We analyzed 2,832 patients on OAC with $\geq$ 4 INRs performed between 3-12 months of randomization who did not have a primary event. A multi-variate regression model was created to define predictors of an out-of-range INR ($<$ 1.8, $>$ 3.2) for each patient.

Results: 17.2% of patients had all INRs in range during the 9 month study period. Country of origin, but not ethnicity, was a powerful predictor of an out-of-range INR. Other positive predictors included the number of INRs, female gender, diabetes, and heart failure. Negative predictors (more likely in range) were prior warfarin use (3.15 times more likely to be in range) and low BMI.

Predictors of Out of Range INR

Predictor	Predictive Power	SE	95% CI	Type III SS	P-Value
Number of INR Values	0.58	0.083	(0.41, 0.74)	17,180.05	<0.0001
Female	2.13	0.89	(0.39, 3.88)	1,998.61	0.017
Age	-0.049	0.047	(-0.14, 0.044)	368.75	0.30
BMI	-0.22	0.076	(-0.37, -0.067)	2,808.30	0.0045
Creatinine $>$ 133 μ mol/L	-0.25	1.46	(-3.11, 2.60)	10.59	0.86
Heart Failure	1.86	0.88	(0.14, 3.58)	1,565.23	0.034
Diabetes	2.94	0.97	(1.04, 4.84)	3,199.52	0.0024
Cancer	-0.83	1.38	(-3.54, 1.87)	127.19	0.55
Aspirin use	-2.05	1.07	(-4.14, 0.047)	1,277.50	0.055
Alcohol	0.49	0.92	(-1.31, 2.29)	97.76	0.60
Prior warfarin use	-3.15	1.17	(-5.44, -0.86)	2,527.05	0.0071
Ethnicity	-	-	-	4,388.93	0.18
Country	-	-	-	92,016.23	<0.0001

Conclusions: Prior OAC use and country of origin are strong predictors of INR control. These data suggest that patient selection based on prior OAC experience and local OAC practice patterns predict INR control.

P463(W) Trend in risk of stroke in patients with a hospital diagnosis of nonvalvular atrial fibrillation: national cohort study in Denmark, 1980-2002



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Aim - We examined trend in incidence of stroke of any nature (ischemic and/or haemorrhagic) in subjects with a hospital diagnosis of nonvalvular atrial fibrillation or flutter in Denmark from 1980 to 2002 by sex, age and conditions of comorbidity.

Methods - We identified all individuals, aged 40-89 years, with an incident hospital diagnosis of atrial fibrillation or flutter and no history of stroke or heart valve disease in the Danish National Registry of Patients, and subjects were followed in the Danish National Registry of Patients for occurrence of an incident diagnosis of stroke of any nature (ischemic and/or hemorrhagic) and in the Danish Civil Registration System (emigration and vital status). We used multivariate Cox proportional hazard regression analysis to estimate trend in incidence of stroke.

Results - Nonvalvular atrial fibrillation or flutter was diagnosed in 141 493 subjects (75 126 men and 66 367 women), and during follow-up 15 964 subjects had an incident diagnosis of stroke. The hazard ratios for stroke in the last three-year period compared to the first five-year period, adjusted for 10-year age group, conditions of comorbidity, and general stroke trend in the Danish population were 0.78 (95% confidence interval 0.70-0.86) in men, and 0.80 (95% confidence interval 0.72-0.88) in women. The reduction in risk of stroke by calendar year was most prominent in patients aged 40-74 years.

Conclusion - We observed a modest decrease in risk of stroke in subject with atrial fibrillation in Denmark during calendar years 1980 to 2002. However, we could not control for any changes in diagnostic performance, admission practice, and medical management of patients with atrial fibrillation.

P464 Predicting embolic events in nonvalvular atrial fibrillation patients: validation of the CHADS2 index in a mediterranean population



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Background: Patients who have nonvalvular atrial fibrillation (NVAf) have an increased risk of embolic events, but the absolute rate depends on age and comorbid conditions. Recently, a new index for predicting embolic events in this setting has been developed, the CHADS2 score, that is formed by assigning 1 point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and by assigning 2 points for history of stroke or transient ischemic attack (TIA). This score has been validated in the National Registry of Atrial Fibrillation, in the United States, but it has not been assessed in a mediterranean population.

Method: Since 1.2.2000 to 1.2.2002, 624 consecutive patients with NVAf were managed in a general outpatient cardiology clinic at an university hospital in the south of Spain, according to a prospective protocol based in scientific societies recommendations, and prospectively followed for embolic events (stroke, transient ischemic attack or peripheral embolism). CHADS2 score was evaluated in those patients who did not receive anticoagulation.

Results: 199 patients (32%) were not anticoagulated, 88 (44%) for contraindications, 84 (42%) for perceived low risk and 27 (14%) for negative of the patient. Mean age was 75±9 years, 41% being male. 12% presented congestive heart failure, 53% hypertension, 58% age of 75 years or older, 15% diabetes mellitus, and 5% previous stroke or TIA. CHADS2 index was 0 in 46 patients (23%), 1 in 56 patients (28%), 2 in 66 patients (33%), 3 in 19 patients (10%) and 4 or more in 12 patients (6%). After a mean follow-up of 21±14 months, with 13 patients lost (6.5%), embolic events rate (per 100 patient-years) for CHADS2 index 0 to 4 or more was 5.19%, 5.95%, 4.46%, 12.70% and 14.29%, respectively (p=0.06). Patients with a CHADS2 score 0-2 presented an embolic rate of 5.19% versus 13.33% for those with a higher score (p=0.023). Excluding transient ischemic attacks, embolic events rate for CHADS2 index 0, 1, 2 or 3 or more was 0%, 3.6%, 3.6% and 7.6% respectively (p=0.002).

Conclusion: CHADS2 score is valid for qualifying risk of embolic events in a mediterranean population of nonvalvular atrial fibrillation patients.

P465 Abnormal platelet adhesion in atrial fibrillation



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Purpose: It remains unclear to what extent platelet activation in non-valvular atrial fibrillation (AF) is due to the underlying cardiovascular diseases in AF. To further investigate the role of platelets in AF patients we assessed platelet adhesion (to fibrinogen) and compared this to both 'healthy controls' and 'disease controls' (patients with hypertension, coronary artery disease, diabetes or stroke but in sinus rhythm).

Methods: Platelet rich plasma obtained from patients and controls was resuspended to 2x10⁸ cells/ml and 100 µl incubated for 1 hour in microtitre plates pre-coated with fibrinogen (5 ng/ml). The supernatant was aspirated, lysed with Triton X-100 and stored at -70°C as supernatant platelet lysate (SPL). After saline wash, bound platelets were lysed with Triton and the lysate stored at -70°C as bound platelet lysate (BPL). Soluble P selectin levels in the SPL and BPL were used to calculate the percentage of platelets adhering to fibrinogen.

Results: AF patients on no anti-thrombotic treatment [N=20] had modestly increased platelet adhesion than 'healthy controls' [N=57] (p=0.044). Initiating treatment with both aspirin and warfarin resulted in significant reduction in platelet adhesion in AF patients [p=0.014 and 0.019 respectively]; so that AF patients on optimal anti-thrombotic therapy [N=98] had no significant difference in platelet adhesion compared to 'healthy controls' [N=57] and 'disease controls' [N=66] controls (p = 0.312). There was no significant difference in platelet adhesion between paroxysmal [N=49] and permanent [N=49] AF (p = 0.618); and those taking aspirin or warfarin (p=0.198). Amongst the clinical parameters that contribute to increased stroke risk in AF, platelet adhesion correlated significantly only with age (Spearman r = 0.215, p = 0.034).

Platelet adhesion in treated AF

	Healthy controls (57)	Disease controls (66)	AF patients (98)	p value
% of platelets bound to fibrinogen	13.33 (5.53-17.23)	9.65 (5.81-16.67)	12.50 (6.59-21.57)	0.312

Data displayed as median (inter-quartile range); analysed by Kruskal-Wallis test

Conclusion: There is significant, albeit weak, excess of platelet adhesion in AF patients on no anti-thrombotic therapy compared to 'healthy controls'. In AF patients on optimal antithrombotic therapy, platelet adhesion is not significantly different compared to controls. Abnormal platelet adhesion may have a small contribution to the pro-thrombotic state in AF.

ATRIAL FIBRILLATION: CATHETER ABLATION

P466 Recurrence patterns of atrial fibrillation after pulmonary veins cryoablation

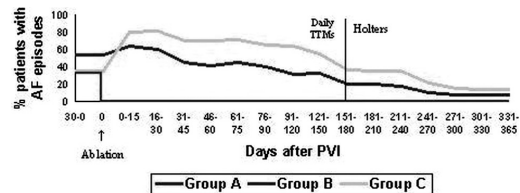


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Background: Early recurrence of paroxysmal atrial fibrillation (PAF) post PVI (pulmonary vein isolation) is a recognized phenomenon. Our study evaluated the clinical characteristics and patterns of AF recurrence up to one year following PVI.

Methods: Patients with PAF selected to undergo PV Cryoablation were recruited from 2001 to 2005. Daily recordings with transtelephonic telemetry were obtained 30 days prior and up to 180 days after the procedure. After this period, Holter monitoring was used in each clinic visit or if symptoms developed.

Results: 60 patients (45 men; mean age 53 y (21 to 68)) were enrolled. We found 3 different patterns of recurrences after PVI: (Table) Group A - 26 pts with no further evidence of AF. Group B - 20 pts with a significant decrease of AF episodes (but not complete elimination). Group C - 14 pts with an increase in AF episodes compared to pre ablation telemetry. Age, gender, duration of AF, LA size, presence of left ventricular hypertrophy, LVEF and number of PVs treated were similar in the 3 groups (p > 0.5). Group A had a significant increase in baseline heart rate post PVI (>25%) compared to the others (p<0.02). History of prior Atrial Flutter was more common in Group C patients (A=30%, B=20%, C=63%, p<0.01).



Conclusions: In the early months and up to one year following PV cryoablation, three different patterns of AF recurrence can be found: A) patients with no further episodes, B) patients with decreased number of episodes (this decline starts 3 months after PVI and levels at 9 months) or C) patients with an immediate increase in the number of events (that decline throughout one year). History of Atrial Flutter is present significantly more in Group C. Augmentation of baseline heart rate > 25% is a marker for complete freedom of events.

P467 Pulmonary scintigraphy has to be preferred to repeated CT scan for detection of pulmonary vein stenosis after ablation for Atrial Fibrillation



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Background: Pulmonary vein stenosis is a potential complication of radiofrequency ablation of AF. Follow-up with repeated CT-scan is of concern because of excessive irradiation for the patient (10-15 mSv per exam). Perfusion scintigraphy (2-4 mSv per exam) could reasonably replace CT-scan for screening.

Objective: To analyse the predictive value of pulmonary perfusion compared to CT-scan in diagnosing pulmonary vein stenosis (PVS).

Methods: We performed a 64 multi-detector spiral CT-scan (Siemens Sensation 64), a pulmonary perfusion scintigraphy (Tc-99m) and if needed a ventilation scintigraphy (Kr 81m) in 86 consecutive patients before and ± 3 months after AF ablation. We analysed the predictive value of abnormal perfusion scintigraphy (PS) and the presence of anatomically significant stenosis detected by spiral CT-scan, defined as a reduction of more than 50% and 70% in diameter.

Results: Fifty patients (58%) had a normal PS; only one of those patients had a significant stenosis on CT-scan: negative predictive value (NPV) = 98% (CI 95%, 84-100); thirty six patients (42%) had an abnormal PS, associated with an abnormal pulmonary ventilation scintigraphy (VS) in only seven patients; thus 29/36 patients (80%) had a normal VS associated with an abnormal PS, twenty out of them with a negative CT-scan: positive predictive value (PPV: 31%) (CI = 31, 15-57).

Conclusion: PS performed after pulmonary vein isolation has a high NPV when validated by CT-scan; it avoids in ±58% of patients repetitive high dose irradiation. However the PPV is very low. Additional ventilation scintigraphy only improves weakly the predictive value. In these patients, CT-scan is mandatory in order to exclude false positive results. Correspondingly, we recommend to perform systematically a PS rather than a CT scan for follow-up after PV ablation, with an additional CT-scan if found abnormal.

P468 Impact of different esophagus visualization techniques on results of catheter ablation of atrial fibrillation

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Background: Atrio-esophageal fistula is a rare but potentially lethal complication of catheter ablation of atrial fibrillation (AF). Strategies to minimize the risk of occurrence of this complication are being conducted by several EP labs. The visualization of esophagus during procedure allowing to avoid radiofrequency (RF) thermal injury over esophagus could be effective to minimize this risk. Although we do not know what would be the impact of this conduct on the result of the procedure.

Purpose: Evaluate if different techniques of esophagus visualization during ablation could have any impact on number of isolated veins after ablation and AF recurrence on follow-up.

Methods: Circumferential catheter ablation of AF using 8mm tip catheter procedures between February 2003 and July 2005 were analyzed. All procedures in our laboratory until the appearance of atrio-esophageal fistula were performed with no esophageal visualization. After this complication (January 2004) an esophagography was performed during the procedure and in the year of 2005 a thermistor was placed in esophagus to indicate esophageal position and luminal temperature during RF application. When esophagus was close to pulmonary vein, no RF was applied or power was titrated (initially 20W) according to esophageal temperature (Max Temp 38°C). Patients were followed by clinical contact on clinics or by telephone and an ECG was performed if symptoms or by chance. Fisher Exact t-test, Kaplan-Meier analysis and Mantel-Cox tests were used for statistic.

Results: A total of 151 procedures were performed, 62(41.06%) were performed without esophageal visualization, 58(38.41%) with contrasted esophagus and 31(20.52%) with esophageal thermistor. The use of contrasted esophagus decreased the number of procedures with all 4 veins isolated (34.38%) compared with no esophageal visualization (64.52%) and with esophageal thermistor (58.06%) ($P=0.001$ and 0.032 respectively). Follow-up time was 11.0 ± 4.92 . Late recurrence was observed in 26.6% of patients with no esophageal visualization and 36.4% with contrasted esophagus ($P=0.06$). Esophageal thermistor group had 28.5% of recurrence ($P=0.36$ to no esophageal visualization).

Conclusion: Exclusive real-time esophageal visualization decreased the number of all 4 pulmonary veins isolation and additional esophageal temperature monitoring increased the number of veins isolated. There was a trend to more recurrence of AF if contrast in esophagus is used.

P469(W) Pulmonary vein potential recordings using a circumferential catheter in patients with and without atrial fibrillation

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Background: Pulmonary vein (PV) potentials at the PV ostium are invariably recordable in patients with atrial fibrillation (AF). However, whether PV potentials are existent in patients without AF is largely unknown.

Methods: During clinical procedures of catheter ablation via a transseptal access, circumferential catheter recordings were attempt in 10 patients with paroxysmal AF and in 9 patients with concealed WPW without history of AF. The existence of PV potentials was verified during sinus rhythm and during atrial pacing at the distal coronary sinus (CS) for the left PVs or at the right atrial appendage for the right PVs. To quantify the extent in which the PV potentials were recordable, the number and percentage of recording channels with PV potentials for each specific vein and for each patient were calculated.

Results: In patients with AF, PV potentials were recorded in 34 of the 37 PVs explored, i.e., they were absent only in the LIPV in 2 patients and in the RIPV in 1 patient. The total recording channels with PV potentials were 80% for the left superior PV, 89% for the right superior PV, 53% for the left inferior PV and 61% for the right inferior PV. In patients with concealed WPW the PV potentials were recorded in 9/36 i.e., there was no PV potentials at all in 3 patients, the PV potentials were recorded in only 1 PV in 4 patients, in 2 PVs in 1 patient and in 3 PVs in 1 patient. The recording channels with PV potentials were significantly less in patients with concealed WPW, in 39% of the LSPV, 33% of the RSPV, 48% of the LIPV, and 20% of the RIPV.

Conclusion: Contrast to the profound PV potentials recordable at the PV ostium in patients with AF, PV potentials were scarcely found in patients with concealed WPW without history of AF. These findings support the involvement of conduction delay and reentrant activities around the PV ostium in the genesis and/or perpetuation of paroxysmal AF.

P470 Pulmonary Vein antrum isolation guided by intracardiac ecocardiography for treatment of atrial fibrillation: long and mid term results

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Introduction: Pulmonary Vein (PV) antrum isolation using intracardiac echocardiography (ICE) precisely identifies the true border of the PV antrum for ablation and allows for the monitoring of the tissue effect of radiofrequency (RF) applications by direct visualization. Objectives: To evaluate the outcome of PV antrum isolation guided by Intracardiac Ecocardiography for the treatment of atrial fibrillation (AF).

Methods: 100 patients (25 female) with symptomatic and refractory AF who have not responded to at least one antiarrhythmic drug were evaluated (56 presented with paroxysmal AF, 28 persistent and 16 with the permanent form). 23 had structural heart disease. Patients undergone PV isolation utilizing the ICE- Guided Technique, which consists in titrating RF power while monitoring for microbubble formation on ICE. For ICE imaging an ultrasound catheter is positioned into the right atrium. An 8 mm ablation catheter and a Lasso catheter is RF application are advanced into the left atrium towards the PV by means of two transeptal punctures. RF energy is set at 20W and ablation is continued in every spot of PV until no more PV potentials are seen and as far as no microbubbles are observed. If microbubbles were detected, RF was immediately terminated and/or power output restricted.

Results: All four PV antra were isolated in all patients. After a mean follow up of 18 months (3-26m), 80 patients (80%) were AF free without antiarrhythmic medication; 12 patients were AF free on drug therapy and 8 (8%) presented with AF recurrence despite medication. Success after the first procedure is therefore about 92%. No patients developed thromboembolic complications during the procedure. No PV stenosis, atrial-enteric fistulae or left atrial flutter was diagnosed during the follow up. One patient with hypertrophic cardiomyopathy presented with a transitory ischemic attack 36 hours after ablation, which resulted in no sequelae.

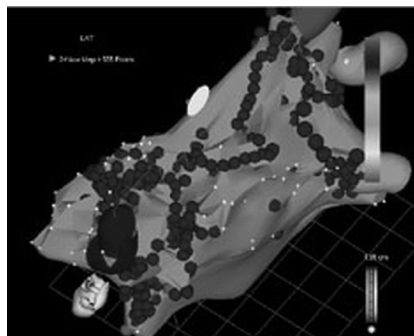
Conclusion: Isolation of the PV antra guided by ICE is both secure and effective a technique for the treatment of AF patients. It allows for the precise identification of the target area of ablation by direct visualization during RF ablation, minimizing the risks PV stenosis. The titration of RF power while monitoring for microbubble formation on ICE minimizes the risks of thromboembolic and mechanical complications.

P471 De-bulking and blocking as mechanism for successful refractory atrial fibrillation ablation

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Background: Pulmonary vein isolation is becoming the physiological therapy of atrial fibrillation in patients with paroxysmal (PAF) and chronic atrial fibrillation (CAF). However, the success rate is significantly higher in patients with PAF than CAF. The deformed left atrium may explain the lower success rate in patients with CAF.

Methods: Twenty-three patients (mean age 72 ± 7 years, 16 males) with refractory CAF and failed defibrillation (2.5 ± 1.6 attempts including high energy biphasic shocks) were selected for the study. All had severely enlarged left atrium. The left atrium was mapped with the use of the latest CARTO version. Extensive and wide ablation lines were completed around the pulmonary veins, a line in the roof of the left atrium and a line in the left isthmus. All the patients were successfully cardioverted with 200 joules biphasic shocks and followed for a mean of 330 ± 110 days. At the end of the follow-up 82.6% are in sinus rhythm, 8.7 with paroxysmal atrial fibrillation and 8.7 with recurrence and not willing a second attempt. If the patient was on antiarrhythmic treatment, it was continued at a reduced or original dose.



Wide ablation lines

Conclusions: Large ablation lines combining pulmonary veins blocking and significant atrial de-bulking modified the fibrillation substrate and made possible the cardioversion and sustained sinus rhythm for the one-year follow-up time. The one year-free of atrial fibrillation percent was similar with the large series pub-

lished in the literature. The wide ablation lines may eliminate essential reentry circles perpetuating the fibrillation (mother rotors).

P472 Ablation of persistent atrial fibrillation using CARTO and the double lasso technique



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Atrial fibrillation (AF) can be treated successfully by pulmonary vein (PV) isolation. A complete isolation of the PVs can be achieved by continuous circular lesions around the ipsilateral PVs. In paroxysmal AF this results in a success rate of 70% after the first procedure and >90% after 2 procedures. Aim of the study was to investigate the success rate and electrophysiological phenomena after ablation of persistent AF.

Methods and results: In 40 patients (pts) with symptomatic persistent AF a complete PV isolation was performed by completely encircling first the right PVs and then the left PVs during ongoing atrial fibrillation using an irrigated CARTO ablation catheter and the double lasso technique. After completion of continuous circular lesions around all PVs AF terminated spontaneously in 12 pts, changed to a macroreentry tachycardia in 10 pts (6 typical atrial flutter, 4 left atrial macroreentry tachycardia), and 18 pts needed electrical cardioversion to convert to sinus rhythm. All atrial macroreentry tachycardia were successfully ablated. Atrial tachyarrhythmia were observed in 15/40 pts (37%) after a median of 4 days post ablation. A re-ablation was performed after a median of 35 days following the initial ablation in 14/15 pts with recurrences. In 13/14 pts (93%) there was recovered PV conduction due to a gap in the previously produced circular ablation lines, and these could be closed by a focal ablation in all pts. After a median follow up of 8±2 months, 38/40 pts (95%) were free of AF.

Conclusion: In pts with persistent AF a complete circular lesion around the ipsilateral PVs results in 55% of pts in either spontaneous termination of AF or in conversion of AF into a macroreentry tachycardia. In most pts the reason for recurrence of atrial tachyarrhythmia is a gap in the PV isolation line, which can be closed by focal ablation. The success rate for ablation of persistent AF using continuous circular lesions around the ipsilateral PVs is 63% after the first ablation procedure and 95% after 2 procedures and this is similar to the results for paroxysmal AF.

P473 Anatomical ablation of Atrial Fibrillation using electroanatomic navigation combined with C-scan image integration



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Background: Atrial fibrillation (AF) catheter ablation based upon an anatomical approach relies on the assumption that the virtual anatomy reconstructed by a 3D mapping system precisely matches the patient's real anatomy. This study investigates whether this postulation is accurate.

Patients and methods: Thirty consecutive patients (23 men, mean age = 51.9±9.9 years) with symptomatic drug-refractory paroxysmal (n=21) or persistent (n=9) AF underwent a circumferential, 2 by 2, pulmonary vein (PV) radiofrequency (RF) ablation using the CARTOMERGE system. Virtual anatomy of the left atrium (LA) was first reconstructed and RF design lines drawn on this virtual surface. After a CT-scan image of the LA was integrated into the 3D system, RF lesions were deployed 10±5mm outside the PV ostia onto the CT-scan LA surface. The match between the actual PV circumferential RF lines and the RF design lines was analyzed off-line after catheter withdrawal.

Results: Circumferential RF design lines were divided into 4 segments: anterior/superior, anterior/inferior, posterior/superior and posterior/inferior, both the left-PV and right-PV encircling lines. Design segments matched the actual RF line segments in a proportion varying from 23% (left anterior/superior segment) up to 83% (right posterior/superior segment). A mean of 2.8±1.6 segments per patient were inaccurately designed. Only one patient had all segments perfectly matching the subsequent RF line segments, but 7 patients (23%) had 4 or more segments incorrectly designed. The inaccurate segments extended a mean of 3.8±2.3mm (range 1 to 12) inside the adjacent PV or 6.7±1.8mm (range 4 to 10) inside the left atrial appendage (LAA).

Conclusions: When AF ablation is performed using a 3D-mapping-assisted anatomical approach, our study suggests that the accuracy of RF lines with respect to the anatomical structures (PV ostia and LAA) is markedly increased when combined with a CT-scan image integration.

P474 Cryoablation as a therapeutical approach in paroxysmal in atrial fibrillation



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Purpose: Pulmonary vein (pv) ostia cryo-ablation (abl) has been introduced as a safe and effective alternative therapeutic approach with a reduced risk of throm-

boembolism, in patients (pts) with atrial fibrillation (AF). We report our experience regarding pv cryo-abl with a circular catheter in pts with paroxysmal AF.

Methods: Twenty-two pts (mean age: 51.7±9.2 years) with drug refractory idiopathic paroxysmal AF were included. All pts had recurrent highly symptomatic episodes (daily episodes) and were on antiarrhythmic medication. Mean duration of AF was 18±3 months. Mean left atrial diameter was 45±5 cm. Mean ejection fraction was 65±3%. Pts underwent an abl procedure with a circular cryocatheter at the ostia of the pvs. Our goal was the elimination or dissociation of electrical signals within the pv ostia. We used single 4-minute freezing cycles at each pv. When electrical signs were not eliminated, a second 4 min application was performed. Follow up was performed with Holter devices every 2 months and by patients' diaries. A 4-grade system was used to evaluate success.

Results: The total time of the procedure and fluoroscopy was 126.3±11.5 min and 25.2±8.1 min, respectively. The number of applications was 6.5±2.0 with a total duration of 16.5±6.7 min. The lowest tissue temperatures achieved at the proximal and distal pole of the catheter were -73.8±6.7°C and -70.5±21.3°C. In 3 pts good contact of the catheter to the tissue was not achieved and temperature was not lower than -20°C. There was 1 major complication (tamponade). At discharge 20 pts were in sinus rhythm. Patients were followed-up for 16.3±6.7 (2-29) months. Total success was noted in 13 pts (61%). A significant reduction, per month, in clinically significant episodes was shown in 6 (12%) pts. Two pts required an additional procedure. In 1 pt AF became chronic.

Results are expressed as mean±SD.

Conclusion: Cryo-abl is a therapeutical approach for pts with AF with major advantages. It seems to be an effective, safe method with low fluoroscopic time. The initiation of catheters with better contact to the pv ostia for a more complete elimination of micropotentials could be promising in the future.

P475 Long term outcome of circumferential left atrial PV ablation using a steerable transseptal sheath



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Background: Current concepts of AF catheter ablation use circumferential left atrial (LA) ablation lines targeting AF-substrate and AF-trigger located within the large pulmonary vein (PV) funnels. Due to improved catheter stability, left atrial wall contact and reach of target potentials the usage of a steerable transseptal sheath has been shown to significantly increase line continuity (measured as rate of complete PV isolation). The current study analyzed and compared freedom from AF in patients with and without usage of the steerable transseptal sheath after a single ablation procedure.

Methods: 110 patients (55±9 years; 77 male, 33 female; 99 paroxysmal, 11 persistent; 95 lone AF) received an electroanatomical (Carto) based AF ablation with circumferential lines around left and right PVs using a single mapping/ablation catheter and a steerable transseptal sheath. The patients received a 7 day holter ECG prior to ablation, immediately after ablation and after 3 months, respectively. Freedom from AF was compared against respective data from 154 patients (57±9 years; 108 male, 46 female; 139 paroxysmal, 15 persistent; 143 lone AF) treated with the same ablation concept but without the steerable sheath technology.

Results: In the 7-day ECG prior to ablation AF was recorded in 83% of the patients treated with the steerable sheath and in 82% of the patients treated conventionally (p=ns.). In the 7-day-ECG immediately after ablation AF recurrences were recorded significantly less often in patients treated with the steerable sheath (55% vs. 73%; p=0.007). That difference remained significant at the 3 months follow-up (30% vs. 42%; p=0.029). In both groups no significantly different outcome could be found in patients with or without complete PV isolation. However, freedom from AF in the postinterventional 7-day-ECG was a powerful predictor for long term success in both groups.

Conclusions: With a single ablation procedure the usage of the steerable transseptal sheath could significantly improve freedom from AF from 27% to 45% in the postinterventional 7-day ECG and from 58% to 70% in the 3 months 7-day ECG. No AF recurrences in the postinterventional holter were the most powerful predictor for long term success.

P476(W) Increased ostial pulmonary vein diameter in congestive heart failure: a multi-slice computed tomography angiography evaluation



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Background and Objectives: The relationship between left atrial (LA) size and congestive heart failure (CHF) is well recognized; however, there is little information on the association of pulmonary vein (PV) diameter and CHF. The purpose of this study was to investigate the changes of PV and LA sizes in CHF patients by multislice computed tomography (MSCT) angiography using a new 64-slice scanner.

Methods and Results: We assessed diameters of PVs ostium and LA by 64-slices MSCT with three-dimensional reconstruction in 25 CHF patients and in 26 age- and sex-matched non-CHF controls. Significant dilation of left superior pulmonary vein (LSPV) and right inferior pulmonary vein (RIPV) in both anterior-posterior(AP) and superior-inferior(SI) directions (P<0.01), dilation of right supe-

rior pulmonary vein (RSPV) in AP direction ($P < 0.05$), and significant increase of LA transverse, AP, and SI diameters ($P < 0.01$) were seen in the CHF group ($P < 0.01$).

Conclusion: Significant dilation of PVs with simultaneous LA enlargement was demonstrated in CHF patients. This anatomic and geometric changes may participate in the perpetuation of AF.

P477 does left atrial scarring determine success in patients undergoing pulmonary vein isolation for atrial fibrillation?



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Atrial scarring as demonstrated by regions of low voltages has been demonstrated in patients with atrial arrhythmias especially atrial fibrillation (AF). These changes could result in initiation and perpetuation of AF. Left atrial (LA) scarring has been reported as a surrogate marker of treatment failure in patients undergoing pulmonary vein isolation for AF.

Aim of the study: 1) To retrospectively evaluate the extent of LA scarring in patients that underwent pulmonary venous isolation for AF and 2) To assess the clinical characteristics of patients with scarring and the implication of scarring to the short and intermediate term outcome of the ablative therapy for AF.

Methods: 30 patients who underwent pulmonary vein isolation using an electroanatomic mapping system CARTO were included. Mapping of the LA was performed using a fill threshold of 10. Areas with a bipolar voltage of < 0.05 mV were designated as scar. Using the CARTO software, the area of the scarred atrial myocardium were measured and expressed as a percentage of atrial area. The baseline clinical characteristics and outcome of the procedure were evaluated in these patients.

Results: 30 patients, 24 without recurrences and 6 with recurrence requiring redo procedures were included. 3 patients were in persistent AF. Patients with persistent AF had significantly larger percentage scar area compared to paroxysmal AF. Median value of scar area percentage for paroxysmal AF 19.00 (interquartile interval 7.3 to 25.00) compared to 43.71 (Q1-Q3=31.45-48.83) in persistent AF; $P = 0.0070$. Patients with a procedural failure and recurrence had larger baseline scar area percentages (median 31.23 Q1-Q3 = 28.63 to 44.99) compared to patients without (median 15.54, Q1-Q3 = 7.15-20.67), $P = 0.0008$.

Conclusion: LA scarring was more common in patients with permanent AF and it was related with the success rate of pulmonary venous isolation for AF. Patients with procedural failure and recurrence of the arrhythmia had significantly larger scar in the LA prior to ablation. A larger scar area may be an indicator of recurrence of AF after pulmonary vein isolation.

P478 Cooled-tip versus 8-mm-tip catheter for Electro-anatomical encircling of Pulmonary Veins for atrial fibrillation. Comparison of efficacy and safety



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Incomplete ablation lines and conduction recovery is a cause of arrhythmia recurrence after electro-anatomical encircling of pulmonary veins (EAE). Whether cooled-tip catheters are safer and more efficacious than 8mm-tip for EAE remains unclear. The aim of this study was to compare the efficacy, safety and lesion extension created by cooled-tip versus 8 mm-tip catheters.

Methods: A cohort of 124 consecutive patients (pts) underwent EAE with additional linear lesions (CARTO system). An 8-mm-tip catheter (50 W, 50°C) was used for the first 81 pts (group 1) and a cooled-tip catheter (30W, 50°C) for the next 43 (group 2). Recurrence was defined as atrial fibrillation (AF) or atrial flutter (AFL) after one month healing period. In a subgroup of pts (22 and 18 of group 1 and 2 respectively) biochemical markers of necrosis (creatin kinase, myoglobin and troponin I) were measured at 12 and 24 hours after the procedure and time of RF application were obtained.

Results: There were no differences between both groups in age (52 ± 10 vs 55 ± 10 y), gender (85% vs 73% male), left atrial diameter (42 ± 6 vs 40 ± 7 mm), structural heart disease (10% vs 4%) hypertension (36% vs 39%) or paroxysmal AF (61% vs 63%). After a 14 ± 9 months follow-up comparable percentage of patients in both groups remained arrhythmia free (64% vs 51%; $p = NS$). Recidives occurred as AF (19% vs 39%) or left AFL (16% vs 9%). As complications from RF energy application there were 5 pericarditis and a transient dyplopy in group 1, and a 2 pericarditis and a cardiac tamponade in group 2. Cardiac lesion measured by troponin I biomarker were significantly larger with an 8mm-tip catheter (4.5 ± 2.3 vs 2.6 ± 1.1 ; $p = 0.02$). In this subgroup of patients there was a tendency toward less RF application time with the 8 mm-tip catheter than with a cooled-tip (2583 ± 725 vs 3028 ± 677 sec; $p = 0.06$). A second procedure was undertaken in 21 patients (19 in group 1 and 5 in group 2) due to refractory symptoms, the remaining relapses were controlled with antiarrhythmic drugs. Conclusion: The cooled-tip catheter showed no benefit and seemed to create smaller lesions than the 8mm-tip catheter in EAE. Higher energy may be required to obtain benefit from the cooled-tip catheter.

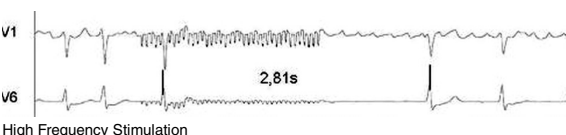
P479 Selective atrial vagal denervation guided by evoked vagal reflex to treat patients with paroxysmal Atrial Fibrillation



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Purpose: The aim of this study was to evaluate whether selective radiofrequency (RF) catheter ablation of the atria sites in which high frequency stimulation induces vagal reflexes prevents paroxysmal atrial fibrillation (AF).

Methods and Results: Twelve patients with refractory paroxysmal AF, no heart disease and presenting most the episodes under vagal tone were selected to percutaneous epicardial and endocardial mapping of the atria searching for sites in which high frequency transcatheter stimulation (20 Hz, 4ms) induced vagal reflexes (Figure). RF pulses (21.0 ± 12.0 patient) were applied on those places in order to abolish all evoked vagal reflexes that were obtained in 9 patients. Three patients without evoked vagal reflex were submitted to circumferential pulmonary veins ablation (CPVA) with an average of 58.0 ± 13.9 RF pulses per patient ($p = 0.022$). Autonomic evaluation was performed before, 48 h and 3 months after the procedure and was consistent with vagal withdrawal in all patients. During a follow-up of 7.7 ± 3.0 (3-15) months, 2 of 9 denervated patients remained asymptomatic without AA, five presented frequent recurrences and were referred to CPVA and two presented sparse AF episodes without AA. The 3 patients without evoked vagal reflex and submitted to CPVA remained asymptomatic without AA. One patient presented transitory gastroparesis after atrial vagal denervation.



Conclusions: RF catheter ablation of selected atria sites in which high frequency stimulation induced vagal reflexes did not abolish AF recurrences in most patients with apparently vagal induced paroxysmal AF.

P480 3D standard CARTO XP mapping versus CT scan image integration to guide AF anatomical ablation



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Purpose: The anatomical approach is currently used for the Radiofrequency (RF) ablation of the Atrial Fibrillation (AF). Integration of the CT scan 3D morphological data in the mapping procedure, using the CARTO Merge (CM; Biosense-Webster, Inc) system, could result in an easier definition of the Left Atrium (LA) and Pulmonary Veins (PVs) anatomy and of their relation with the Esophagus (E). The aim of the study was to compare the new CM system with the classical Carto XP one, with regard to the main procedural times.

Methods: 155 patients (pts) underwent an AF ablation procedure, using either the Carto XP system (N=80, gr A), or the CM system (N=75, gr B). A CT scan with a 3D reconstruction of the LA, PVs and E was obtained before the procedure for the gr B and was incorporated in the CARTO system.

Results: The results are summarized in table 1.

	Gr A (Carto XP)	Gr B (Carto Merge)	p
Fluoro total procedure time	35.3 ± 16.5 min (16 to 59)	17.2 ± 9.8 min (5,1 to 35)	< 0.001
Total procedure time	245 ± 60 min (85 to 420)	186 ± 34 min (121 to 270)	< 0.001

Conclusions: 1. The integration of the CT scan LA image in the electroanatomical 3D Carto system reconstruction of the LA model is feasible, with a shorter procedural and fluoroscopy time comparing with standard Carto XP procedure. 2. The Carto Merge system is a safe tool and helps to identify the precise anatomical relation between the LA, PVs and Esophagus to guide the anatomical AF ablation in order to minimize the risk of the ablation procedure.

P481 Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation



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Objective: Pulmonary vein isolation remains a challenging procedure for which a number of different approaches have been used. This study was designed to assess the feasibility, efficacy and safety of an occluding cryoballoon catheter.

Method: 15 patients with lone, drug resistant paroxysmal atrial fibrillation underwent a single session PV isolation with a 29 mm cryoballoon. PV potentials were registered before and after ablation. The cryoballoon was inflated and advanced to achieve complete occlusion of the PV ostium as assessed by intracardiac ul-

trasound and contrast injection. If isolation could not be obtained, additional segmental isolation was performed with a conventional 8 mm tip cryocatheter.

Results: Table 1 shows the number of applications given per vein with the results. A total of 43 (74%) out of 58 attempted PV's were isolated with the cryoballoon, 12 (21%) required a conventional cryocatheter to achieve isolation with a median of 2 (range 1-6) applications. This amounts to 56 (97%) isolated veins. Two inferior veins (3%) in one patient, could not be isolated due to anatomical reasons. One patient experienced a reversible phrenic nerve paralysis, but no other complications were observed due to this technique.

Results of PVI with a 29 mm cryoballoon

Vein	Nr	Average (mm)	Number of applications (median, [range])	Number Isolated (nr (%))	Additional Catheter (nr (%))	Total Isolated (nr (%))
LSPV	15	21,1	5 [1-7]	11 (73)	2 (13)	15 (100)
LIPV	14	19,2	5 [2-10]	10 (71)	4 (29)	13 (93)
RSPV	15	19,8	3 [1-4]	12 (80)	3 (20)	15 (100)
RIPV	14	19,1	2 [1-4]	10 (71)	3 (21)	13 (93)
Total	58	19,8	13 [7-18]	43 (74)	12 (21)	56 (97)

PVI: pulmonary vein isolation; Nr: number; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein

Conclusion: Catheter based pulmonary vein isolation using a cryoballoon is both feasible and effective. Follow up data is required to assess its long term efficacy.

P482 Relevance of early AF recurrences to predict long term success after circumferential left atrial PV ablation



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Background: Current concepts of AF catheter ablation use circumferential left atrial (LA) ablation lines around the pulmonary vein (PV) funnels to treat AF trigger and to modify the AF substrate. Substrate modification has been described to result in early AF recurrences with delayed cure. The present study analyzed the impact of early AF recurrences on the long term success rate using multiple serial 7-day holter ECGs.

Methods: 181 patients (53±10 years; 126 male, 55 female; 152 paroxysmal, 29 persistent; 156 lone AF) received an AF ablation using an electroanatomic mapping system (CARTO) for placement of circumferential lines around left and right PVs and linear lines at the left atrial roof and to the mitral annulus. A 7-day holter ECG was recorded prior to ablation, immediately after ablation, after 3 and 6 months. Long term success (3 and 6 months after ablation) was compared between patients with and without early AF recurrences during the 7-day holter immediately after ablation.

Results: Prior to ablation 149 patients (82%) showed AF on the 7-day holter. After ablation that number declined to 129 (71%), 72 (40%) and 76 (42%) patients, respectively. The 52 patients (29%) without early AF recurrences showed a significantly better long term success compared to the 129 patients (71%) with early AF recurrences. The rate of SR after 3 and 6 months was 44/52 (85%) vs. 66/129 (51%) ($p=0.001$) and 46/52 (89%) vs. 59/129 (46%) ($p=0.001$), respectively. Comparing the rate of complete PV isolation no significant difference could be found between these 2 groups.

The positive predictive value of continuous SR during the postinterventional 7-day-ECG to predict long term ablation success measured 89%. The negative predictive value of continuous SR during the postinterventional 7-day-ECG to predict long term AF recurrences measured 54%, indicating that in some of these patients delayed cure does indeed occur.

Conclusions: Freedom from AF during the 7-day holter immediately after ablation is a powerful predictor for long term ablation success. However, also for patients with early recurrences 50% become free from AF during follow-up 3 and 6 months later, indicating an effect of delayed cure after AF substrate modification.

P483 Spontaneous baroreflex sensitivity after pulmonary veins isolation in predicting recurrence of atrial fibrillation



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Aims: One of the hypotheses proposed to explain the clinical success of pulmonary veins isolation (PVI) in curing atrial fibrillation (AF) assumes a denervating effect of RF lesions in PV ostia region, leading to changes in autonomic control of the heart (ACH). Our aim was to evaluate the effects of PVI on ACH and AF recurrences, assessed through the quantification of spontaneous baroreflex sensitivity (BRS).

Methods: In 20 patients (16 M, 4 F, age: 60.4±5.3) undergoing PVI for AF, beat-to-beat BP monitoring and ECG monitoring was performed for 10 min at controlled

breathing rate 1-2 days before and 1 month after PVI. All patients were in sinus rhythm during each recording. The follow-up was 6 months. Baroreflex function was assessed by frequency domain BRS (Alpha coefficient and the modulus of PI/SBP transfer function (H) at low (LF, 0.04-0.14 Hz) and high frequency (HF, 0.15-0.50 Hz)) and by the slope of UP (Seq+/+) and DOWN (Seq-/-) PI/SBP sequences.

Results: During the follow-up, 6 patients had AF recurrence. As compared to baseline, no recurrence of arrhythmia was observed only in patients with a BRS reduction 1 month after PVI (alpha LF 7.6±4.6 vs 3.8±2.3ms/mmHg, $p=0.02$; alpha HF 11.0±4.4 vs 6.5±1.3ms/mmHg, $p=0.02$; H-LF 6.0±3.7 vs 3.0±1.9ms/mmHg, $p=0.02$; H-HF 8.8±3.4 vs 5.1±1.0ms/mmHg, $p=0.02$; Seq+/+ 12.1±5.6 vs 6.8±1.6ms/mmHg, $p=0.04$; Seq-/- 11.1±4.3 vs 6.1±2.2ms/mmHg, $p=0.02$). This was the case also for a reduction in pulse interval (973±74ms vs 911±117ms, $p=0.05$). The patients with AF recurrence were characterized by almost no change or even a slight increase in BRS after PVI. Univariate analysis focusing on clinical predictors of AF recurrence identified BRS, computed as alpha HF and H-HF 1 month after PVI, as predictors of AF recurrence ($p=0.02$ for both). In multivariate Cox analysis, including age, sex, duration and frequency of AF, left atrium size, left ventricle ejection fraction, alpha HF or H-HF as independent variables, the predictive power of BRS became marginally significant. Patients were more likely to remain in sinus rhythm if the ratio of BRS (alpha LF, H-LF) below ablation/after ablation was greater than 2 (for both $p=0.03$, log-rank test).

Conclusions: PVI was successful in preventing AF recurrences only in patients who displayed a significant reduction in spontaneous BRS after PVI. This suggests that lack of vagal cardiac denervation after PVI could be an important factor determining the probability of AF recurrence.

ATRIAL FIBRILLATION: ROLE OF ATRIAL REMODELLING INFLAMMATION AND RENIN-ANGIOTENSIN SYSTEM

P484 Markers of inflammation and recurrence of atrial fibrillation after electrical cardioversion



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Purpose: Several studies have indicated that atrial fibrillation (AF) is associated with inflammatory processes. A few small studies have indicated that low levels of C-reactive protein are associated with less AF-"burden" and a lower recurrence rate of AF after electrical cardioversion (EC). However, data on the role of other markers of inflammation in AF is limited. We therefore hypothesised that patients remaining in sinus rhythm after EC have lower levels of other markers of inflammation.

Methods: In the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study, 171 patients with AF scheduled for EC were randomised to receive candesartan 8 mg o.d. or placebo for 3-6 weeks before and 16 mg o.d. or placebo for 6 months after EC to reduce the recurrence rate of AF. Candesartan had no effect on recurrence rate of AF. As part of this study, levels of inflammatory markers (TNF α , IL-6, CRP, CD40L, P-selectin, E-selectin and VCAM-1) were measured at 3-6 weeks before EC. Values are given as median (25, 75 percentiles), and non-parametric statistical tests have been used.

Results: Patients still in sinus rhythm (SR) 6 months after EC ($n=40$) were compared with patients with either unsuccessful cardioversion or a relapse of AF ($n=113$). The levels of CRP and E-selectin were significantly lower in patients still in SR at 6 months after EC: 2.36 mg/L (1.28, 4.09) vs. 3.44 mg/L (1.66, 6.05), $p=0.031$ and 32.0 ng/mL (22.6, 42.2) vs. 37.4 ng/mL (28.1, 50.5), $p=0.042$, respectively. There was also a tendency towards lower levels of P-selectin among patients remaining in SR: 31.5 ng/mL (25.6, 41.2) vs. 35.6 ng/mL (29.4, 42.8), $p=0.080$. The levels of TNF α , IL-6, CD40L and VCAM-1 were not statistically different between patients who remained in sinus rhythm and those who did not.

Conclusion: Levels of CRP and E-selectin measured 3-6 weeks before electrical cardioversion were lower in patients still in sinus rhythm 6 months after EC, whereas other inflammatory variables were not significantly different, when compared with patients with unsuccessful cardioversion or a relapse of AF. These findings may suggest a partial influence of inflammation on the rhythm outcome after EC.

P485 Electrical remodeling induced by atrial tachycardia is prevented by nitric oxide in a sheep model



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Background: Rapid atrial pacing leads to a decreased expression of endocardial NO-synthase in pigs (Cai Circulation 2002). We hypothesized that decreased levels of NO may play a role in electrical remodeling during atrial tachycardia.

Methods: We examined the effect of molsidomine, a NO-donor (bolus 0.1 mg/kg; IV 0.025 mg/kg/h), L-NAME, a NO-synthase inhibitor (bolus 5 mg/kg; IV 1 mg/kg/h) and placebo on electrical remodeling occurring during 4 hours of rapid

atrial pacing in sheep. Six ewes (48.42 ± 15.41 kg) were anesthetized and medication was started as a continuous infusion after a bolus injection. After 1 hour the sheep were subjected to 4 hours of atrial pacing at 900 bpm. Hemodynamic and electrophysiologic parameters were measured at baseline, after 1 hour medication, after 2 h pacing and after 4h pacing (3 and 5h medication). Animals were allowed at least 1 week rest between different experiments.

Results: In the control group, rapid atrial pacing led to a shortening of the atrial effective refractory period (AERP) from 184 ± 5.4 ms to 164 ± 7.1 ms after 4 hours. L-NAME had no significant effect on AERP shortening. However, treatment with molsidomine prevented this remodeling effect. AERP remained unchanged after 4h of pacing (188 ± 9.5 ms to 187 ± 6.2 ms, $p < 0.05$). Medication had no effect on P-wave duration, Wenckebach cycle length, wedge pressure, right atrial and ventricular pressure. Infusion with molsidomine resulted also in a significant decrease in arterial pressure of 11 ± 3.1 mmHg compared to placebo. To exclude an effect on AERP of this difference in blood pressure, additional experiments were performed with urapidil, a vasodilator (bolus 1 mg/kg; IV 0.5 mg/kg/h). Despite a same decrease in blood pressure, treatment with urapidil during 4 hours of rapid atrial pacing led to a shortening in AERP, which was comparable with the control group. We could furthermore show that serum nitrite and NOx levels increased during administration of molsidomine.

Conclusion: Treatment with molsidomine, a NO-donor, prevented short-term shortening of the AERP during rapid atrial pacing in sheep. This effect could not be explained by its hemodynamic effects. Our results suggest a possible role of NO in the remodeling processes underlying atrial fibrillation.

P486 Elevated levels of C-reactive protein are associated with new onset atrial fibrillation in patients with acute myocardial infarction



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Background: New-onset atrial fibrillation (AF) is observed in 10-15% of patients with acute myocardial infarction (AMI) and is associated with adverse clinical outcome. Recent studies have implicated systemic inflammation in the genesis and maintenance of atrial arrhythmias. C-reactive protein (CRP), a sensitive marker of systemic inflammation, has been shown to predict new-onset AF. However, information is lacking concerning the association between CRP levels and AF in patients with AMI.

Methods: We prospectively studied 1143 patients admitted with AMI. CRP was measured by a high-sensitivity assay within 12-24 hours after symptoms onset. The relationship between CRP and AF occurring at any time during hospital course was examined using univariate and multiple logistic regressions.

Results: During hospital stay AF developed in 135 patients (11.8%). AF occurred in 6.6%, 11.1%, and 17.8% of the patients in the 1st, 2nd and 3rd CRP tertile, respectively (P trend < 0.0001). In a univariate logistic regression, compared to patients in the 1st CRP tertile, the odds ratio (OR) for AF was higher in patients in the 2nd and 3rd CRP tertile (Table). After adjustment for age, gender, baseline creatinine, history of hypertension and diabetes, anterior infarction, ST-elevation infarction, Killip class on admission and ejection fraction, CRP remained independently associated with AF (Table), together with age > 60 y (OR 2.2; 95% CI 1.1-4.5, $P = 0.02$), Killip class II-IV (OR 2.1; 95% CI 1.2-4.0, $P = 0.02$) and ejection fraction $< 45\%$ (OR 1.5; 95% CI 1.0-2.3, $P = 0.03$).

Relationship between CRP and AF events

CRP tertile	CRP (mg/L)	AF events (%)	Unadjusted OR	P trend	Adjusted OR	P trend
1st tertile	< 7.6	25 (6.6)	1.0	< 0.0001	1.0	0.007
2nd tertile	7.6-25.5	43 (11.1)	1.8 [1.1-2.9]		1.5 [0.9-2.5]	
3rd tertile	> 25.5	67 (17.8)	3.1 [1.9-5.0]		2.0 [1.2-3.4]	

Conclusion: In a large cohort of patients with AMI, there was a graded positive association between elevated CRP and new-onset AF during hospital course. These results suggest that inflammation may contribute to the development of AF in the setting of AMI.

P487 The influence of betablocker-treatment on Connexin 40 and 43 expression



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Objective: Since atrial fibrillation (AF) is associated with abnormal gap-junctional intercellular communication and since our previous findings indicated a possible role of alpha- and beta-adrenoreceptors, we investigated in cultured rat cardiomyocytes (CRC) and patients with AF the expression of CX40 and CX43 and the influence of beta-adrenergic-agonist treatment on it.

Methods: Left atrial tissue samples were obtained from patients with AF (with betablocker $n=85$; without betablocker $n=38$) or sinus rhythm (with betablocker $n=20$; without betablocker $n=17$). Additionally, CRC were exposed to noradrenalin alone (1-1000nM) and noradrenalin+propranolol (100nM). In both, human tissue and CRC, CX40 and CX43 protein levels were measured by quantitative Western Blotting techniques.

Results: In CRC, CX43 expression was increased in a concentration-dependent manner by noradrenalin ($p < 0.05$), which was enhanced in presence of 100nM propranolol. CX43 expression in patients with AF was significantly higher (219 ± 19) vs. patients with SR (114 ± 15). There was significantly higher expression of CX43 in AF with betablocker (245 ± 25 , $p < 0.05$) compared to AF without betablocker (180 ± 28), SR without betablocker (101 ± 20) and also to SR with betablocker (124 ± 22). The expression of CX40 was not influenced by betablocker treatment, neither in rat cardiomyocytes nor in human left atrial tissue.

Conclusion: Adrenergic stimulation leads to an upregulation of CX43, but not CX40, in cultured rat cardiomyocytes and patients with AF, that was potentiated by betablockers. This suggests a possible role for betablockers in gap junctional remodeling by blocking of beta-adrenergic and PKA mediated negative feedback-response to alpha-adrenergic-receptor.

P488 ProBNP levels are associated with arrhythmia-related symptoms in atrial fibrillation



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Purpose: Exercise intolerance, dyspnoea, fatigue, palpitations and dizziness are frequent symptoms in atrial fibrillation (AF). However, the mechanisms behind these symptoms are poorly understood. We have studied the relationship of these symptoms to serum levels of ProBNP in patients in the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study.

Methods: Blood samples for measurement of proBNP were collected at baseline in 165 patients with persistent AF who were scheduled for electrical cardioversion. Patients with heart failure were not entered into the study. Information on arrhythmia-related symptoms was recorded. Values are given as median (25, 75 percentiles). Non-parametric statistical tests have been used.

Results: Patients who reported dyspnoea, exercise intolerance and/or fatigue ($n=107$) had higher levels of proBNP than patients without these symptoms: 93.6 pg/mL (56.7, 152.6) vs. 77.4 pg/mL (44.8, 122.5), $p=0.020$. When analysing with regard to the separate symptoms, the same pictures were seen. Analysing 78 patients with lone AF only, the levels of proBNP were still higher in 44 patients with dyspnoea and/or exercise intolerance: 82.6 pg/mL (45.5, 117.0) vs. 69.7 pg/mL (39.1, 83.6), although not statistically significant ($p=0.078$). ProBNP levels were not related to the presence of palpitations or dizziness.

Conclusion: In persistent atrial fibrillation, the arrhythmia-related symptoms dyspnoea, exercise intolerance and fatigue are associated with higher levels of proBNP, suggesting more severe myocardial affection.

P489 Prognostic significance of plasma brain natriuretic peptide and markers of inflammation in chronic heart failure patients with atrial fibrillation



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Background: Prognostic significance of elevated plasma levels of brain natriuretic peptide (BNP), pro-inflammatory cytokines and markers of inflammation have been reported in patients (pts) with chronic heart failure (CHF) in sinus rhythm (SR). However the role of these markers in the prediction of survival in pts with CHF and AF has not been well established.

The aim of study was to estimate the role of BNP, tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) for the prediction of adverse outcomes in pts with CHF and AF.

Methods: The value of plasma BNP levels, TNF- α , IL-6 (pg/ml) and hsCRP (mg/l), determined by ELISA, in the prediction of mortality was prospectively assessed in 57 pts with permanent AF and in 59 pts in SR with ischemic dilated cardiomyopathy and NYHA III functional class CHF without concomitant intercurrent inflammatory or neoplastic diseases. The groups of patients were not significantly different for age, sex, ejection fraction and medical therapy.

Results: At baseline BNP (874 ± 97 vs. 372 ± 75), TNF- α (45 ± 3.1 vs. 31 ± 2.1), IL-6 (97 ± 7.3 vs. 62 ± 5.7) and hsCRP (42 ± 5.7 vs. 22 ± 2.2) levels were significantly higher in patients with AF compared to those with SR ($p < 0.001$, for all). After a mean follow-up of 25 ± 0.9 months, cardiovascular mortality was comparable in both groups (27.1% vs 23.7%; $p=ns$). In AF and SR patients with CHF levels of plasma BNP (adjusted hazard ratio [HR] 7.7 and 3.1, $p < 0.01$), serum IL-6 (adjusted HR 3.5 and 2.6, $p < 0.05$), hsCRP (adjusted HR 4.2 and 2.9, $p < 0.05$) and TNF- α (adjusted HR 3.7 and 2.8, $p < 0.05$) were independent determinants of cardiovascular mortality. Kaplan-Meier survival curves demonstrated a survival rate of 63% and 87% for pts in SR with BNP level ≥ 350 and BNP < 350 , and 64% and 85% for pts with AF and BNP level ≥ 450 and < 450 , 68.7% and 85.1% for pts with SR and hsCRP level ≥ 27 and < 27 and 65% and 87% for pts with AF and hsCRP level ≥ 32 and < 32 , respectively ($p < 0.01$ for all). Similar probability of survival ($p < 0.01$) was shown in pts in SR and AF with TNF- α < 35 and ≥ 40 (89.1% and 87.5%) and IL-6 level < 70 and ≥ 100 and those with TNF- α < 35 and ≥ 40 (64.1% and 63.5%) and IL-6 ≥ 70 and ≥ 100 (66.7% and 63.2%), respectively.

Conclusions: 1) Pts with CHF and AF have significantly higher levels of BNP, TNF- α , IL-6 and hsCRP than pts with CHF and SR. 2) Despite of these differ-

ences, levels of BNP and markers of inflammation can be used as powerful prognosticators in pts with CHF, irrespective of the presence or absence of AF.

P490 Atrial electrical remodeling during spontaneous episodes of atrial fibrillation

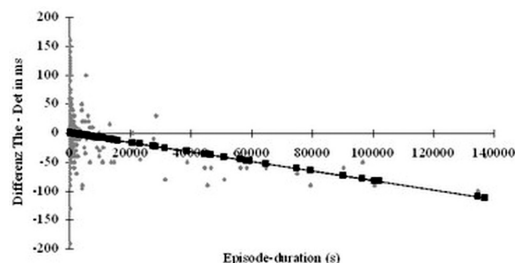


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Background: During (induced) episodes of atrial fibrillation (AF) in animal models, significant shortening of the atrial action potential duration has been observed. However, it is unknown whether this electrical 'remodeling' is also occurring during spontaneous episodes of AF in humans. New pacemaker systems have the ability to store atrial electrograms, allowing long-term analysis of atrial cycle length (CL) during spontaneous episodes of AF.

Methods: 20 patients (pts) (mean age 70 (39-85) yrs, 55% male, CAD: 55%, art. hypertension: 65%) who received a DDDR-pacemaker (PM) system (AT500, Medtronic) for paroxysmal AF and a class I PM indication were included in this prospective trial. Stored intracardiac electrograms at the beginning of the episode and before atrial pacing-therapies were delivered were analyzed for each episode.

Results: Following a 4-6 week observation period after implantation, 1103 AF-episodes occurred with stored intracardiac electrograms available which were analyzed. There was a significant decrease in atrial CL during sustained episodes of AF, and the decline in CL correlated with the duration of the episode (Figure): whereas there was little change in atrial CL in episodes of < 10 min duration (from 224±55 to 225±58 ms), the CL decreased significantly in episodes lasting > 10 in (baseline 203±32 to 188±22 ms).



Conclusions: (1) Atrial remodeling is observed during spontaneous episodes of AF in humans. (2) The significant decrease in atrial CL correlates with the duration of the AF episode.

P491 Effects of electrical cardioversion on CRP and NT-proBNP levels in patients with persistent atrial fibrillation

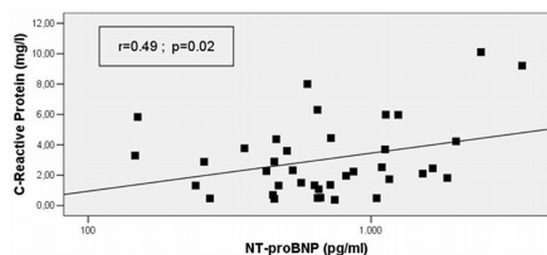


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Fibrosis and abnormal stretch of atrial myocytes are major determinants of atrial fibrillation (AF). Recent evidence also supports the pathogenetic role of sub-clinical inflammation. We evaluated the effects of AF and sinus rhythm restoration on two markers of mechanical stretch and inflammation commonly used in clinical practice.

Methods: We measured B-type natriuretic peptide (NT-proBNP) and high sensitivity C-reactive protein (CRP) in 58 patients (mean age 66±7 years) with persistent AF before and 3 weeks after successful electrical cardioversion (ECV). All subjects had no signs of systemic inflammatory disease and preserved left ventricular ejection fraction (LVEF; 57±8%). Left atrial dimension and appendage emptying velocity (AEV) were determined during trans-oesophageal echocardiography. Data are expressed as mean±SD.

Results: Before ECV, 40% of patients exhibited CRP levels superior to the upper normal cut-off limit of 3.00 mg/L, whereas 93% of patients presented increased NT-proBNP values in spite of a preserved LVEF. CRP and NT-proBNP were significantly correlated. AEV and LVEF were correlated with NT-proBNP but not with CRP levels. Restoration of sinus rhythm was associated with a reduction of NT-



proBNP (from 850±695 to 346±394 pg/ml; $p < 0.001$) whereas CRP remained substantially unchanged (3.2 ± 0.8 to 2.8 ± 0.7 mg/L).

Conclusions: These data indicate that more than one third of patients with persistent AF have evidence of a sub-clinical inflammatory state that seems unaffected by sinus rhythm restoration. On the contrary, recovery of a more physiological hemodynamic function in the atria is associated with a significant reduction in NT-proBNP. This finding has to be taken into consideration when considering the use of BNP testing in patients with heart failure and AF.

P492 The relationship between atrial fibrillation and inflammation markers



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Background: Atrial fibrillation (AF) is associated with atrial structural changes that may have an inflammatory basis. The failure in preventing the recurrence of AF has led to new searches in its pathogenesis. Perhaps inflammation is one of most popular mechanisms of AF. A classical marker of inflammation, C-reactive protein (CRP) and proinflammation agent Interleukin -6 were found elevated in patients with AF. In this study we aimed to investigate the role of inflammation markers in different categories of AF.

Methods: 78 patients with AF (mean age 53.6 ± 9.3) where enrolled in this study. AF was subdivided on paroxysmal and chronic types. Control group was consisted of 22 healthy persons. After the enrollment the echocardiography examination and 24-hour ambulatory Holter monitoring ECG were registered in each patient. Blood samples were tested on the serum level of high-sensitive C-reactive protein (hs-CRP) and plasma level of Interleukin-6 (IL-6).

Results: The obtained results have shown that the level of hs-CRP in both chronic (0.72 ± 0.52 mg/dL) and paroxysmal (0.51 ± 0.42 mg/dL) types of AF were significantly higher in comparison with control group (0.28 ± 0.11 mg/dL, $p < 0.001$). The level of IL-6 in chronic type (32 ± 21 vs 12.1 ± 8.9 pg/ml, $p < 0.05$) and in paroxysmal type (27 ± 25 vs 12.1 ± 8.9 pg/ml, $p < 0.05$) was significantly higher than those in control group. Moreover there was no difference in inflammation markers between paroxysmal and chronic types of AF.

Conclusion: hs-CRP and IL-6 inflammation markers play important role in pathogenesis of AF.

P493 Impact of atrial remodeling on long-term results of surgical ablation for mitral valve disease related atrial fibrillation: outcomes from prospective registry



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Objective: We sought to estimate the impact of atrial arrhythmia risk factors (non-selected versus selected population) on long-term results of surgical ablation for atrial fibrillation in patients referred to mitral valve surgery.

Methods: From January 2003 (enrollment start) to September 2005 all patients (no selection, n=87) with atrial fibrillation (AF) referred to mitral valve repair/replacement with or without other concomitant procedures underwent endocardial ablation with either irrigated unipolar radiofrequency or cryotherapy device. Patients were at mean age of 61.4 (±10) years, with mean AF duration 4.1 (±4.2) years and mean left atrial (LA) diameter 53 (±10) mm. Patients were off anti-arrhythmic medications and prospectively followed after 3, 6, 12, 24 months including echocardiography and 24-hours Holter ECG.

Results: In the group of non-selected, consecutive patients stable sinus rhythm (SSR) was maintained in 46 (68.6%), 45 (71.4%), 27 (64.2%), 14 (54%) patients after 3, 6, 12, 24 months, respectively. After 24 months pacemaker was implanted in 2 patients. Multivariate regression revealed LA diameter > 60 mm and age > 70 years old as risk factors for unsuccessful ablation. In the group of selected patients (age < 70 years old and LA diameter < 60 mm) SSR was observed in 33 (80.4%), 31 (79.1%), 21 (80.7%), 11 (68%) patients after 3, 6, 12, 24 months, respectively.

Conclusions: Data from prospective registry show that AF in patients with mitral valve disease may be successfully treated in all "real-life" cases. The question of preoperative atrial remodeling factors remains crucial for reliable long-term estimation of clinical effectiveness of ablation procedures.

P494 Heat-Shock Protein 72 (HSP72) prevents angiotensin II-induced atrial fibrosis and fibrillation in rat heart



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Purpose: Atrial fibrillation (AF) is a common arrhythmia and has been known to be promoted by stimulation of renin-angiotensin system (RAS). Further, previous studies have also suggested the suppressive effects of HSP 72 on the post-

operative development of AF. Hence, we tested the hypothesis that angiotensin II (All)-mediated atrial fibrosis and AF could be prevented by induction (over expression) of HSP72.

Method: Protocol 1. Hyperthermia (HT; 42°C) was applied for 30 min on cultured rat atrial fibroblasts. Twenty-four hours later, All (100 nM) was added to the medium for 8 min, and cells were collected and studied. Protocol 2. Osmotic mini-pump was subcutaneously implanted for continuous infusion of All (400 ng/kg/min) in male rats, and All was infused for 4 weeks. Whole-body HT (43°C, 20 min) was introduced 24 hours before and 7, 14 and 21 days after the start of All administration. Four weeks later, each heart was isolated and set for later analysis, namely for both molecular and hemodynamic studies.

Results: We observed the following. 1) In cultured fibroblasts, HT induced HSP72 over expression, which was paralleled with the attenuation of All-induced phosphorylation of ERK1/2. 2) HT induced atrial HSP72 over expression, which was in association with attenuation of All-induced left atrial fibrosis, when assessed by Masson's trichrome staining. Continuous All infusion caused inter-atrial conduction delay without significantly affecting atrial refractory periods. In All-treated heart, extra stimuli from right atrial appendage resulted in a high prevalence of repetitive atrial responses (RARs, 100%), which was not observed in the HT-treatment rats (38%, $p < 0.05$). The siRNAs targeting HSP72 prevented the effect of HT-induced effects in response to All-induced phosphorylation of ERK1/2.

Conclusion: Our results suggest that an induction of HSP72 could be a useful strategy for preventing the development of AF substrate where RAS activation is involved.

P495 Long term angiotensin converting enzyme-inhibition and postoperative risk of atrial fibrillation following coronary artery bypass grafting



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Postoperative atrial fibrillation (AF) occurs in up to 50% of patients and represents the most common complication after coronary artery bypass grafting (CABG). AF deteriorates haemodynamic parameters, is associated with the risk of embolic events and prolongs hospital stay. The reduction of the occurrence of postoperative AF is a desirable goal in preventive strategies. Recent studies demonstrated significant reduction of paroxysmal AF in the groups of patients with hypertension, heart failure, after myocardial infarction or cardioversion treated with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers.

The AIM of the study was to determine whether chronic ACEI therapy has an impact on the incidence of postoperative AF after isolated CABG.

Methods: The study was performed in 360 patients with coronary artery disease of mean age 61.9±8 years, 72.5% males, 12.8% with unstable angina, average EuroSCORE 3±2.3, mean number of diseased vessels 2.6±0.7, average CCS 2.6±0.7. The study was designed as a prospective, observational study. 255 patients receiving ACEI - long term therapy for at least one month, and 105 patients without ACEI (control group) underwent isolated CABG.

Results: Postoperative AF was observed in 20.4% of ACEI group and 32.4% of controls ($p=0.015$). Multivariate analysis identified three risk factors of postoperative AF: age (OR 1.06; 95% CI 1.02-1.09; $p<0.001$), history of paroxysmal AF (OR 5.2; 95% CI 2.4-11.2; $p<0.001$), circumflex artery stenosis (OR 2.2; 95% CI 1.1-4.5; $p<0.001$). ACEI therapy was the only independent factor decreasing the risk of postoperative AF in patients after CABG (OR 0.44; 95% CI 0.25-0.78; $p<0.001$). Relative risk reduction of postoperative AF for ACEI therapy equals 37%.

Conclusion: Long term angiotensin converting enzyme-inhibition significantly reduces postoperative AF in patients undergoing coronary artery bypass grafting.

P496 No effect of angiotensin II type 1 receptor blockade on markers of inflammation in patients undergoing electrical cardioversion for atrial fibrillation



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Purpose: Several studies have suggested that treatment with angiotensin II type 1 receptor blockers (ARBs) prevents the development of atrial fibrillation (AF). The underlying mechanisms are poorly understood, but modulation of inflammatory processes has been proposed. Thus, we hypothesised that treatment with the ARB candesartan would reduce the levels of inflammatory markers in patients with AF undergoing electrical cardioversion (EC).

Methods: In a randomised, double blind study (Candesartan in the Prevention of Relapsing Atrial Fibrillation, CAPRAF), 171 patients with persistent AF scheduled for EC received candesartan 8 mg o.d. or placebo for 3-6 weeks before and 16 mg o.d. or placebo for 6 months after EC. Treatment with candesartan had no effect on recurrence rate of AF. As part of this study, levels of inflammatory markers (TNF α , IL-6, CRP, CD40L, P-selectin, E-selectin and VCAM-1) were measured 3-6 weeks before EC and at the end of study in 101 patients (45 in the candesartan group). Patients who had a relapse of AF during follow-up had their blood sample taken at the time relapse of AF was diagnosed.

Results: Median time on treatment was 90 days (25, 75 percentiles 39, 211) in the candesartan group and 75 days (41, 207) in the placebo group. Baseline values, values at the end of study and changes from baseline were compared using non-parametric statistical tests. Irrespective of outcome after EC, there were no statistically significant differences between the candesartan and placebo groups for any of the markers analysed.

Conclusion: Treatment with the angiotensin II type 1 receptor antagonist candesartan had no effect on inflammatory markers in our population of patients undergoing electrical cardioversion for persistent atrial fibrillation.

P497 Effect of angiotensin II type 1 receptor (AT1R) blockade on atrial electrogram morphology in a burst paced goat model of AF



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Background: It has been postulated that the self-perpetuation of AF is caused in part by localised abnormalities in cell-to-cell conduction (structural remodeling) and that this process may be inhibited by angiotensin II type 1 receptor blockade. We examined this hypothesis in a conscious goat model of AF.

Method: Fifteen goats underwent pacemaker implant. Three goats were kept in sinus rhythm (controls) and twelve underwent atrial burst pacing as per the Allessie protocol for 1 month (3 candesartan, 3 placebo) and 3 months (3 candesartan, 3 placebo). Goats were cardioverted and atrially paced at 400ms. Epi-cardial mapping was performed on the right atrium using a rectangular array of 70 unipolar electrodes with a 3.57mm separation. The morphology of the unipolar electrograms were divided into 3 categories: single potential, double potentials (amplitude of the smallest being $\geq 25\%$ of the largest) and fractionated potentials (>2 negative deflections). Atrial conduction velocity was calculated by the method of triangulation.

Results: After 3 months of AF the atrial electrograms were more prolonged and fractionated (see table). There was no difference in atrial conduction velocities between any of the groups. There was no significant difference between the placebo and candesartan group in terms of any of the measured parameters.

	Control	1 month placebo	3 month placebo	p value
Electrogram duration (ms)	34±3	35±3	56±11	$p<0.01$
Double electrograms	15±13%	11±3%	30±17%	$p=ns$
Fractionated electrograms	0%	0%	38±10%	$p<0.01$
Conduction velocity (cm/s)	89±14	86±9	83±18	$p=ns$

	Control	1 month candesartan	3 month candesartan	p value
Electrogram duration (ms)	34±3	35±3	58±11	$p<0.01$
Double electrograms	15±13%	10±9%	26±3%	$p=ns$
Fractionated electrograms	0%	0%	29±24%	$p<0.01$
Conduction velocity (cm/s)	89±14	89±15	78±13	$p=ns$

Conclusion: Local atrial electrograms increase in duration and are more fractionated after 3 months of AF, with no change in macroscopic conduction velocity. These findings are consistent with localised conduction abnormalities as a contributory cause to the self perpetuation of AF and are unaffected by AT1R blockade.

P498 Treatment with the angiotensin II type 1 receptor antagonist candesartan does not reduce recurrence rate of atrial fibrillation after electrical cardioversion



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Purpose: To study the effect of treatment with the angiotensin II type 1 receptor antagonist candesartan on the recurrence rate of atrial fibrillation (AF) after successful electrical cardioversion (EC).

Methods: In a double blind, placebo-controlled study (Candesartan in the Prevention of Relapsing Atrial Fibrillation, CAPRAF), 171 patients with persistent AF were randomised to receive candesartan 8 mg once daily ($n = 85$) or placebo ($n = 86$) for 3-6 weeks before and candesartan 16 mg once daily or placebo for 6 months after EC. Primary endpoint was recurrence of AF after successful EC.

Results: Nine patients converted to sinus rhythm before EC, 6 in the candesartan group and 3 in the placebo group. Three patients in the candesartan group were withdrawn before EC (adverse events 2, withdrawn consent 1). EC was unsuccessful in 22 patients, 9 in the candesartan group and 13 in the placebo group. A total of 68 patients in the candesartan group and 69 patients in the placebo group were successfully cardioverted. Forty-eight patients (71%) in the candesartan group and 45 (65%) in the placebo group had a recurrence of AF during six months follow-up. Kaplan-Meier analysis showed no difference in survival free of AF (log rank test: $p=0.421$). Median time to recurrence was 8 and 9 days in the candesartan and placebo groups, respectively.

Conclusion: Treatment with the angiotensin II type 1 receptor antagonist candesartan for 3-6 weeks before and 6 months after electrical cardioversion had no effect on the recurrence rate of atrial fibrillation.

P499 Inflammation, atrial fibrillation and acute myocardial infarctionS. Patane¹, R. Saviolo², F. Patane³, F. Marte⁴, P. Pugliatti⁵.¹Cardiologia Nuovo Presidio Ospedaliero Cutroni Zodda-Barcellona Pdg(Me)Ausl5Me, Italy; ²Cardiologia Universitaria Aso San Giovanni Battista Molinette Torino, Italy; ³Cardiologia Aso San Giovanni Battista Molinette Torino, Italy; ⁴Cardiologia Nuovo Presidio Ospedaliero Cutroni Zodda-Barcellona Pdg(Me)Ausl5Me, Italy; ⁵U.O.C. Cardiologia E Riab.Card.Policlinico Universitario G.Martino Messina, Italy

Aim of study: C-reactive protein (CRP) is a high-sensitivity commonly used marker for acute inflammatory response. Inflammatory cells release cytokines, which stimulate hepatocytes to release CRP. Elevation in CRP levels are associated with poor prognosis in acute coronary syndromes. The presence of systemic inflammation determined by elevations in CRP has also been associated with persistence of atrial fibrillation (AF) and there is mounting evidence to support the influence of inflammation in the pathogenesis of AF. Aim of this study was to investigate if there were relations among peak serum CRP levels, white blood cell count and adverse cardiac events in patients with Acute Myocardial Infarction (AMI) and without previous occurrence of atrial fibrillation who developed AF during AMI.

Methods: We studied, in a retrospective analysis, 226 patients with AMI [149 patients with Non-ST-Segment Elevation Myocardial Infarction (NSTEMI) and 77 patients with ST-Segment Elevation Myocardial Infarction (STEMI)], divided in groups according to the development of AF during AMI (27 patients, named af group) or not (199 patients, named n af group). So we investigated the serum CRP levels, white blood cell count and the results of coronary angiography. Coronary angiography was possible in 221 patients (17 patients of af group and 171 patients of n af group). We fixed a scale of 3 levels of angiographic findings: 0 = stenosis <75%; 1 = one stenosis >75%; 2 = two stenosis >75%; 3 = three stenosis >75%. So we fixed a simple endpoint (recurrent angina, recurrent AMI, heart failure, death) within 12 months from hospitalization and a composite endpoint with at least a single adverse event.

Results: We found significant correlations as follows:

Wbc (af group 11837,04 SD 2666,91; n af group 0198,79 SD 989,75) P value < 0,001

CRP (af group 85,22 SD 64,59; n af group 32,78 SD 47,72) P value < 0,001

Ejection Fraction (af group 44,33% SD 6,61%; n af group 50,81% SD 5,31%) P value < 0,001

Recurrent AMI (af group 22,22% (6p); n af group 4,52% (9p) P value 0,002

Events (comp. endpoint) (af group 59,26% (16p); n af group 25,13% (50p) P value < 0,001

Degree of stenosis (af group 1,65 SD 0,70 (17p); n af group 1,32 SD 0,58 (171p) P value 0,029

Conclusions: These data suggest that in patients with AMI, the occurrence of AF has significant correlations with a higher wbc and serum CRP levels, with a higher degree of Coronary Artery Disease, with a higher incidence of recurrent AMI and with a higher incidence of major adverse cardiac events.

PROGNOSIS

P500 Depression as a controlled risk factor for heart failure progression in patients with coronary heart disease. The influence of patients education

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The aim of this study is to prove the relation between severity of depression and course of heart failure and to estimate the influence of patients structured education on the prognosis of the disease.

Methods: The study comprised 147 patients aged 51 to 73 (mean 63,3 ± 7,5) with 2-3 functional class of heart failure (NYHA) and mild and moderate depression level. The participants were randomized to two groups: the main, consists of 73 educated with a special program patients and 74 control- non educated. These groups were comparable by clinical and haemodynamical characteristics. Physical health status and exercise tolerance (the six-minute walk test) were assessed in baseline and 6 months after education. Also, in both groups were assessed the number of readmissions, the quality of life with Minnesota Living with Heart Failure Questionnaire (MLHFQ) and compliance with semistructural clinical interview and the Likerts scale. Depressive disorders were detected by the Zung self-estimation test.

Results: At baseline, the patients with higher functional class of heart failure and lower tolerance to physical load have higher severity of depressive symptoms ($r=0,58$; $p<0,001$), and also, high level of depression was associated with low quality of life ($r=-0,6$; $p<0,001$) and compliance to treatment ($r=-0,5$; $p<0,001$). After year we observed the decrease of functional class of heart failure in 12% patients in the intervention group and in 14% in control group the course of disease progressed. In the educated patients the level of depression became lower, which was associated with improving indicators of compliance and quality of life ($D=60,1 \pm 8,2\%$ and $D=24,4 \pm 5,1\%$, respectively; $p<0,05$; $D=-8,4 \pm 2,4\%$ and $D=2,3 \pm 0,8\%$ respectively; $p<0,05$) compared with control group. In control

group the number of patients with moderate depression has increased. During once year of follow up the intervention group has the fewer number of readmission due to the progression of the symptoms of heart failure (7,4% and 12,5%, respectively; NS) compared with control group.

Conclusions: Depression symptoms constitute an independent risk factor for progression of heart failure in patients with coronary heart disease. Depression in such patients is associated with lower quality of life and compliance to treatment. A formal education reduces the symptoms of depression, improving the indicators of compliance and quality of life, reduces functional class of heart failure and number readmissions.

P501 Renal pulsatility index is an independent predictor of the progression of renal dysfunction in chronic heart failure patients

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Purpose: Renal dysfunction is often observed in chronic heart failure (CHF) patients and is associated with adverse prognosis. The pulsatility index (PI) is used as a Doppler measurement of downstream renal artery resistance and is related with the rate of decline in renal function in patients with chronic renal disease. We now hypothesized that in CHF patients an increased renal PI may correlate with progression of renal dysfunction.

Methods: 68 consecutive CHF patients with dilative cardiomyopathy and ejection fraction (EF) < 45% (mean age 63.8±9.8 years; 60 males) were prospectively studied. At baseline all underwent clinical evaluation, a complete echocardiography and Doppler investigation of right renal artery flow at interlobar level. The PI, obtained from the formula $(V_{max}-V_{min})/V_{mean}$, was measured. Blood drawings were performed at baseline and 6 months and creatinine clearance (CL) was calculated using the Cockcroft-Gault equation. The relation between the difference of creatinine clearance over time (D CL) and clinical, biochemical, echocardiographic and renal Doppler parameters was assessed.

Results: At univariate analysis, the only variables which correlated significantly with D CL were PI ($r=-0,35$; $p=0,0036$) and furosemide milligrams per day ($r=-0,28$; $p=0,02$) while the relationship between NYHA class and D CL did not reach statistical significance ($r=-0,21$; $p=0,08$). A trend towards a significant worsening of CL was found in non statins ($p=0,053$), non β -blockers users ($p=0,13$) and smokers ($p=0,06$). Multiple regression analysis found that only PI ($p=0,04$) was independently associated with D CL. No relationship was evidenced between EF, blood pressure or CL at baseline and D CL.

Conclusions: In CHF patients renal PI is an independent predictor of the progression of renal dysfunction.

P502 Heart rate and heart rate variability predict total mortality beyond conventional risk factors, C-reactive protein, and NT-pro Brain Natriuretic PeptideA. Sajadieh¹, O.W. Nielsen¹, V. Rasmussen², J. Fischer Hansen¹.¹Bispebjerg Hospital, Copenhagen, Denmark; ²Hvidovre Hospital, Cardiology, Copenhagen, Denmark

Background: Previous studies show that reduced heart rate variability (HRV) and increased heart rate (HR) are independent risk factors for total mortality. However their prognostic value in the era of new and potent biomarkers has not been evaluated.

Methods and results: 638 middle-aged and elderly subjects with no apparent heart disease were selected from community and studied by interview, clinical, laboratory examination, and 24-h Holter monitoring. Time domain measures of HRV were studied. All subjects were followed for up to five years. Cut-off points for CRP was set at 2.5 µg/ml and for NT-pro BNP at 15 pmol/l. In separate Cox models, CRP, NT-pro BNP, HR, and HRV were all associated with total mortality after adjustment for conventional risk factors. In combined COX models (Table 1) with CRP, NT-pro BNP, conventional risk factors, and HR or SDNN (standard deviation for the mean value of the time between normal complexes), both HR and SDNN remained as independent risk factors of total mortality.

Table 1. Cox-proportional hazard models (full models) showing the associations between variable of interest with mortality

		Total mortality Hazard Ratio (95% CI)	P-value
Model 1*	NT-pro BNP	1.42 (0.73-2.78)	0.31
	CRP	2.05 (1.04-4.06)	0.020
	SDNN	0.67 (0.47-0.95)	0.025
Model 2*	NT-pro BNP	1.47 (0.75-2.88)	0.26
	CRP	2.06 (1.04-4.10)	0.038
	Heart Rate	1.29 (1.03-1.62)	0.034

NT-pro BNP: above versus below 15 pmol/l. CRP: above versus below 2.5 µg/ml. SDNN: for one standard deviation. HR for each 10 bpm. *Adjusted for conventional risk factors.

Conclusions: Both HR and HRV remain as independent risk factors for total mortality in the new era, after adjustment for CRP, NT-pro BNP, and conventional risk factors.

P503 High sensitivity C-reactive protein predicts cardiovascular death in low risk subjects whereas N-terminal pro brain natriuretic peptide predicts cardiovascular death in moderate to high risk subjects

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Background: We have shown that N-terminal pro brain natriuretic peptide (NT-proBNP), high sensitivity C-reactive protein (hsCRP) and urine albumin/creatinine ratio (UACR) predicted cardiovascular (CV) events in a general population aged 41, 51, 61 or 71 years. The aim of this study was to investigate the impact of cardiovascular risk on the prognostic importance of NT-proBNP, hsCRP and UACR in the general population.

Methods: In 1993 we measured CV risk factors, serum NT-proBNP, UACR and serum hsCRP. CV death was assessed after 9.5 years.

Results: The 2482 subjects were divided in four groups: A high risk group of 437 subjects who received cardiovascular medication or had diabetes, prior myocardial infarction or stroke. The remaining apparently healthy subjects were divided in a low risk group of 536 subjects without any elements of the metabolic syndrome defined by the International Diabetes Foundation, a moderate/low risk group of 1098 subjects with 1-2 elements and a moderate/high risk group of 411 subjects with more than 3 elements of the metabolic syndrome. HsCRP above the median value of 1.81 mg/l was associated with CV death in the low risk group (Table 1, $P < 0.05$ for interaction), whereas NT-proBNP above the median value of 66.5/32.1 pg/ml (women/men) was associated with CV death in the moderate to high risk groups (Table 1, $P = 0.06$ for interaction). UACR above the median value of 0.30/0.20 mg/mmol (women/men) was associated with CV death in all groups.

Incidence of cardiovascular death

Risk Group:	Low	Low-moderate	Moderate	High
Low NT-proBNP	1.3%	1.1%	1.6%	4.1%
High NT-proBNP	2.1%, NS	5.2%, $P < 0.001$	8.6%, $P < 0.01$	20.3%, $P < 0.001$
Low hsCRP	0.8%	2.3%	2.9%	15.6%
High hsCRP	4.1%, $P < 0.01$	4.3%, $P = 0.09$	5.2%, $P < 0.05$	14.7%, NS
Low UACR	0%	1.9%	2.6%	8.6%
High UACR	3.6%, $P < 0.01$	4.6%, $P < 0.05$	6.6%, $P = 0.051$	17.8%, $P < 0.05$

Conclusion: CV death was predicted in low risk subjects by hsCRP, in moderate to high risk subjects by NT-proBNP and in all subjects by UACR. This supports the hypothesis that hsCRP is elevated early in the development of atherosclerosis, NT-proBNP is a marker of subclinical CV damage later in the atherosclerotic process, whereas UACR is a marker of subclinical CV damage at all stages of the process.

P504 The impact of racial differences on morbidity and mortality in Asian patients with congestive heart failure: A study of the multiracial population in Singapore

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Aims: We assessed the impact of racial differences in predicting morbidity and mortality in Asian patients with congestive heart failure (CHF).

Methods: 668 patients (Age 66±12 years, Ejection fraction 29±13%, NYHA 1 to 4) were prospectively followed up for 36±12 months. The majority of patients were Chinese (72%), followed by Malays (17.1%), and Indians (10.9%). Occurrence of cardiac events, defined as the combined end-point of death or CHF readmission was documented.

Results: 188 patients (28%) reached the combined end-point (63 deaths, 125 readmissions). Diabetes (61% vs 54% vs 44%, $p = 0.013$), hyperlipidemia (70% vs 53% vs 55%, $p = 0.036$), and peripheral vascular disease (8.5% vs 0.9% vs 3.6%, $p = 0.031$) were significantly more prevalent in Indians compared to Malays and Chinese. Indians were also significantly more likely than Malays or Chinese

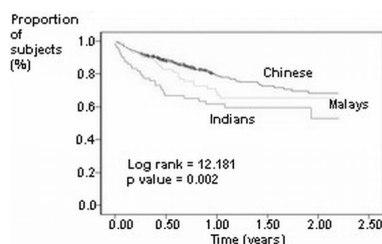


Fig. 1. Kaplan-Meier survival curves comparing cardiac event free survival between Indian, Malay and Chinese patients with CHF.

to either die or be readmitted (39% vs 27% vs 21%, $p = 0.003$) or be readmitted (32% vs 24% vs 16%, $p = 0.001$). Mortality was not significantly different between Indians, Malays or Chinese (14% vs 8% vs 9%, $p = 0.380$). Survival free from CHF readmission or death was significantly lower in Indians compared to Malays or Chinese (log rank = 12.181, $p = 0.002$) (Figure 1).

Conclusion: Indians with CHF had a worse clinical outcome compared to Malays or Chinese, due mainly to a higher CHF readmission rate. This may in part be due to the higher prevalence of diabetes in their population.

P505 An elevated cholesterol has a protective effect in patients with heart failure who have an increased inflammatory response

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Background: An elevated hsCRP has been shown to confer a poor prognosis in patients with systolic heart failure. Some have advocated the use of statin therapy as anti-inflammatory therapy. Paradoxically an elevated cholesterol level confers a better prognosis in such patients. Cholesterol may protect patients from increased inflammation secondary to endotoxins. We aimed to see if elevated cholesterol was protective and if statin therapy was safe in patients with systolic heart failure.

Methods: A group of 888 patients with left ventricular systolic impairment were followed up for a period of three and a half years.

Results: The mean age of the population was 71±10 yrs. 635 (72%) were men. 462 (52%) of the patients were receiving statin therapy. In our population the median value of CRP was 5 (inter-quartile range 2.8 to 11). For total cholesterol we had a median value of 4.7 (inter-quartile range 4.1 to 5.5). Those receiving a statin had a better prognosis than those who did not receive one. The relative risk (RR) being 0.93 (confidence interval, 0.88 to 0.99, $p = 0.03$) in the statin group. To examine how CRP and cholesterol interacted we graded patients into 4 groups using the population medians of CRP and cholesterol to act as the points at which we would describe the values as high or low. We found that those with a high CRP and low cholesterol had the highest RR of 1.28 (1.18 to 1.40). Those with a high CRP and high cholesterol though still at a higher risk of death with a RR of 1.17 (1.08 to 1.27) had an improved survival compared to the high CRP low cholesterol group. In both groups with a CRP lower than the population median survival was better. The higher cholesterol group had the greater relative risk of 1.03 (0.96 to 1.09) though this was not significant. When examining the effect of statin therapy in each of these groups we did not see a difference in relative risk except for those in the worst prognostic group (high CRP, low cholesterol). The use of a statin in this group indicates a strong trend toward a protective benefit with a relative risk of 0.86 (0.74 to 1.01, $p = 0.096$).

Conclusion: In patients with systolic heart failure raised CRP and low total cholesterol confers a poorer prognosis. Increased total cholesterol appears to be protective in patients with an increased inflammatory response. Interestingly the use of statins in those with a low cholesterol and high CRP appears to improve prognosis. The use of statins in the other groups showed little significant benefit. Further studies are required to determine at what level cholesterol may be protective in the setting of an elevated CRP.

P506 Structural markers of carotid atherosclerosis and left ventricular hypertrophy as independent predictors of cardiovascular events

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Purpose: Carotid intima-media thickness (IMT) and left ventricular hypertrophy (LVH) are anatomic markers of preclinical disease which predictive value has been well demonstrated. However it is not still known which among structural markers of vascular and cardiac alterations better stratifies the risk of cardiovascular (CV) events.

Aim: Compare the prognostic value of IMT and LVH in a sample of subjects with cardiovascular risk factors, with or without previous CV disease.

Methods: We prospectively studied 244 patients (47% male, mean age 48±14) with at least one CV risk factor, who had performed a vascular and cardiac ultrasonographic examination. Intima-media thickening was defined as IMT > 0.85 mm. LVH was defined as left ventricular mass (LVM) > 104 g/m² for women and > 116 g/m² for men.

Results: Hypertension was present in 31% of cases, type 2 diabetes in 12%, hypercholesterolemia in 48% and previous CV disease in 10% (Framingham risk 14±3%). The mean clinical follow-up was 85±27 months. The primary end point was fatal and non fatal CV events. Secondary end points were CV and all cause mortality. Subjects with baseline LVH (group 1=12%) have an higher relative risk (RR) of CV events, (RR=2.98, IC 1.27-7.79), all cause mortality (RR=2.3, IC 0.39-13.6) and CV mortality (RR=6.1, IC 0.95-39.3) than subjects with normal LVM (group 2=88%). Kaplan Meier curves show a lower CV events free survival and CV mortality free survival in group 1 than in group 2 (both $p < 0.0001$ log-rank test). The same analysis was performed to analyze the prognostic value of IMT. Subjects with baseline IMT > 0.85 mm (16%) show an higher risk of CV events, (RR=2.89, IC 1.89-4.42) and all cause mortality (RR=2.29, IC 1.55-6.45) than

subjects without vascular alterations (84%), while the risk of CV mortality not significantly increased (RR=0.84, IC 0.32-1.24). Survival analysis shows a lower CV events free survival in presence of IMT ($p < 0.0001$ log-rank test). In a multivariate analysis after previous CV disease ($p < 0.001$), LVH ($p < 0.01$) followed by IMT ($p < 0.02$), were independent predictors of CV events, while conventional CV risk factors and their changes during clinical follow-up did not enter the model.

Conclusion: In our population LVH and IMT show a similar performance in stratifying the risk of CV events, but LVH seems to predict better CV and all cause mortality than IMT.

P507 Cardiac 123I-MIBG Imaging is a useful tool for the evaluation of diastolic heart failure as well as systolic heart failure



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Background: Cardiac sympathetic nerve activity evaluated by cardiac 123I-MIBG scintigraphy has been shown to have diagnostic and prognostic significance in systolic heart failure (S). However, it remains unknown whether this is true in diastolic heart failure (D). In this study, we evaluated cardiac 123I-MIBG imaging in D subjects and compared the findings with those of either S or control subjects.

Methods: The subjects were 94 consecutive patients hospitalized for chronic heart failure (CHF), and 30 consecutive patients with hematological neoplasm served as a control group without CHF (C) between April 2003 and March 2004. Patients with CHF were classified into 2 groups: group D (LVEF $\geq 50\%$; mean $64.7 \pm 7.1\%$, $n=47$, 77.9 ± 8.6 years) and group S (LVEF $< 50\%$; mean $34.9 \pm 7.9\%$, $n=47$, 66.4 ± 13.9 years). Group C had normal LV function (mean LVEF $67.1 \pm 4.6\%$, $n=30$, 49.2 ± 13.0 years). Cardiac 123I-MIBG scintigraphy was evaluated as the heart-to-mediastinum ratio in the delayed image (H/M) and the washout rate (WoR). NYHA class and plasma BNP concentration were also determined in each subject with CHF.

Results: In group D, H/M was significantly lower and WoR was significantly higher than that in group C, although no significant differences were observed in either H/M, WoR, NYHA class or plasma BNP concentration between groups D and S (H/M ($D1.91 \pm 0.45^*$, $S1.90 \pm 0.41^*$, $C2.95 \pm 0.44$), WoR ($D50.8 \pm 17.4^*$, $S55.6 \pm 14.2^*$, $C27.7 \pm 10.7\%$), BNP ($D728 \pm 796$, $S826 \pm 711$; pg/ml), NYHA ($D2.7 \pm 0.5$, $S2.8 \pm 0.4$), $^*p < 0.01$ vs. C).

Conclusions: These results suggest that 123I-MIBG imaging is a useful tool for the evaluation of D. Furthermore, cardiac sympathetic nerve activity in D is accelerated to the same degree as S.

P508 The frequency and prognosis of newly diagnosed heart failure with preserved systolic function: a contemporary UK population-based experience



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Background: Epidemiological studies demonstrate an early high risk period for patients with incident heart failure (HF) with up to 25% not surviving six months. In the mid-1990s, two UK (Hillingdon and Bromley, London) population-based studies reported preserved left ventricular (LV) systolic function in 15-20% of incident HF cases. Data are scarce on the early prognosis for patients with newly diagnosed preserved systolic heart failure (PSHF) in the general population.

Aims: To describe the frequency and survival of a population-based cohort of patients in the first six months after a new diagnosis of PSHF.

Design: Two-centre UK population-based study (The Hillingdon Hospital, London, and The Conquest Hospital, Hastings).

Methods: New cases of HF were identified by daily surveillance of general practitioner referral and acute hospital admissions. Patients with suspected HF underwent clinical assessment, chest radiography, electrocardiography and echocardiography. A diagnosis of HF was made based on the ESC criteria. Patients were flagged at the Office of National Statistics for mortality. Cases of HF were defined as PSHF in the absence of left ventricular (LV) systolic dysfunction or significant valve disease, on echocardiographic assessment.

Outcome measures: All-cause mortality.

Results: Between Jan 2004 and Oct 2005, 396 patients with incident HF (61% males, median age 75.2 (SD 12.3) years) were identified. Of the total cohort, 45 patients (11%) had PSHF. A diagnosis of PSHF (vs. other HF) was associated with older age (mean 79.4 (9.1) vs. 72.7 (12.5) years; $p < 0.001$), female gender (71% vs. 35%; $p < 0.0001$), a history of hypertension (84% vs. 50%; $p < 0.0001$), higher systolic blood pressure (152 (29) vs. 131 (25) mmHg; $p < 0.0001$), an increased inter-ventricular septal diameter (mean 1.32 (0.26) vs. 1.08 (0.24) cm; $p < 0.0001$) and an increased LV posterior wall thickness (mean 1.17 (0.17) vs. 1.05 (0.23) cm; $p = 0.01$) at baseline. There was no statistical difference in symptom severity (87% vs. 88% in NYHA class III/IV). Overall, there were 59 deaths during a median follow up of 10 months. In the PSHF group, six-month mortality was 5% vs. 16% ($p = 0.04$) in the other HF group.

Conclusions: In the UK general population, a diagnosis of heart failure with pre-

served left ventricular systolic function accounts for approximately one in ten incident cases and is more common in older women with hypertensive heart disease. Despite similarly severe symptoms at presentation, a diagnosis of preserved systolic heart failure is associated with better early prognosis than other types of heart failure.

P509 The significance of cardiac sympathetic nerve imaging with 123I-metaiodobenzylguanidine (MIBG) for predicting ventricular tachycardia in patients with idiopathic dilated cardiomyopathy



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Background and Objectives: Ventricular arrhythmia is an important cause of death in idiopathic dilated cardiomyopathy (IDCM). Decreased uptake or increased "washout" of 123I-metaiodobenzylguanidine (MIBG)-derived radioactivity is associated with worse prognosis or more severe disease in cardiac diseases. This study is designed to assess the relation between cardiac MIBG uptake and occurrence of ventricular tachycardia (VT) in patients with IDCM.

Methods and Results: Twenty-one patients (13 men, mean age 56.8 ± 11.3 years) with angiographically proved IDCM were studied and divided into 2 groups with clinically documented VT (group A; 5 patients) and without VT (group B; 16 patients). Echocardiography, myocardial dual SPECT imaging with MIBI and MIBG were performed in all patients. 123I-MIBG was evaluated by early (15min) and delayed (3hours) uptake, heart to mediastinum uptake (H/M) ratio, global and regional washout ratio (WOR) defined as [early H/M ratio - delayed H/M ratio] / early H/M ratio $\times 100$. We also quantified the presence of MIBI/MIBG mismatched regions. The clinical variables, echocardiographic parameters and 123I MIBG-derived parameters were compared between the 2 groups.

Results: There were no significant difference in age, LVEF ($27 \pm 16\%$ versus $28 \pm 13\%$), LVESD and LVEDD between the 2 groups. A significant negative correlation was present between early H/M ratio and LVEDD (Spearman's correlation, $r = -0.638$, $P = 0.03$), early H/M ratio and LVESD ($r = -0.624$, $P = 0.03$). Delayed H/M ratio also showed a significant negative correlation with LVEDD ($r = -0.483$, $P = 0.036$) and LVESD ($r = -0.448$, $P = 0.054$). Group A patients had lower early or delayed H/M ratio and higher general WOR than group B, although statistically not significant. The regional WOR at inferior wall and septum showed a tendency to be higher in group A (10.18 ± 11.54 versus 2.94 ± 5.34 ; $P = 0.23$ and 12.8 ± 13.9 versus 3.9 ± 6.5 ; $P = 0.093$, respectively) than group B.

Conclusion: Cardiac 123I-MIBG scan partially reflect the vulnerability to VT occurrence in IDCM. These results support the feasibility of cardiac 123I-MIBG scan as a prognostic tool in IDCM patients.

P510 Intrathoracic impedance monitoring to predict cardiac decompensation

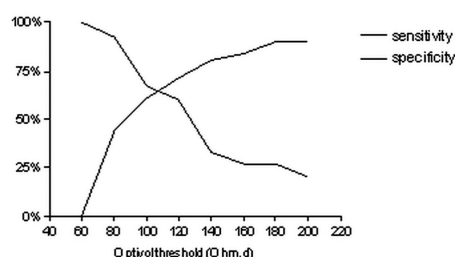


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Background: Monitoring pulmonary fluid status may be valuable in heart failure patients to decrease hospitalizations for decompensated heart failure. Intrathoracic impedance measurement has been introduced in the Insync Sentry biventricular ICD (Medtronic Inc). An audible alarm (Optivol alert) can be triggered when the impedance index rises above a predefined level. In this study we evaluated the clinical value of this alarm and its prediction for decompensated heart failure.

Methods: One-hundred-fifteen consecutive patients (NYHA class 3.0 ± 0.5 and LVEF $25 \pm 5\%$) received an Insync Sentry biventricular ICD. The default setting for the alarm was set at $60 \Omega \cdot d$. When presenting with Optivol alert, current hemodynamic status was evaluated by history, drug use, physical examination, laboratory tests and chest x-ray.

Results: During follow-up (9 ± 5 months), there were 46 presentations with Optivol alert in 31 patients. Only in 15 cases (32%) clinical signs and symptoms of heart failure were present, whereas in the remaining patients clinical signs of heart failure were absent ($P < 0.05$). The proposed cut-off value of $60 \Omega \cdot d$ was very sensitive to detect heart failure, but at the cost of a very low specificity. ROC curve analysis (Figure) showed that increasing the threshold for Optivol alarm



ROC analysis on Optivol threshold

provided a better balance between sensitivity and specificity for heart failure, with the optimal cut-off value identified at 120 Ω -d.

Conclusion: Intrathoracic impedance measurement as present in the Insync Sentry biventricular ICD may be a useful tool for pulmonary monitoring fluid status. The proposed threshold for Optivol alert 60 Ω -d is very sensitive but not specific for assessment of heart failure; adjustment of threshold settings may yield a superior balance between sensitivity and specificity.

P511 Clinical events preceding the development of heart failure in patients with stable angina pectoris



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Background: The clinical characteristics of patients with stable angina pectoris who develop heart failure and the events preceding its onset are poorly documented. The ACTION trial, which compared treatment with long-acting nifedipine GITS 60 mg to placebo, followed 7665 stable angina patients for a mean follow-up of 4.9 years.

Methods and results: Baseline characteristics were compared between patients who did and those who did not develop new heart failure during follow-up. Acute myocardial infarction, coronary revascularisation (PCI or CABG), chest pain requiring hospitalisation and atrial fibrillation or irregular pulse were considered as prior clinical events. These events during follow-up were compared between cases of new heart failure and follow-up duration-matched controls. 207 patients (2.7% (of 7665)) developed new heart failure during follow-up. Compared to patients who did not develop heart failure, patients were significantly ($p < 0.001$) older and had a more extensive baseline cardiovascular history which included a higher prevalence of diabetes, atrial fibrillation, irregular pulse rate or history of heart failure, a lower left ventricular ejection fraction, a higher serum creatinine and glucose, a lower haemoglobin, were more frequently on diuretics and had more frequently a history of hypertension treated with drugs ($p < 0.002$). The preceding clinical events for the 207 patients were chest pain requiring hospitalisation (23%), acute myocardial infarction (23%), atrial fibrillation or an irregular pulse rate (23%) and a revascularisation procedure (7%). No short-term precipitating event was identified for the remaining 24% of patients. Nifedipine reduced the incidence of heart failure from 0.65 to 0.46 events per 100 years at risk [hazard ratio (HR) 0.71, 95% CI 0.54 - 0.94; $P = 0.015$]. The reduction was not related to a decline in myocardial infarction or arrhythmias but in part may be explained by lowering of blood pressure and reduction of minor ischemic events.

Conclusion: The development of heart failure is uncommon in patients with stable angina, and is even rarer in the absence of an obvious precipitating factor.

P512 5 year follow up of systolic, diastolic and right heart failure; do they carry the same prognosis?



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Introduction: Systolic heart failure (SHF) has a poor prognosis, however the prognosis in diastolic (DHF) and right heart failure (RHF) is less well known. The aim of this study was to study outcomes in patients with SHF, DHF & RHF attending a teaching hospitals heart failure clinic.

Methods: Patients were prospectively enrolled (2000-2005). Data collected at visits included type and aetiology of heart failure, NYHA functional class and medication use. The primary endpoint was mortality, with outcome data referenced to medical records.

Results: 659 patients were enrolled with a mean age of 71 ± 14 years, with 65%

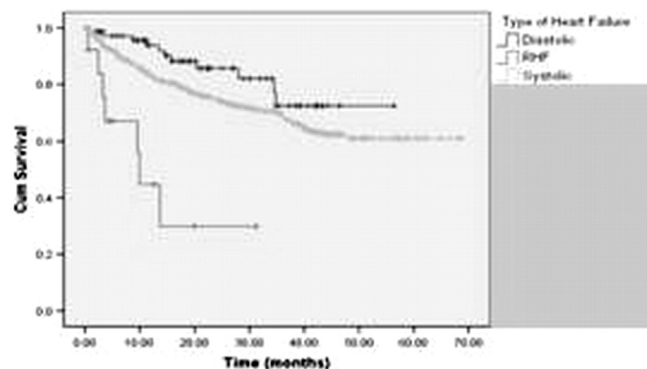


Fig. 1. Kaplan-Meier plot of cumulative survival in subjects according to the type of heart failure (log rank $p < 0.001$).

male and 35% female. 22% were in class I, 55% class II, 22% class III and 2% class IV. The mean followup period was 11 ± 14 months. 568 (86%) had SHF, 76 (12%) DHF and 15 (2%) RHF. SHF aetiologies were ischaemia (62%), idiopathic (22%), hypertension (6%), alcohol (5%), post chemotherapy (2%) and other (3%). DHF aetiologies were hypertension (74%), respiratory (4%), and other (22%). All RHF were due to respiratory causes. 10.0% of subjects with SHF were not on B Blockers due to side-effects (25%) or contraindications (75%), 3% were not on ACE/ARB due to side-effects (44%), renal impairment (31%) or contraindications (25%), whilst 43% were on spironolactone. The primary endpoint of mortality occurred in 159 (28%) patients with SHF, 11 (14%) with DHF and 7 (47%) with RHF ($\chi^2 = p < 0.001$; Figure 1). At final visits 23% were in class I, 52% class II, 22% class III and 3% class IV.

Conclusions: Patients with DHF have a better prognosis than patients with SHF, whilst those with RHF have a worse prognosis. Heart failure of any aetiology carries a poor prognosis and is best treated in a specialised, multidisciplinary clinic setting.

P513 Prognostic values of laboratory markers for haemostasis, rheology, inflammation and endothelial function in patients with left ventricular systolic dysfunction



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Introduction: Left ventricular systolic dysfunction (LVSD) is associated with haemostatic and rheologic abnormalities, inflammation and endothelial dysfunction that may be prognostically important.

Methods 455 consecutive patients attending a local hospital heart failure service with at least mild-to-moderate LVSD and on stable treatment were followed for 1 year. Baseline blood samples were analysed for D-dimer (DD), tissue plasminogen activator (t-PA), plasminogen activator inhibitor 1, von Willebrand factor (vWF), soluble E-selectin, soluble P-selectin, fibrinogen, full blood count, haematocrit (Hct) and high-sensitivity c-reactive protein (hs-CRP). Data are presented as percentage patients and median (inter-quartile range) and hazard ratios as HR (95% confidence interval).

Results The median age was 72 (64 - 74) years and 78% were men. Aetiology of LVSD was ischaemic in 77% of the patients and idiopathic in 12%. Prevalence of hypertension, supraventricular arrhythmias and diabetes was 40%, 31% and 23% respectively. 32% of the patients had severe LVSD and 22% had NYHA III/IV breathlessness. The prescription rates for angiotensin converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker and anti-platelet or warfarin were 91%, 84% and 79% respectively.

Patients with NYHA III/IV had higher hs-CRP [5.5 (2.6-12.0) v 3.5 (1.6-7.0) mg/L] and vWF [4.1 (2.3-3.7) v 3.0 (1.8-4.5) μ g/ml] and lower haemoglobin (Hb) [12.6 (11.6-13.7) v 13.4 (12.2-14.2) g/dL], all $p < 0.01$. The level of all markers was not affected by sex, aetiology and severity of LVSD.

10% of patients had died by 1 year. These patients had higher DD [181 (93-345) v 91 (38-216) ng/ml, $p < 0.001$], vWF [3.9 (2.6-5.2) v 3.1 (1.9-4.8) μ g/ml, $p < 0.05$] and hs-CRP [6.6 (2.9-9.9) v 3.7 (1.7-7.5) mg/L, $p < 0.01$] but lower Hb [12.4 (11.2-13.6) v 13.3 (12.2-14.2) g/dL, $p < 0.001$]. DD, Hb, and t-PA were associated with all-cause mortality on univariate logistic regression analysis. After correction for sex, aetiology and severity of LVSD, NYHA, renal dysfunction and medications, DD was the only haemostatic markers that provide independent prognostic information [HRs: 2.5 (0.5-13.3), 2.2 (0.7-7.1) and 4.8 (1.8-12.8) for second, third and fourth quartiles compared to first quartile respectively, $p = 0.01$].

Conclusion In patients with heart failure and LVSD, haemostasis is perturbed especially in patients with more marked symptoms. D-dimer, a marker of fibrin generation, is independently associated with higher all-cause mortality.

P514 Increased serum bilirubin levels coincident with heart failure decompensation indicate the requisite administration of intravenous inotropic agents



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Background: We have reported heart failure (HF) patients with increased serum bilirubin levels coincident with acute decompensation have a poor prognosis, indicating simultaneously severe congestion and low cardiac output. However, the appropriate management to deal with this condition remains to be elucidated.

Methods & Results: We retrospectively investigated 112 decompensated HF patients demonstrating LVEF $< 40\%$ and systolic BP < 120 mmHg stratified with total bilirubin levels (Bil) upon hospital admission. In patients with high Bil (> 1.2 mg/dL), the immediate use of intravenous inotropics (Group A; $n = 27$) contributed to significantly more abundant diuresis (1738 ± 413 vs. 1436 ± 448 mL/day, $P < 0.01$), body weight reduction (-3.1 ± 1.7 vs. -1.9 ± 2.2 kg, $P < 0.05$), and decreased Bil (-0.7 ± 0.5 vs. -0.1 ± 0.2 mg/dL, $P < 0.001$) during the first 5 in-hospital days compared to those without (Group B; $n = 31$), in spite of a similar cumulative dose of diuretics between the 2 groups (Figure). On the other hand, there was no significant difference of clinical parameters indicating improvement from decompensation de-

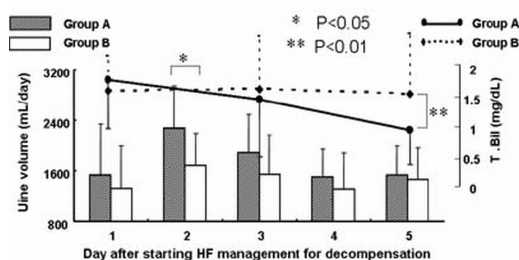


Fig. 1

scribed above between the groups of low Bil (<1.2 mg/dL) with (Group C; n=13) and without (Group D; n=41) inotropics (1546±339 vs. 1516±429 mL/day, NS; -3.1±1.7 vs. -2.8±1.6 kg, NS; -0.2±0.4 vs. -0.1±0.2 mg/dL, NS; respectively). Subsequent intravenous inotropics were administered due to unsatisfactory improvement more frequently in Group B than in Group D (27 vs. 3%, P<0.01).

Conclusion: Increased Bil coincident with HF decompensation can be a useful marker indicating the necessity of intravenous inotropics.

P515 Flow mediated dilation predicts improved cardiovascular outcomes with atorvastatin therapy in patients with nonischemic heart failure

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Background: Measurement of flow mediated dilation (FMD) is used for the evaluation of vascular endothelial function. FMD can predict cardiovascular events in several disorders including heart failure. Despite advances in therapy, morbidity and mortality from HF remain high.

Methods: 58 normolipidemic patients with non-ischemic HF and a left ventricular ejection fraction less than 35% underwent brachial artery reactivity testing (BART) to determine FMD. All patients were on appropriate medical therapy and were free of clinical symptoms for at least three months. The patients were then placed on atorvastatin (20 mg/day) for a 12-month period. A similar group (n=54) was placed on placebo. Cardiovascular morbidity and mortality, including cardiovascular death and hospitalization for HF or acute coronary syndrome (ACS), were determined in both groups.

Results: In the atorvastatin group, there was a reduction of cardiovascular deaths, hospitalizations for heart failure, and acute coronary syndrome by 26%, 32%, and 6%, respectively, when compared to placebo. In the cohort of patients treated with atorvastatin, 37 patients had an FMD less than 7.0% and 21 patients had an FMD greater than 7.0%. The most significant reduction in clinical events was observed in the group of patients with FMD greater than 7.0% (see Table).

CV outcomes: Non-ischemic heart failure

	CV Death	HF Hospitalization	ACS
Placebo (n=54)	33.7%	38.9%	17.0%
Atorvastatin FMD>7.0% (n=21)	19.8% p<0.005	23.7% p<0.005	14.1% p=0.019
Atorvastatin FMD<7.0% (n=37)	28.9% p=0.043	31.2% p=0.012	17.8% NS

Conclusions: Treatment with atorvastatin in patients with non-ischemic HF reduces cardiovascular outcomes, notably in patients with higher FMD values.

P516 Improved survival for patients with incident heart failure in the UK population

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Background: In the mid-1990s, two UK population-based (Hillingdon and Bromley, London) studies demonstrated a poor prognosis for patients with incident heart failure (HF). Mortality rates were 16% at 1-month, 22% at 3-months and 25% at 6-months in the combined studies. Population-based studies in the US suggest an improvement in survival in the past decade, but data from comparable studies in a European population are lacking.

Aims: To describe the temporal trend in survival of the first six months after a new diagnosis of heart failure.

Design: Two-centre UK population-based study (The Hillingdon Hospital, London and The Conquest Hospital, Hastings) conducted in 2004-5 compared with the earlier London studies (1995-7).

Methods: Case ascertainment was as in the London studies- new cases of HF were identified by daily surveillance of general practitioner referral and acute hospital admissions. Patients with suspected HF underwent clinical assessment, chest radiography, electrocardiography and echocardiography. A diagnosis of HF was made based on the ESC criteria. Patients were flagged at the Office of National Statistics for mortality.

Outcome measures: All-cause and cardiovascular (CV) mortality.

Results: Between Jan 2004 and Oct 2005, 396 patients (61% males, median age 75.2 (SD 12.3) years) with incident HF were identified. At the time of presentation, 314 (79%) were inpatients and 88% were in NYHA class III/IV. Prior to initial discharge or death, 28% tolerated both a β -blocker and an ACE inhibitor or ARB, 51% an ACE inhibitor or ARB alone and 3% a β -blocker alone. Five (1%) patients underwent successful ICD implantation. There were 59 deaths over a median follow up of 10 months; 86% (n=51) were CV deaths. Nineteen inpatients died during the first hospital admission (case fatality rate=6%). Overall, all-cause mortality rates were 6% [95% confidence interval (CI) 4-8%] at 1-month, 11% [8-14%] at 3-months and 14% [11-17%] at 6-months. All-cause mortality was significantly lower compared to the earlier London studies at each time-point (p<0.05). Older age, lower systolic blood pressure, lower serum sodium and higher serum urea at baseline were independently associated with the risk of CV mortality on multivariable analysis but gender, aetiology of HF and LV function were not.

Conclusions: This study demonstrates that early mortality remains high among patients with incident HF in the UK general population. However, when compared with the earlier London studies, which used similar methodology in comparable populations, our data suggest improvement in early survival over the past decade in the UK.

P517 Hospital treatment of heart failure in Poland-the results of the recent national polish study (POLKARD 2005)

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Background: In 2005 year in Poland, the large national study had been conducted, which assessed actual situation about effectiveness of heart failure (HF) management, its costs and the access to the diagnostic methods and therapeutic interventions at different levels of hospital care.

Aim: The aim of this paper was to present the recent data concerning HF management in hospitals and clinics in Poland.

Material and Methods: The study was undertaken in 2005, as a part of The National Project of Prevention and Treatment of Cardiovascular Disease - POLKARD. The survey was performed among random sample of 259 Polish hospital units, including 20 university hospitals, using questionnaire method, completed by doctors, based on medical documentation, concerning diagnosis and treatment during last 5 hospitalizations of patients with HF. The data were obtained from 1296 patients' medical documentations.

Results: Mean age of the patients was 69.8±11.4 years; 57.8% were men; 70.0% were in II or III NYHA class. Most of them had CAD (71.3.0%) and hypertension (70.9.6%). In patients with available results of echocardiography (n=807) mean ejection fraction (EF) was 38.5±13.2% (range:10-82%); 71.4% subjects' EF not more than 45%. Patients under 50 years old receive B-blockers more often (84.6%) than patients after 81 (64.8%; p<0.001). Almost 77% of the patients in NYHA class II and III take B-blockers. Table 1. shows medication used in patients with HF in internal medicine and cardiology units of hospitals and university hospitals.

Table 1

Treatment	Internal Medicine Units	Cardiology Units	University Hospitals
ACE-I	84,7%	88,5%	89,9%
AT II antagonist	2,4%	2,6%	2,7%
B-blockers	72,2%	85,1%***	82,7%
Diuretics	90,7%	86,5%*	83,5%
Spirolonolacton	64,6%	69,0%	69,3%
Digitalis	40,0%	37,3%	37,8%

*** p,0.001* p<0,005

Conclusion: The more specialized hospital unit uses more intense and closer to ESC guidelines treatment. HF medication has been still unsatisfactory, especially in older patients.

P518 Unrecognised acute coronary findings in heart failure patients with sudden or circulatory death - an autopsy report from COMET

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Background: Unrecognised acute coronary findings (ACF) as a trigger for sudden death (SD) have been reported at autopsy in patients with heart failure treated with ACE inhibitors without beta-blockade. In COMET all patients received beta-blockade in addition to ACE inhibition, thus allowing to assess whether ACF remain a common, unrecognised cause of death in patients with heart failure despite combined treatment.

Methodology: Adjudicated modes of death (SD, circulatory failure (CF), other cardiovascular (CV), non-CV or unknown) were compared with autopsy reports,

reviewed for ACF (pre-mortem coronary thrombus, ruptured plaque, or recent or acute myocardial infarction [MI]), presence of coronary disease, old MI and pulmonary congestion. Preceding symptoms and diagnosis of pre-mortem acute MI were derived from the case record forms.

Results: 94 autopsy reports were available with the following modes of death: 50 SD, 27 CF, 5 other CV, 7 non-CV and 5 unknown. ACF were present in 17 SD and 6 CF, 34% and 22%, respectively. In patients with coronary disease and SD (n=36) or CF (n=16) ACF were present in 47% and 37%, respectively. ACF were only diagnosed pre-mortem in 1 SD patient. Preceding chest pain without signs of acute ischaemia or acute MI was noted in 2 other SD and 2 CF patients with ACF, and in 2 SD without ACF. Ventricular fibrillation or cardiac arrest occurred in 4 SD with and 4 SD without ACF. Old MIs were equally present in SD with or without ACF, 64% and 70%, respectively, but pulmonary congestion was reported more often at autopsy in SD without (64%) than with ACF (35%).

Conclusion: Acute coronary events still occur frequently in heart failure patients despite combined ACE inhibition and beta-blockade, and are clinically unrecognized with few preceding symptoms suggestive of ischaemia. Arrhythmias preceding sudden death are also infrequent and equally distributed in patients with and without ACF. As acute coronary events occur predominantly in patients with coronary disease and sudden death, they are likely to trigger death in this setting.

P519 Gender differences in clinical practice: Lessons from the Euro Heart Survey on Heart Failure



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Background: Women who have heart failure more often have preserved LV systolic function and are more likely to have a history of hypertension but less evidence of coronary heart disease compared to men. However, these differences could reflect the fact that women with heart failure are, on average, older than men.

Methods: The Euro Heart Survey on Heart Failure screened consecutive deaths and discharges during 2000-2001 in 115 hospitals from 24 countries belonging to the ESC, to identify patients with known or suspected heart failure. Gender differences were assessed, among older and younger patients, and in patients with and without preserved left ventricular function.

Results: A total of 10,653 patients (47% women) were enrolled. Mean age was 74.5 years among women and 68.5 years among men. Fifty-five per cent of the women but 66% of the men had evidence of coronary artery disease (CAD) ($p < .001$), but women were more likely than men to have hypertension, diabetes, or valvular heart disease. Fewer women than men had had an investigation of left ventricular function (58% vs. 72%, $p < .001$). Amongst those investigated, 41% of women and 67% in men ($p < .001$) had left ventricular systolic dysfunction. After adjusting for age, most of the observed gender differences remained statistically significant. Drugs with a documented impact on survival, i.e. ACE-inhibitors, beta-blockers, and spironolactone were given less often to women, even after adjusting for age and clinical characteristics (OR 0.68: 95%CI 0.63-0.74, OR 0.90: 95%CI 0.83-0.99, and OR 0.80: 95%CI 0.72-0.88, respectively). After adjustment for age, women and men had similar 12-week mortality: 11.9% vs. 14.1% (OR 0.98: 95%CI 0.88-1.11).

Conclusions: The observed gender differences persisted after adjusting for age, and in patients with and without preserved ventricular function. Women were less likely to receive appropriate investigation and treatment even after adjusting for age and clinical characteristics.

P520 Metabolic syndrome in patients with asymptomatic left ventricular dysfunction. Results from a multicenter study. Daves by Italian society



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It has been observed that metabolic syndrome (MS) is associated with a greater risk of atherosclerotic cardiovascular disease than any of its individual components. Although MS is associated with increased cardiovascular risk, its relationship with heart failure (HF) and left ventricular dysfunction (LVD) is not fully known. We sought to determine whether the MS is associated to left ventricular systolic and diastolic dysfunction in a sample of asymptomatic patients for HF from multicenter DAVES survey (75 centers).

Methods: We enrolled all consecutive patients admitted to echo-lab without symptoms of HF. We calculated Systolic function by Simpson biplane methods. Diastolic function was calculated using validated parameters by Doppler (mitral and pulmonary venous flow. MS was diagnosed in presence of three or more CV risk factors.

Results: from the overall database of 16099 screened patients we selected 6679 patients asymptomatic for heart failure. We could assess systolic function in 6384 patients and diastolic function in 3980 patients. We observed an overall prevalence of systolic dysfunction of 11.7% (n=744); in the group of patients with MS (n=545) the prevalence of systolic dysfunction was 16% (n=87), while in 5839 patients without MS (5839) was 11.3% (n=657) with a statistical significant difference (OR 1.5; CI 95% 1.1 - 1.9). In multivariate analyses with the systolic dysfunction as the dependent variable we observed a significant, independent association with MS after controlling for age and gender (OR 1.38; CI 95% 1.08 - 1.77). Regarding to diastolic dysfunction we observed an overall prevalence of 33.2% (n=166), with a prevalence of diastolic dysfunction of 45.2% (n=166) in the group of patients with MS (n=367; 9.2%), while in patients without MS (3613) was 32% (n=1157) with a statistical significant difference (OR 1.75; CI 95% 1.4 - 2.1). In multivariate analyses with the diastolic dysfunction as the dependent variable we observed a significant, independent association with MS after controlling for age and gender (OR 1.49; CI 95% 1.2 - 1.9).

Conclusion: our data show that left ventricular asymptomatic dysfunction, systolic and diastolic, is correlated to MS and demonstrate a point out that echocardiography is useful tool to detect patients at high risk for HF. Echocardiography in patients with MS and without symptoms of HF may help to establish therapy at early stages to prevent future cardiovascular events and clinical heart failure. Follow-up of our study may help to clarify prognostic impact of these findings in selected cohorts of patients.

P521 The prognostic importance of body mass index in patients with coronary artery disease



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Aim: To investigate the prognostic importance of baseline body mass index (bBMI) in three different populations with coronary artery disease (CAD) during short-term, intermediate-term and long-term follow-up.

Methods: CONSENSUS II: 5547 patients with acute myocardial infarction (AMI) (301 deaths). OPTIMAAL: 5388 patients following complicated AMI (908 deaths). 4S: 4367 patients with CAD (421 deaths). Patients were classified into 4 bBMI groups; underweight <22, normal-weight 22-24.99, overweight 25-29.99 and obese ≥ 30 kg/m². In multivariable Cox proportional hazard analysis the prognostic importance of baseline BMI group was examined and expressed as hazard ratio (HR) and 95% confidence interval (CI). The follow-up period had a median length of 139 days in CONSENSUS II, 2.8 years in OPTIMAAL, and 5.4 years in 4S. In order to compare the trials over a similar time period, analysis was also performed at 6 months in OPTIMAAL and 2.8 years in the 4S.

Results: In all three studies underweight patients had/tended to have increased adjusted mortality risk compared to normal-weight patients (HR:s 1.053-1.418, p-values 0.863-0.004). Overweight patients had a neutral mortality risk compared to normal-weight patients in all studies (HR:s 0.991-1.001, all p=ns). Compared to normal-weight patients, obese patients tended to have decreased adjusted mortality risk during short-term follow-up (6 months) but increasing adjusted risk with the length of follow-up: CONSENSUS II (6 months), HR 0.65, 95% CI 0.324-1.294, p=0.218; OPTIMAAL (6 months), HR 0.97, 95% CI 0.686-1.364, p=0.849; OPTIMAAL (2.8 years), HR 0.88, 95% CI 0.698-1.114, p=0.293; 4S (2.8 years), HR 1.08, 95% CI 0.65-1.78, p=0.773; 4S (5.4 years) HR 1.32 95% CI 0.955-1.826, p=0.092. The test for equal proportional hazards for obese versus normal weight patients was significant (p=0.047), indicating an increased adjusted HR over time for obese patients.

Conclusion: Irrespective of time of follow-up and patient population, underweight was associated with increased risk compared to normal-weight after AMI. Overweight was associated with neutral risk. Obesity was associated with a trend towards decreased risk during short-term follow-up but a trend towards increased risk during long-term follow-up. The risk associated with obesity, compared to normal-weight, increased significantly over time. Our observation suggests that there may be a short-term survival benefit associated with obesity after AMI, but a long-term negative effect on survival.

P522 Prognostic value of serum adiponectin level in patients with congestive heart failure



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Background: Impaired free fatty acid metabolism, and myocardial inflammation and hypertrophy are common features of congestive heart failure (CHF). Adiponectin can improve these pathological conditions in experimental CHF.

Purpose: To assess the significance of serum adiponectin as a prognostic marker for CHF.

Methods: Serum adiponectin levels were measured in 54 CHF patients with left ventricular ejection fraction (LVEF) <50% and 55 age- and gender-matched con-

trols. CHF patients underwent simultaneous clinical assessment, and measurements for plasma BNP. Association of adiponectin levels with BNP and clinical or biochemical parameters at baseline were analyzed using a linear regression analysis. Cumulative rates of survival in CHF patients stratified into 2 groups on the basis of median adiponectin level were compared by Kaplan-Meier analysis and a log-rank test. Survivals were also compared between higher and lower adiponectin groups in 24 ischemic or 30 non-ischemic CHF patients. Associations of each variable to patient survival and independence of each predictor for mortality were assessed by a univariate and a multivariate Cox proportional hazards analyses.

Results: Serum adiponectin levels were significantly higher in CHF (17.48 ± 1.40 $\mu\text{g/ml}$) than in controls (9.35 ± 0.89 $\mu\text{g/ml}$, $p < 0.0001$). In CHF, adiponectin positively correlated with BNP ($p = 0.0014$, $r = 0.43$) and negatively with BMI ($p = 0.0025$, $r = -0.41$). High serum adiponectin was associated with higher mortality (Fig. 1, A), particularly in ischemic CHF (Fig. 1, B) but not in non-ischemic CHF (Fig. 1, C). A multivariate analysis employing adiponectin, BNP, LVEF, age and BMI as co-variables indicated that serum adiponectin was an independent predictor of overall mortality.

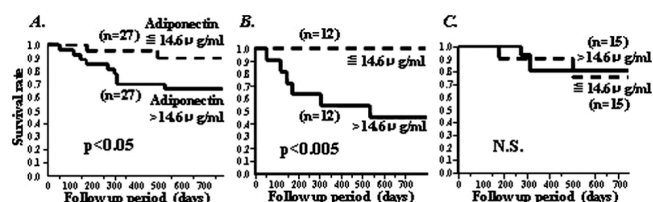


Fig. 1. A: All CHF, B: Ischemic, C: Non-ischemic

Conclusion: Adiponectin may be an informative prognostic marker in ischemic CHF.

P523 The influence of low level of haemoglobin and elevated white blood cell count on survival in patients with chronic heart failure



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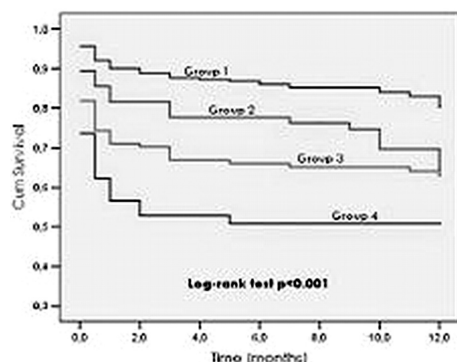
Anaemia (A) is common in patients (pts) with chronic heart failure (CHF). In pts with severe CHF lower haemoglobin concentrations is associated with an adverse prognosis and reduced the quality of life. Recent studies have established that systemic inflammation is important in prognosis in pts with CAD. In pts with CHF inflammation may play a prognostic role not only in ischemic but also in non-ischemic aetiology.

We evaluated the relationship between white blood cell count (WBC) and low level of haemoglobin on survival during one-year follow-up in CHF pts.

Methods: A total of 501 consecutive pts with CHF hospitalized were enrolled to study. Baseline clinical parameters were measured immediately after the admission. After the measurement of haemoglobin level we divided the pts on A pts (with haemoglobin level < 12 g/dl) and non-A pts (haemoglobin level ≥ 12 g/dl). After that pts were divided into the 4 groups based on the WBC and haemoglobin level: gr I WBC count < 11 000 and non-A pts; gr II: WBC > 11 000 and non-A pts; gr III: WBC < 11 000 and A pts; gr. IV WBC > 11 000 and A pts; Pts were followed up for 1 year.

Results: Age, gender, ischemic aetiology, co morbidities (HTN, DM), renal dysfunction significantly differ between groups ($p < 0.05$). During one-year follow-up 18 vs.36 vs. 33 vs. 49%, death occurred in the I, II, III and IV groups ($p < 0.05$). K-M curve showed lower survival with higher level of WBC count and low level of haemoglobin (figure 1). A multivariate logistic regression analysis showed that WBC count over 11,000 and A are strong predictor of mortality (RR: 2.53, CI: 1.20 - 5.35, $p < 0.05$).

Conclusions: Admission WBC count over 11.000 and anemia are independent predictors of mortality in pts with CHF and provides useful prognostic information.



Kaplan-Meier curve

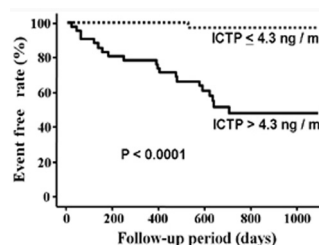
P524 Serum carboxy-terminal telopeptide of type I collagen (ICTP) predicts cardiac events in patients with preserved left ventricular systolic function



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Background: A number of epidemiological studies have documented that a high proportion of patients with heart failure have preserved left ventricular systolic function, and this condition is commonly referred to as diastolic heart failure (DHF). Although morbidity and mortality rates in DHF are high, clinical markers to predict outcomes have not yet been established. Interstitial collagen metabolism is related to left ventricular integrity and function in patients with HF. We examined whether carboxy-terminal telopeptide of type I collagen (ICTP), a marker of collagen degradations, is useful to determine the prognosis of heart failure patients with preserved left ventricular systolic function.

Methods and Results: Serum levels of ICTP were measured at admission in 64 consecutive patients hospitalized for chronic heart failure and left ventricular ejection fraction $> 40\%$ (preserved left ventricular systolic function). Patients were prospectively followed during a mean follow-up period of 643 ± 354 days with the end points of cardiac death and progressive heart failure requiring rehospitalization. Based on median of ICTP level, patients were divided into high ICTP (> 4.3 ng/ml) group and low ICTP (≤ 4.3 ng/ml) group. Patients with high ICTP group had lower cardiac event free rate than those with low ICTP group (figure). The Cox multivariate proportional hazard analysis showed that ICTP was an independent predictor of cardiac events (hazard ratio 1.210, 95% confidence interval 1.013 - 1.446, $P < 0.05$).



Kaplan-Meier analysis of cardiac event

Conclusion: Serum ICTP level is reliable for risk stratifying patients with preserved left ventricular systolic function.

P525 Cardiac troponin T in heart failure: results from Val-HeFT



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Background: Small studies have shown that cardiac troponin T (cTnT) is associated with adverse outcomes in patients with heart failure (HF). However, little is known about the profile of HF patients with elevated cTnT, and whether de novo release of cTnT during long-term follow-up of patients with stable chronic HF influences prognosis.

Methods: cTnT (Roche Diagnostics) was measured at baseline ($n=4071$) and at 4 months ($n=3862$) in patients randomized to Valsartan Heart Failure Trial. Baseline characteristics of patients with or without detectable cTnT were compared using Chi-square or T-tests. Cox proportional-hazards regression models were used to assess the association between multiple baseline explanatory variables and time to death, first morbid event, or hospitalization for HF.

Results: At baseline, there were 423 (10.4%) patients with detectable cTnT (median 0.027 ng/mL, range 0.01 to 0.58 ng/mL). These patients had worse HF with higher NYHA class, greater volume overload, lower blood pressure, lower EF, reduced glomerular filtration rate, higher CRP, norepinephrine, BNP, aldosterone and plasma renin activity, and lower use of beta-blockers (all $p < 0.01$). However, elevated cTnT was not associated with ischemic etiology. Presence of cTnT increased the risk of time to death (HR 3.33, 95% CI 2.83-3.93), first morbid event (HR 3.0, 95% CI 2.61-3.44), and first hospitalization for HF (HR 3.14, 95% CI 2.61-3.79). In a multivariable model that included age, sex, LV size, LVEF, ischemic etiology, use of statin, aspirin and other HF medications, cTnT remained a significant independent predictor of the risk of mortality (HR, 1.6, 95% CI, 1.3-2.0), first morbid event (HR 1.5, 95% CI, 1.24-1.74), and hospitalizations for HF (HR, 1.37, 95% CI, 1.09-1.73). During follow-up, de novo release of cTnT was found in 114 (3.6%) patients at 4 months. This was associated with an even higher adjusted risk of subsequent mortality (HR, 3.23, 95% CI, 2.31-4.51), first morbid event (HR, 3.0, 95% CI, 2.26-4.0), and hospitalizations for HF (HR, 3.14, 95% CI, 2.16-4.58).

Conclusions: cTnT is an important prognostic marker for adverse events in HF patients, independent of other markers and unrelated to ischemic etiology.

P526 Creatinine clearance calculated by Cockcroft's formula: a highly predictive prognostic factor for two years mortality in heart failure patients



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Kidney dysfunction is frequent in patients (P) with heart failure (HF). It is well known that P with overt kidney insufficiency and HF had poor prognosis, but even mild degrees of kidney dysfunction might have prognostic value in such P. The aim of this study was to evaluate if creatinine clearance (CrC) values calculated with Cockcroft formula $[(140 - \text{age (years)}) \times \text{weight (kilograms)}] / [72 \times \text{plasma creatinine level (mg/dl)}]$ adjusted by sex, correlated with survival at two years of follow-up in a general HF population admitted to an outpatient HF Unit. We analyzed 4 subgroups of P according their CrC: ≥ 90 , 89-60, 59-30, and < 30 ml/min. Kidney failure was defined as CrC < 60 ml/min.

Patients (P): CrC at first visit and survival status at 2 years of follow-up were available in 385 P out of 403 P admitted to the Unit (71% men, mean age 65.3 ± 10.8 years). Aetiology of HF was mainly ischemic heart disease (61%), followed by idiopathic dilated cardiomyopathy (13%). Mean LVEF was $31.6\% \pm 12.7\%$. Most of the patients were in NYHA class II (47%) or III (43%).

Results: mortality was 3.3% in P with CrC ≥ 90 ml/min, 13.4% in P with CrC between 89-60 ml/min, 24.2% in P with CrC between 59-30 ml/min, and 62.5% in P with CrC < 30 ml/min, OR 3.2 [2.23-4.58], $p < 0.001$. Actuarial survival curves diverged markedly in two years of follow-up (figure 1). Two years mortality was 31% in P with kidney insufficiency and 10% in P without it ($p < 0.001$), OR 3.96 [2.26-6.94], $p < 0.001$.

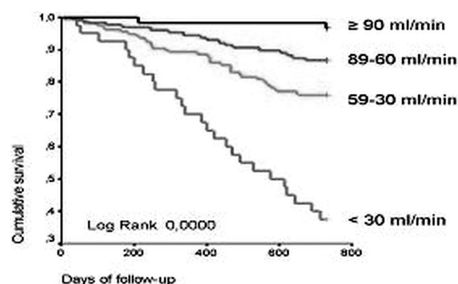


Figure 1. Creatinin clearance and 2 years survival

Conclusion: CrC values calculated by Cockcroft's formula had a highly predictive prognostic value in our P with HF. Even mild degrees of CrC impairment showed higher mortality rates than normal values. When kidney insufficiency was already present mortality at 2 years was almost four times higher.

P527 High levels of circulating C-terminal pro-endothelin-1 identify patients with chronic heart failure with very poor prognosis



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Background: Recent studies revealed that measurement of endothelin-1 (ET1) in peripheral blood may allow to identify patients (pts) with advanced chronic heart failure (CHF) who are at a particularly high risk of death. Clinical applicability of this test is limited due to ET-1 instability. We studied if plasma C-terminal pro-ET-1 (CT-proET-1), a stable ET-1 precursor, would carry the same prognostic information.

Methods: We examined 191 stable pts with systolic CHF (age: 63 ± 11 y [mean $\pm$ SD], NYHA class [I/II/III/IV]: 11/69/79/32, LVEF: $28 \pm 9\%$). Plasma CT-proET-1 was detected using luminescence immunoassay.

Results: Mean plasma CT-proET-1 was 67.7 ± 48.5 pmol/L (range: 1.9-259.0 pmol/L). In a multivariate model, CT-proET-1 was related to NYHA class ($r = 0.39$, $p < 0.0001$), plasma NT-proBNP ($r = 0.30$, $p < 0.0001$), glomerular filtration rate (GFR, $r = -0.19$, $p = 0.001$). During follow-up (mean: 34 ± 41 months, > 12 months in all survivors), 75 (39%) pts died; cumulative 3- and 12-month mortality was 9% and 20%, respectively. In univariate models, CT-proET-1, NT-proBNP, NYHA class, LVEF, GFR, age (all $p < 0.01$), predicted survival. In a multivariate stepwise Cox model, CT-proET-1 remained an independent prognosticator (HR: 1.13 per 10 pmol/L increase, 95%CI: 1.06-1.19, $p < 0.0001$), together with NYHA class ($p < 0.05$), LVEF ($p < 0.01$), GFR ($p < 0.0001$). CHF pts with increased CT-proET-1 in the highest tertile (> 75.7 pmol/L) had outstandingly unfavourable outcome with

a 3- and 12-month mortality of 25% and 47%, respectively, as compared to pts with CT-proET-1 in the middle (40.8-75.5 pmol/L) and the lowest (< 40.8 pmol/L) tertiles (3%/9% and 0%/5% for 3-/12-month mortality, respectively) ($p < 0.001$). Elevated CT-pro-ET-1 levels carried prognostic value across several subgroups. Hazard ratios for death for the highest vs. lowest tertile (using the above cut-offs for CT-proET-1) were: age < 65 y (median) (HR=12.74, $p < 0.0001$), age > 65 y (HR=3.99, $p = 0.001$), LVEF $< 28\%$ (median) (HR=8.92, $p < 0.0001$), LVEF $> 28\%$ (HR=9.91, $p = 0.0004$), NT-proBNP < 1770 pg/mL (median) (HR=5.19, $p = 0.006$), NT-proBNP > 1770 pg/mL (HR=5.38, $p = 0.0006$).

Conclusions: Plasma CT-proET-1 constitutes a powerful new prognostic marker in CHF pts, independently of other established prognostic factors (including NT-proBNP, renal function). The presence of excessive activation of CT-proET-1 (expressed as the highest tertile) allows to distinguish the CHF population of particularly fatal outcome.

P528 Impact of high aldosterone and cortisol plasma levels on mortality risk in chronic heart failure



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Background and aims: In patients with systolic heart failure (S-HF), high levels of plasma aldosterone (ALD) are associated with an adverse prognosis. In addition, elevated levels of plasma cortisol (CORT) were observed in chronic HF, but their relation to prognosis has not been investigated. We investigated the relationship between plasma ALD and CORT and all-cause death in patients with chronic S-HF as well as non-systolic heart failure (NS-HF).

Methods: In a community-based prospective follow-up study, 295 consecutive patients presenting with symptomatic or asymptomatic S-HF [fractional shortening (FS) $< 24\%$] or symptomatic NS-HF were characterized in detail between 6/2002 and 12/2003. ALD and CORT were measured from plasma drawn at baseline between 8-11 am. Vital status was ascertained in 10/2005 in all patients.

Results: Median age was 68y, 65% male; 52% NYHA class I-II, 48% class III-IV; 58% S-HF, 42% NS-HF; 67% betablockers, 81% ACEi/ARB, 82% diuretics, 28% ALD-antagonists. During a median follow-up of 803d (IQR 314-1098) the mortality rate was 27%. In multivariate Cox regression adjusting for age, sex, NYHA class, FS, and all classes of HF pharmacotherapy, increasing tertiles of ALD and CORT were associated with increased mortality risk (figure): hazard ratio (HR) ALD 2.3 (95%CI 1.3-4.0; $P = 0.004$ for highest vs lowest tertile), HR CORT 3.2 (95%CI 1.7-6.1, $P < 0.0001$). Further adjustment for NT-proBNP as a marker for CHF severity did not diminish these associations.

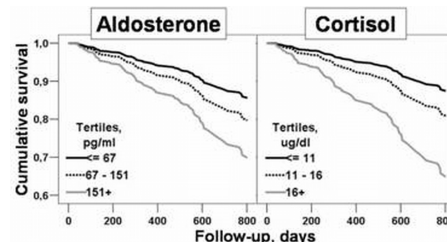


Figure 2. Mortality risk and ALD/CORT levels

Conclusions: In patients with S-HF as well as NS-HF, higher plasma levels of both ALD and CORT are independently associated with increased mortality risk, even within the normal concentration ranges. We conclude that higher levels not only of ALD but also of CORT adversely influence outcome in chronic HF.

P529 Can CA 125 predict prognosis in patients with advanced heart failure?



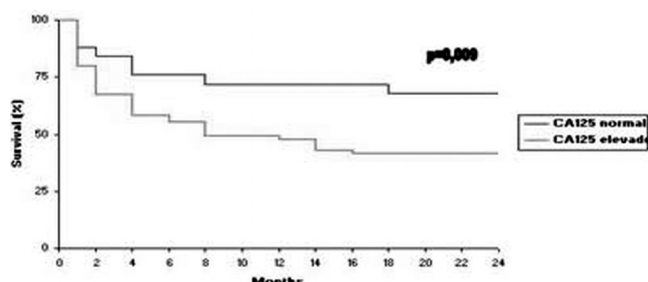
S. Monteiro, F. Franco, P. Monteiro, S. Costa, H. Vieira, L. Oliveira, L. Coelho, L. Providencia. *Coimbra, Portugal*

Introduction: Serum levels of CA125, a tumoral marker related with ovarian cancer, are often high in patients with advanced heart failure (AHF). Therefore, measurement of plasma CA125 has potential as a prognostic marker for AHF. Aim: To determine the predictive value of plasma CA125 in forecasting the occurrence of death or cardiac transplant in a population of AHF patients.

Methods: 90 AHF patients (63 male, 27 female, age 53.5 ± 13.8 years), were referred for heart transplant. CA125 was determined in all patients in addition to standard evaluation for heart transplant. Patients were divided into 2 groups based on CA125 levels: normal (CA125 < 27 U/ml) and elevated (CA125 ≥ 27 U/ml). Events (death or heart transplant) were monitored over a period of 13 ± 7 months after CA125 determination.

Results: 25 patients had normal CA125 (15.3 ± 6.1 U/ml), while 65 had elevated levels (215.6 ± 260.2 U/ml). Compared to the elevated CA125 group, patients with normal CA125 had significantly higher systolic (110.2 ± 18.1 vs 97.2 ± 14.3 mmHg; $p = 0.01$) and diastolic blood pressure (66.1 ± 14.2 vs 57.0 ± 10.3 mmHg; $p = 0.02$) and significantly higher oxygen consumption rates in the cardiorespiratory stress test (16.0 ± 5.1 vs 13.8 ± 3.4 ml/kg/min; $p = 0.049$). Type B Natriuretic peptide lev-

els (461.2 ± 296.6 vs 1662.5 ± 1033.1 pg; $p=0.0003$) were significantly lower in this group. Patients with normal CA125 had also a significantly better prognosis, with less events (death or heart transplant) during the follow-up (28% vs 69%; $p=0.009$).



Event-free survival curve: Heart transplant and death.

Conclusion: In patients with AHF, plasma CA125 was an effective prognostic marker. Its determination may contribute to better risk stratification in this patient population.

P530 Do biomarkers add prognostic information to routine measures of the severity of heart failure?

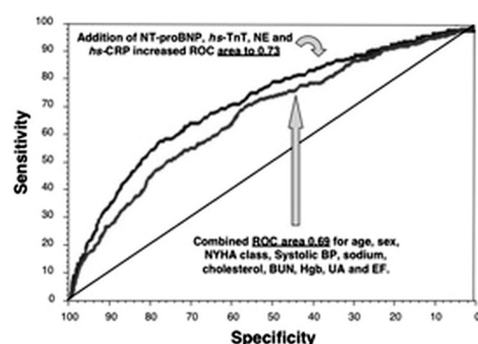


I.S. Anand¹, T. Rector², R. Latini³, S. Masson⁴, A.P. Maggioni⁵, J.N. Cohn⁶ on behalf of Val-HeFT investigators. ¹VA Medical Center and University of Minnesota, Cardiology, Minneapolis, United States of America; ²VA Medical Center, Research, Minneapolis, United States of America; ³Instituto Mario Negri, Milano, Italy, Cardiology, Milano, Italy; ⁴Instituto Mario Negri, Milano, Italy, Cardiology, Milan, Italy; ⁵ANMCO Research Center, Florence, Italy, Cardiology, Florence, Italy; ⁶University of Minnesota, Cardiology, Minneapolis, United States of America

Background: Several routinely measured variables are associated with mortality in patients with heart failure. Additional prognostic information gained by measurement of NT-proBNP, norepinephrine (NE), C-reactive protein (hs-CRP), and high sensitivity troponin (hs-TnT, Roche Diagnostics, under development) remains unclear.

Method: Baseline variables from Val-HeFT were used to predict death at 1-year. Data from patients with all 4 biomarkers were then included in the analysis ($n=3720$, 320 deaths). Discrimination of deaths was quantified by the area under the receiver-operator characteristic curve (ROC).

Results: ROC derived by logistic regression of death within 1-year on age, sex, NYHA class, systolic BP, cholesterol, blood urea nitrogen, hemoglobin, uric acid (UA), and ejection fraction (EF) was 0.69 (95% CI 0.66-0.72). Individual ROCs were 0.71 (0.67-0.73) for NT-proBNP, 0.70 (0.67-0.73) for hs-TnT, 0.63 (0.60-0.66) for NE and 0.59 (0.55-0.62) for hs-CRP. Addition of all 4 biomarkers to the model significantly increased the ROC to 0.73 (0.70-0.76, $p<0.001$). Sequential deletion of hs-CRP, NE and hs-TnT did not reduce the ROC significantly. NT-proBNP significantly increased the ROC from 0.69 to 0.72 (0.69-0.75, $p<0.001$).



Conclusion: NT-proBNP alone discriminated as well as the combined use of EF and several routinely measured variables, and added significant prognostic information. Measurement of hs-CRP, hs-TnT and NE did not improve the identification of patients who would die within 1-year.

P531 Heart-type fatty acid-binding protein is more sensitive than troponin T to detect the ongoing myocardial damage

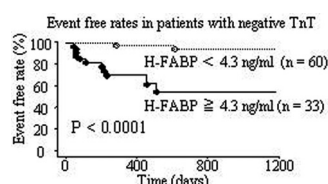


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Background: Heart-type fatty acid-binding protein (H-FABP) is a small cytosolic protein and released into the circulation when the myocardium is injured. Previous

studies have demonstrated that both H-FABP and troponin T (TnT) are detectable in chronic heart failure (CHF) patients, suggesting the presence of ongoing myocardial damage (OMD). We hypothesized that a cytosolic marker (H-FABP) is more sensitive than a myofibrillar component (TnT) in the detection of OMD in CHF.

Methods and Results: We measured serum H-FABP and TnT levels in 126 consecutive CHF patients, and patients were followed up with a mean period of 474 ± 328 days. Cut off values for H-FABP (4.3 ng/ml) and TnT (0.01 ng/ml) were determined from previous studies. Positive rate of H-FABP was higher than that of TnT in all CHF patients (46% [58/126] vs. 26% [33/126], $P < 0.0001$), and in severe CHF patients with NYHA III/IV (69% [34/49] vs. 47% [23/49], $P = 0.0121$). There were 27 cardiac events during a follow-up period. In those patients, H-FABP was more frequently detected than TnT (88% [24/27] vs. 44% [12/27], $P = 0.0103$). There were 33 patients with positive H-FABP among 93 patients with negative TnT. Those patients had more severe NYHA class, higher levels of BNP, and higher rates of cardiac events (36% vs. 5%, $P < 0.0001$) compared with those both H-FABP and TnT were negative. Kaplan-Meier analysis demonstrated that in patients with negative TnT, positive H-FABP group had higher risk for cardiac events than negative H-FABP group (Figure). A multivariate Cox proportional hazard analysis showed that H-FABP was the only independent predictor of cardiac events (hazard ratio 15.677, $P = 0.0001$).



Conclusion: H-FABP was more sensitive to detect OMD and could identify patients at high risk more effectively than TnT.

P532 Prevalence and prognosis of HF in post MI patients



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Background: Acute myocardial infarction (AMI) is a common cause of heart failure (HF), which may develop early and persist or resolve or develop late. The cumulative incidence, persistence and resolution of HF after AMI are poorly described.

Aim: To describe the natural history and prognosis of HF after an AMI.

Method: Patients who were hospitalised with or developed an AMI during hospitalisation in 1998 were identified from the Hull & East Yorkshire Hospitals Trust Information Department. HF was defined as signs and symptoms consistent with that diagnosis (principally breathlessness and signs of fluid retention) resulting in treatment with loop diuretics. HF was considered to have resolved if loop diuretic therapy could be stopped without recurrence of symptoms. The Trust serves a population of approximately 600,000.

Results: In 1998, 1,013 patients were hospitalised with an AMI or developed one during hospitalisation, of whom 62% were managed primarily by a cardiologist. Overall, 52% died by December 2005. Preliminary data on the first 775 is reported in this abstract and complete data will be available when presented. HF occurred during the index admission in 366 (47%) patients (mean age 74 ± 10) but was transient in 67 (18%) and resulted in death in 151 (41%) during the index hospitalisation compared to 8% in those without HF (mean age 65 ± 11). Thus, 148 (19%) were discharged with HF. Amongst these patients, HF resolved in a further 20 and 92 (63%) died. Of 67 patients with transient HF during the index admission, 32 (49%) had recurrence of HF and 34 (52%) died during FU, 20 after the recurrence of HF. Amongst patients who never had HF during the index admission, 96 (27%) subsequently developed HF and of these patients 49 (51%) died during follow-up compared to 42 (15%) amongst 260 patients who never developed HF at any time. Thus, of 217 deaths occurring after discharge from an AMI, 177 (81%) occurred subsequent to the development of HF.

Conclusion: The development of transient or persistent HF precedes death in most patients who die within 6 years of an AMI. Effective prevention and management of HF is important after AMI.

P533 Restrictive filling pattern is a powerful predictor of development of heart failure post-acute myocardial infarction: a literature-based meta-analysis



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Background: Restrictive filling pattern (RFP) has been linked to prognosis in patients with chronic heart failure (CHF) and post acute myocardial infarction (AMI). We recently showed in two literature-based meta-analyses (LMA) that the presence of RFP was associated with a 4-fold increase in the risk of all-cause death in both groups. This similar analysis evaluated the link between RFP and morbidity (HF development and hospitalisation).

Methods: We searched online databases for prospective studies of patients post-AMI and with CHF. HF events (post-AMI: development of HF; CHF: HF readmissions) were compared between the patients with and without RFP. Review Manager version 4.2.7 software was used for the analysis.

Results: Twelve post-AMI studies (1286 patients, 271 events) and 5 CHF studies (647 patients, 221 events) were identified. Mean pooled age was similar between both groups but average pooled LVEF was lower in the CHF group (see Table). While RFP was less prevalent in the post-AMI group (22%) compared with the CHF group (39%) it was associated with a higher OR for HF events than in the CHF group (see Table). Interestingly, the HF event rate in the RFP group was the same regardless of disease category (49% post-AMI, 45% CHF).

Restrictive Filling and HF event rate

Disease Category	RFP (events/N)	non-RFP (events/N)	Age (yrs) (pooled average)	EF (%) (pooled average)	OR (95% CI)
Post AMI	140/287 (49%)	131/999 (13%)	63	45	10.10 (7.02,14.51)
CHF	112/250 (45%)	109/397 (27%)	30	30	2.66 (1.81,3.90)

CI = 95% Confidence interval, OR = odds ratio, N = number at risk, RFP = restrictive mitral diastolic filling pattern, non-RFP = non-restrictive filling pattern, OR = odds ratio.

Conclusions: Restrictive filling is associated with high rates of HF admissions in both post-AMI patients and patients with existing heart failure. This literature-based meta-analysis confirms that RFP is a powerful predictor of HF development especially in patients post-AMI and should be incorporated into routine clinical practice.

P534 The clinical importance of diastolic LV function evaluation in ischaemic heart failure patients treated with surgical ventricular restoration. Mid-term follow up study

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Background: Surgical ventricular restoration (SVR) is an established method of treatment in ischemic heart failure patients post anterior myocardial infarction leading to the reduction of the left ventricular (LV) volume and LV shape reorientation. Menicanti modification of this method have employed an intracavitary patient-matched balloon in order to optimize the size and shape of the remodeled LV thus preventing from the restriction that might occur post surgery. Restrictive filling pattern is associated with worse prognosis in heart failure pts.

Aim of the study: To evaluate postoperative LV diastolic function and its relation to the clinical outcome at mid-term follow up.

Methods: The 68 heart failure patients (aged 57y±6; 56M) post anterior myocardial infarction with dominant anterior akinesis/dyskinesis (EDV-202 ml±86, ESV 154±70ml, NYHA 2.1±0.5, EF-31±7%) underwent SVR using BSA-matched balloon size (m.Menicanti). In addition to SVR, CABG was performed in 58/68(85%), MVplasty in 24/68 (35%). Thirty day mortality was 5.9%. The follow up clinical and echocardiographic evaluation was performed at 18,4±9,4 months post SVR. Doppler mitral inflow and tissue doppler annular velocity data were recorded. Patients were divided into groups according to postoperative E/E': gr I (E/E' > 15) and gr II (E/E' < 15). Mann-Whitney test was used for group comparison.

Results: The follow up measurements were as follow: EF 42±8%, p<0.001 vs baseline; EDV-139±40 ml, p<0.001 vs baseline; ESV-85±24, p<0.001 vs baseline NYHA 1.5±0.7, p<0.001 vs baseline. One patient in Gr I developed severe MR post SVR. Restrictive pattern with E/E' > 15 mm HG was found in 46,5% of pts. See table for the diastolic measurements.

	E/E'	E'[m/s]	E[m/s]	E/A	EDV[ml]
Gr.I E/E' > 15	22.4±7.4	0.05±0.01	1.11±0.4	1.71±0.94	122.9±30.4
Gr.II E/E' < 15	9.3±3.1	0.1±0.1	0.73±0.20	1.16±0.62	153.8±32.2
p value	0.001	0.001	0.003	0.04	0.003

Conclusions: Despite of the excellent systolic LV function improvement post SVR a substantial number of patients developed restrictive LV filling. E/E' index may better characterize patients with deteriorated filling post surgical ventricular restoration.

P535 Low systolic and mean arterial pressures are predictive for increased all-cause mortality in heart failure patients

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Background: The association between low blood pressure (BP) and prognosis

in the heart failure (HF) population has been controversial, with some reports suggesting an increased mortality for patients with the lowest BP. The relationship between all-cause mortality and BP in patients with HF has not been previously prospectively evaluated.

Objectives: The goal of the study was to determine the relationship between systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and survival among HF patients intolerant to ACE-I and therefore treated by valsartan in addition to standard HF therapy.

Methods: In the prospective multicenter study (69 outpatients cardiologists and internists) 1415 patients with documented HF (mean age 66.64±9.76 yrs, 680 men, 735 women) were followed for a mean 883.6±382.2 days. Cox proportional hazards models were used to identify covariates predictive of all-cause mortality. **Results:** Among 1415 HF patients 87% had hypertension, 51% prior MI and 29% diabetes mellitus (mean EF 40.4±10.2%, NYHA class II. 36%, NYHA III. 52%). Patients were divided into 5 categories according to SBP, DBP and MAP with regular increase of blood pressure level by 15 mmHg, 10 mmHg and 15 mmHg, respectively. During follow-up 198 patients died (13.9%). The all-cause mortality was as follows: S1 = 27.0%, S2 = 24.3%, S3 = 12.7%, S4 = 10.4%, S5 = 11.2%, D1 = 23.8%, D2 = 23.5%, D3 = 14.7%, D4 = 14.0%, D5 = 8.3% and M1 = 30.7%, M2 = 17.3%, M3 = 12.3%, M4 = 9.64%, M5 = 9.3%, in SBP (S), DBP (D) and MAP (M) group, respectively. In unadjusted comparisons using the Kaplan-Meier survival curves, there was consistent trend toward a higher mortality among the patients with lower SBP levels (log rank 33.6, P < 0.0001), and MAP (log rank 32.9, P < 0.0001). The adjusted all-cause mortality rate during the follow-up period for patients in the lowest SBP group (< 110 mm Hg) was twofold higher than that of the reference group of patients with SBP of 125 to 139 mm Hg (HR 1.94, 95% CI 1.13-2.90, P < 0.014). The relationship between SBP and all-cause mortality expressed as continuous variable in adjusted Cox regression analysis was significantly positive (HR 0.99, 95% CI 0.984-0.997, P < 0.006) as well as the relationship between MAP and all-cause mortality (HR 0.98, 95% CI 0.976-0.996, P < 0.006).

Conclusions: In HF patients population with high prevalence of hypertensive patients, lower SBPs and MAPs were associated with higher risk of all-cause mortality.

P536 Systolic blood pressure levels below 120mmhg are associated with a lower survival among heart failure patients independently of left ventricular ejection fraction

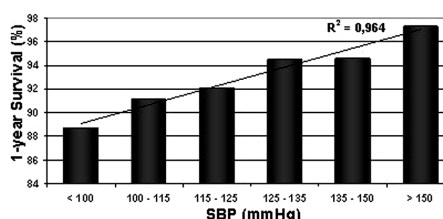
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The relationship between blood pressure and heart failure (HF) prognosis is not well established.

Aims: 1) to evaluate whether low blood pressure levels are associated with a poorer survival (SV) in HF patients independently of other prognostic predictors; 2) to establish the relationship between blood pressure and left ventricular ejection fraction (LVEF) and if this is the responsible for the blood pressure's impact on the prognosis.

Method and results: Data base of Spanish national "Sudden death in heart failure patients" registry was evaluated. Inclusion period was initiated in 2003 and more than one thousand HF patients characterized by a mean age of 64.7±11.7 years, 72% males, mean LVEF of 36.9±14.3% and being 72% of them in NYHA functional class II, were recruited. Basal systolic (SBP) and diastolic (DBP) blood pressure levels were of 126.8±21.7 mmHg and 74.3±12.1 mmHg, respectively. After a mean follow-up of 1.9±0.6 a significant relationship between SBP and SV rate was observed (Hazard ratio (HR): 0.986; p=0.004), however it was not significant for DBP. Although there was a strong direct correlation between SBP and LVEF (r=0.293; p<0.001), the protective effect of SBP on SV (HR: 0.984; p=0.021) was independent of LVEF, age, gender, HF aetiology, functional class, body mass index and DBP in the Cox multivariable analysis.

Conclusions: there is a direct and lineal relation between SBP levels and SV of HF patients which is independent of LVEF and other prognostic determinants.



P537 Prevalence and prognostic importance of lung function impairment in patients suspected of congestive heart failure



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Background Chronic obstructive pulmonary disease (COPD) is an important differential diagnosis in patients admitted on suspicion of congestive heart failure (CHF), and has previously been shown to be an important prognostic factor.

Purpose: To determine the prevalence and prognostic importance of decreased lung function i.e. COPD, in patients admitted on suspicion of CHF.

Methods: The study is a substudy to a CHF study (ECHOS). In 10 centers 498 patients hospitalized with symptoms of CHF had echocardiography and spirometry performed. Median follow up time was 3.2 years (range 2.6-3.7).

Results: Mean FEV1 was 65.0% of expected (95% C.I. 63.2-66.9), mean FVC 70.7% of expected (95% C.I. 69.1-72.4) and mean LVEF 39.3 (95% C.I. 37.8-40.8). Anamnestic COPD was found in 21.8% of patients and COPD defined from spirometric values (COPDs) was present in 33.3% (95% C.I. 29.6%-37.9%). In patients with COPDs only 44% had anamnestic COPD. In patients without COPDs 11% had anamnestic COPD. Positive and negative predictive values of anamnestic COPD were 0.67 resp. 0.76.

In multivariate analysis including all variables with a univariate prognostic importance, both FEV1 in % of expected (HR 0.987, 95% C.I. 0.977-0.996) and FVC in % of expected (HR 0.990, 95% C.I. 0.981-0.999) were predictors of death.

Patients with COPDs had higher mortality than patients without COPDs (HR 1.50 95% C.I. 1.12-2.02).

Conclusion: In patients with suspected CHF the prevalence of COPD is high and anamnestic information only identifies a minority of these patients. COPD is prognostic important. Spirometry should therefore be a mandatory examination in all patients suspected for CHF.

P538 Nocturnal breathing disorders are an independent predictor of cardiac death and of recurrent hospital admissions in chronic heart failure patients



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Background: Alterations of the breathing pattern, with regularly recurring cycles of hyperventilation and apnoea/hypopnea (periodic breathing, PB), are frequently observed in heart failure (HF) patients. Previous studies in small groups of patients (n<70) have shown that PB is associated with an increased mortality.

Methods: We tested the prognostic power of PB in the multicentre European Community funded study HHH (Home or Hospital in Heart failure, QLGA-CT-200 1-02424, carried out in Italy, Poland and UK), and, for the first time, we also investigated the relationship between PB and hospital readmissions.

A baseline 24-hour cardiorespiratory recording (Report-24, FM, Monza) was carried out in 443 clinically stable HF patients (age: 60 ±11 years, NYHA class 2.4±0.6, LVEF 29±7%). 396 recordings were eligible for the study (> 2.5 hours of good quality respiratory signal during the night). Nocturnal breathing disorders were quantified by the apnoea index (AI, events/hour), the apnoea/hypopnea index (AHI, events/hour) and the duration of PB (% of night-time). We investigated the association between these indices and i) total cardiac death (Cox regression), ii) number of readmissions due to heart failure (log-linear analysis). All analyses were multivariable, adjusting for age, NYHA class, LVEF, LVEDV, aetiology, systolic pressure, heart rate and sodium blood level.

Results: During 1-year follow-up, 6% of patients experienced cardiac death and 10% and 7% had respectively 1 or ≥2 hospital readmissions due to heart failure. Using either AI, AHI or % duration, nocturnal PB was an independent predictor of cardiac death with the following hazard ratios (95% CI, p value): AI ≥ 10 events/hour 2.5 (1.03-5.80, 0.04); AHI ≥ 15 events/hour 2.9 (1.30-6.70, 0.01), night-time duration ≥ 10%: 2.7 (1.04-7.10, 0.04).

Two or more readmissions occurred in 14% of patients with AHI ≥ 15/hour and in 5% of those with AHI <15/hour (p=0.01 in univariable analysis, p=0.07 adjusting for covariates). Percentages were similar in patients experiencing a single hospitalization (11% vs 8%, p>0.3 in univariable and multivariable analysis).

Conclusions: This study, conducted in a large population of mild-to-moderate HF patients, confirms the independent predictive power of alterations of the breathing pattern, whatever the abnormality index taken into account (apneas, apneas/hypopneas, duration of PB). For the first time, we have also provided evidence that patients with frequent nocturnal apnoeas/hypopneas are at higher risk of recurrent readmissions.

P539 Prevalence of significant cardiac dyssynchrony in patients with severe ischemic dysfunction undergoing surgical myocardial revascularization: impact on functional outcomes



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Background: Presence of cardiac dyssynchrony is associated with higher myocardial oxygen consumption and reduced left ventricular (LV) function. Therefore, the objective of the present study was to assess the prevalence of cardiac dyssynchrony and its impact on functional outcomes in patients with ischemic cardiomyopathy undergoing surgical myocardial revascularization (CABG).

Methods: The study consisted of 143 consecutive patients with ischemic cardiomyopathy (age 66 ± 8y; 78% males, LV ejection fraction 31 ± 8%) undergoing CABG. Cardiac dyssynchrony was calculated by tissue-Doppler imaging (TDI) from measurements of regional electromechanical coupling times in basal segments of the right and left ventricle (DYS). A patient with baseline or follow-up DYS value of ≥ 100 ms was considered to have significant dyssynchrony. In healthy individuals, mean value of DYS is 10 ± 8 ms. Patients symptoms were quantified with the Seattle Angina Questionnaire (SAQ) and LV ejection fraction was assessed by echocardiography (biapical Simpsons method) before and one year after CABG.

Results: At baseline, sixty patients (42%) showed significant DYS. Patients with significant baseline DYS had lower LV ejection fraction and larger LV volumes as compared to patients with smaller DYS (all p<0.0001). All other baseline characteristics were similar. At follow-up, forty-nine (34%) patients had significant residual DYS. Patients with follow-up DYS showed higher prevalence of angina, worse SAQ score and ejection fraction as compared to patients with smaller follow-up DYS (all p<0.0001). During follow-up (median, 565 ± 187 days), 10 cardiac deaths and 13 hospitalizations occurred in 49 patients with severe DYS as compared to 5 deaths and 15 hospitalizations in 94 patients with smaller follow-up DYS (47% vs. 21%, p<0.0001) (Table 1).

Table 1

	Cardiac events (n=43)	ΔEF (%) baseline vs. 1 year
Follow-up DYS ≥ 100 ms (n=49)	23 (47%)	2 ± 8
Follow-up DYS < 100 ms (n=94)	20 (21%)	19 ± 8

Conclusions: This study demonstrated high prevalence of significant cardiac dyssynchrony in patients undergoing CABG. Persistence of severe asynchrony after CABG is associated with worse functional outcomes and prognosis despite revascularization.

P540 Right ventricular function is an independent predictor of mortality in CHF. An ECHOS sub-study

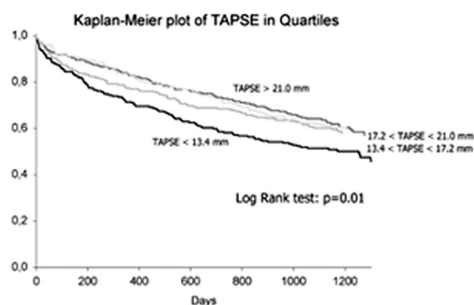


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Purpose Right ventricular (RV) dysfunction has been shown to be related to increased mortality in smaller population with advanced heart failure (HF) or myocardial infarction. We evaluated the long-term prognostic information from Tricuspid annular plane systolic excursion (TAPSE) as a measure of RV ejection fraction (EF) in a large consecutive population admitted for HF.

Methods Trans-thoracic echocardiography was performed as part of the baseline screening for the ECHOS trial (a placebo-controlled, randomized trial of a Dopaminergic agonist). TAPSE was measured by M-mode echocardiography of the lateral tricuspid annulus as the average of 5 cardiac cycles and left ventricular EF was estimated by wall motion score. Data is presented as median (25 and 75 percentiles)

Results A total of 911 patients with measurements of TAPSE were followed for



3.0(1.4-3.3) years. The median age was 74 (66 to 81) years, 60% were male, and 64% had a medical history of CHF. TAPSE was 17.2(13.2-21) mm and left ventricular EF 30(19-39)%. A Kaplan Meier plot of survival in relation to TAPSE is shown in Figure. A Cox model showed that TAPSE was an independent predictor of mortality (hazard ratio (HR)=0.97, 95% CI:0.95-0.99 per mm increase), independent of a medical history of HF (HR=1.40, CI: 1.09-1.81), valvular disease (HR=1.46, CI: 1.17-1.84), renal failure (HR=1.76, CI: 1.30-2.39), current smoking (HR=1.45, CI: 1.13-1.86), and age (HR=1.62, CI: 1.45-1.82 per 10 year increase).

Conclusion: Decreased right ventricular ejection fraction, as estimated by tricuspid annular plane systolic excursion, is significantly associated with long-term mortality in patients admitted for heart failure. This simple non-invasive estimation of right ventricular function provides improved risk stratification in patients with heart failure.

P541 The independent and incremental value of left atrial volume in predicting outcome of patients with dilated cardiomyopathy



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Purpose: It has recently been established that left atrial volume (LAV) is a powerful predictor of outcome in patients with chronic heart failure (CHF) independently of symptomatic status, age and left ventricular (LV) function. Whether LAV provides independent and incremental information compared with exercise tolerance parameters is unknown.

Methods: 273 CHF patients (62±9 years; 13% female) were prospectively enrolled and underwent a complete clinical assessment, echocardiography and exercise testing with maximal oxygen consumption (VO₂). The composite end point was survival free of hospitalization and cardiac transplantation.

Results: At Cox proportional hazard analysis, LAV normalized for body surface area (LAV/BSA) was strongly associated with mortality (HR 1.027 (95% IC 1.018 10.4; p<0.0001). Multivariate analysis showed that the predictive value of LAV/BSA was independent of VO₂ and left ventricular ejection fraction (EF) (HR 1.015 (1.005 1.026) p=0.004; HR 0.95 (0.91 0.99) p=0.01; HR 0.89 (0.81 0.97) p=0.009 for LAV/BSA, EF and VO₂ respectively). ROC analysis identified the best cut-off values for the prediction of the end point. LAV/BSA > 63 mL, EF <30% and VO₂ < 16 mL/kg/min were considered to be risk factors. Patients with 3 risk factors had a hazard ratio of 38 (95% IC 11 129) compared with patients with no risk factors. The area under the curve of the risk factor model (0.80±0.03) was significantly higher than the AUC of VO₂ (0.69±0.04) (p<0.0001).

Conclusion: LAV provides powerful prognostic information incrementally and independently of VO₂. LAV, EF and VO₂ can be used to build a risk prediction model, which can be used clinically.

P542 Left atrial enlargement as predictor of all-cause cardiovascular death and sudden cardiac death in patients with congestive heart failure



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Objectives: To assess the prognostic value of left atrial (LA) size to predict sudden and non-sudden cardiac death in a consecutive cohort of patients with congestive heart failure (CHF). Background: Data are lacking on the relation of LA enlargement to cardiovascular death (CVD) in patients with CHF and on the interaction of LA size with other clinical variables as they relate to outcome.

Methods: A cohort of 563 patients with established CHF had baseline echocardiographic and NT-proBNP measurements and were followed for 599±180 days.

Results: 61 patients died of all-cause CVD, of whom 32 suffered sudden cardiac death (SCD). Independent predictors of all-cause CVD and SCD were indexed LA size >26mm/m², elevated NT-proBNP levels, and history of myocardial infarction. At 24 months, risk of all-cause CVD was 25% for patients with indexed LA>26mm/m² and 6% for patients with indexed LA≤26mm/m² (p<0.0001), and risk of SCD was 15% and 3%, respectively (p<0.0001). Patients with indexed LA≤26mm/m² and NT-proBNP <708ng/L had 24-month mortality of 1% (both all-cause CVD and SCD); by contrast, all-cause CVD reached 26% and SCD 18% in patients with indexed LA>26mm/m² and NT-proBNP >708ng/L (p<0.0001). Patients with indexed LA>26mm/m² and BMI ≤ 30 kg/m² also had worst prognosis both in the analysis of all-cause CVD and SCD (p<0.0001). Indexed LA size (mm/m²) introduced in the multivariate Cox model emerged as the strongest predictor of all-cause CVD and SCD (p<0.0001).

Conclusions: Indexed LA size, a routinely performed echocardiographic measurement, is a powerful surrogate risk marker of all-cause CVD and SCD in CHF patients.

P543 Mitral regurgitant volume is an independent predictor of clinical events in patients with dilated cardiomyopathy



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Purpose: Restrictive filling (RMP) is an established marker of poor prognosis in patients with dilated cardiomyopathy. It reflects diastolic dysfunction and increased filling pressure, but it is also influenced by the volume overload of mitral regurgitation (MR). Whether the predicting value of RMP is independent of MR is uncertain, mainly because of lack of study with quantitative evaluation of MR.

Methods: Patients referred for evaluation of dilated cardiomyopathy who had a quantitatively assessment of functional MR, were electronically identified in the echo-lab data base. Restrictive pattern was defined as E/A > 1 and E wave deceleration time < 140 msec or E/A > 2. Mitral regurgitant volume (MRVol) was measured by means of PISA. The combined clinical end point was death or hospitalization for worsening heart failure.

Results: 250 patients (mean age 66±14; 73% male) formed the study population. At Cox univariate analysis, RMP (HR 2.7 95% CI 1.3 5.8; p=0.006), MRVol (HR 1.026 95% CI 1.01-1.04; p=0.0005) and systolic right ventricular pressure (HR 1.03 95% CI 1.002-1.061; p=0.04) were significantly associated with the clinical end point.

Cox bivariate analysis showed that RMP did not predict prognosis (HR 1.77 95% CI 0.78 3.95; p=NS) independently of MRVol (HR 1.05 95% CI 1.02 1.08; p=0.003).

Conclusion: MRVol is strongly associated with prognosis in patients with dilated cardiomyopathy. The predicting value of RMP is at least partly determined by the effect of MR.

P544 The prognostic significance of the presence and severity of mitral regurgitation for survival in patients with chronic heart failure



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Background: Still there is a considerable controversy about the predictive power for many echocardiography parameters on long-term survival in patients with heart failure. Therefore, this study interrogated the value of mitral regurgitation in prediction of two-year survival in patients presenting with heart failure.

Methods: This study included 286 consecutive patients (117 females and 169 males) admitted in hospital with heart failure. Study patients were divided in five groups according to the presence and severity (scale from 1+ to 4+) of mitral regurgitation. Ninety three patients did not have regurgitation and 193 patients had regurgitation with different severity (107, 42, 33 and 11 patients respectively). Two-dimensional echocardiography and Doppler study were performed in all studied patients. Patients were clinically followed for two years (26.4±6 months).

Results: There were no significant differences among groups for sex, age, prevalence of hypertension, diabetes, smoking, hyperlipidemia and obesity. In addition, there were no significant differences extra-cardiac diseases. Ejection fraction was significantly different among patients without regurgitation and with regurgitation (divided in 4 levels of severity (50.7%, 46.2%, 37.1%, 37.3%, 32%, P<0.001). Increased severity of regurgitation translated in a higher incidence of death (19.6%, 35.7%, 48.5% and 63.6% respectively in scales from 1+ to 4+). In multivariate analysis, mitral regurgitation remained significant independent predictive factor on mortality in patients with heart failure with odd ratio, 1.67 (CI, 1.05, 2.65, P=0.03).

Conclusions: Mitral regurgitation in chronic heart failure patients presents an independent risk factor for mortality at two years clinical follow-up. With increasing severity of mitral regurgitation increases the risk for adverse clinical event in patients with heart failure.

P545 The importance of myocardial performance index in prognosis of patients with clinical heart failure



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Purpose: Left ventricular myocardial performance index (MPI) is assumed to reflect the overall myocardial function as it incorporates both systolic and diastolic time intervals of the left ventricle. It reflects disease severity in patients with heart failure and has a strong relation to outcome in the early phase after myocardial infarction. In the present study we investigated the prognostic importance of MPI in patients with congestive heart failure (HF) and other co-morbidities.

Methods: MPI was measured by trans-thoracic Doppler echocardiography in 481 consecutive patients as part of the baseline screening in a multi-center study (ECHOS) in patients admitted for HF. Screening criteria were medical treatment for clinical HF, current NYHA class II-IV, and at least one episode of dyspnea or fatigue at rest or during slight exertion within the last month corresponding to

NYHA class III or IV. MPI was obtained as (ICT+IRT/ET), where (ICT+IRT) are the summation of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) and (ET) is equal to ejection time as mean of 5 measurements. Left ventricular ejection fraction was estimated by wall motion index (WMI) and systolic HF was defined as WMI < 1.6 corresponding to an ejection fraction of less than 0.45. The study end-point was all-cause mortality. Patients were followed for 3.3 (2.9-3.9) years.

Results: The median age was 73 (± 12) years and 55% were male. WMI was less than 1.6 in 271 patients. The mean value of MPI was significantly higher in patients with WMI < 1.6 compared to patients with WMI ≥ 1.6 (0.78 ± 0.26 vs. 0.61 ± 0.24 , $p < .0001$). Multivariable proportional hazards analysis showed MPI as a predictor of mortality (HR=1.07, 95% CL: 1.02-1.13, $\chi^2=6.9$, $p=.009$; per 0.1 unit increase of MPI). Other independent variables in the model were age, COPD and glycoside treatment. No interaction was found between these variables. In the subgroup of diabetic patients, MPI was found as a strong predictor of mortality (HR=1.34; 95% CL: 1.16-1.55; $\chi^2=15.32$; $p<.0001$) vs. non-diabetic patients (HR=1.16; 95% CL: 0.97-1.09; $\chi^2=1.16$; $p=.28$).

Conclusions: Myocardial Performance Index had a modest, although significant prognostic value in patients with HF. MPI was found to be of increased prognostic value in diabetics.

P546 Independent prognostic value of aortic stiffness in patients with chronic heart failure due to dilated cardiomyopathy



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Purpose: the stiffening of the large elastic arteries is an independent risk factor of cardiovascular morbidity and mortality in various diseases. In patients with chronic heart failure (CHF) due to dilated cardiomyopathy (DCM), aortic stiffness is associated with reduced oxygen consumption at peak exercise and increased extracellular matrix turnover, established markers of poor prognosis in CHF. However, whether an increased aortic pulse wave velocity (PWV), a well known marker of arterial stiffness, may predict poor outcome in DCM patients has never been reported.

Methods: 161 patients (mean age 66 ± 13 years; 73% male), with a mean left ventricular ejection fraction (LVEF) $33 \pm 8\%$, were followed up for a mean duration of 37 ± 19 months. At baseline all patients underwent to a clinical examination, a complete echocardiography with a PWV measured by Doppler ultrasonography and peak oxygen consumption (peak VO₂) measured by bicycle exercise testing with expiratory gas exchange monitoring.

Results: during follow up 35 patients reached the combined end-point (death or hospital readmission). On the basis of a series of Cox bivariate models, after adjustment for established clinical and echocardiography variables associated with CHF severity (age, diastolic blood pressure, pulse pressure, LVEF, E wave velocity, E wave Deceleration time) a PWV resulted always an independent predictor of poor prognosis ($p < 0.05$ for all models). Particularly, after adjustment for peak VO₂ the hazard ratio of the combined end-point for values in the 2 upper tertiles relative to the lowest tertile of PWV was 4.02 (CI 1.2-13.4, $p=0.02$).

Conclusions: increased aortic stiffness, determined by aortic PWV, is a predictor of death and worsening heart failure in DCM patients. This predictive role is independent of other risk markers of CHF severity.

P547 The 6-minute walk test is a powerful predictor of both morbidity and mortality in Asian patients with congestive heart failure on contemporary medical therapy



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Aims: We sought the value of the 6-min walk test (6MWT) in predicting morbidity and mortality in Asian patients with congestive heart failure (CHF).

Methods: 668 patients (Age 66 ± 12 years, Ejection fraction $29 \pm 13\%$, NYHA 1 to 4) were prospectively followed up for 36 $\pm$ 12 months. 386 patients (58%) took the 6MWT. Cardiac events, defined as the combined end-point of death or heart failure readmission were documented.

Results: 188 patients (28%) reached the combined end-point (63 deaths, 125 readmissions). In a multiple logistic regression model, 6MWT distance was an independent predictor of cardiac events (OR = 4.9, 95% CI = 1.5-16.0, $p=0.008$), as were beta-blocker or spironolactone use (OR=0.44, 95% CI=0.20-0.78, $p=0.008$ for both), diabetes (OR=2.0, 95% CI = 1.0-4.0, $p=0.042$), low monthly income (OR=2.1, 95% CI = 1.1-4.0, $p=0.030$), and NYHA class (OR=5.1, 95% CI = 1.7-15.3, $p=0.003$). A 6MWT distance < 340 metres predicted occurrence of cardiac events with a sensitivity of 69%, specificity of 48%, negative predictive value of 87%, and positive predictive value of 23%. Although both 6MWT distance and NYHA class could accurately predict the combined end-point, 6MWT distance (log rank=10.03, $p=0.018$) was better at discriminating mortality as compared to NYHA functional class (log rank=5.4, $p=0.145$) (Figure 1).

Conclusion: The 6MWT is a safe and simple clinical tool which could predict both morbidity and mortality in a large population of Asian patients with CHF of differ-

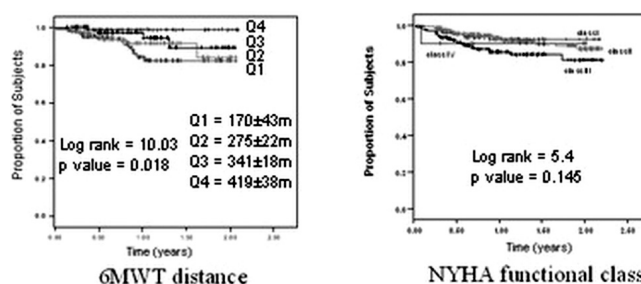


Fig. 1. Kaplan-Meier survival curves comparing mortality free survival based on quartiles of 6MWT distance and NYHA functional class.

ing etiology and severity, and may be superior to NYHA class at discriminating mortality.

P548 QTc time interval predicts risk for heart failure deaths and hospitalisations but not sudden death



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Background: QT duration represents the time from earliest ventricular depolarisation to the end of the last repolarisation potential. The duration is primarily dependent on myocyte action potential development and velocity of depolarisation. Heart failure may interfere with QT corrected for heart rate duration in a complex manner. Scar formation and myocardial remodelling will prolong the QT interval, while autonomic imbalance may cause shortening of the QT duration. Previous studies have demonstrated an association between QT_c time interval (Bassett correction for heart rate) and myocardial dysfunction rather than to autonomic imbalance. This may have bearings on mode of death.

Methods: In order to study the implications of QT duration to mode of death, QT_c was studied in patients from the MERIT-HF trial. Only patients in sinus rhythm and QRS duration < 0.12 sec were included. A total of 742 patients were eligible and followed for an average of 12 months. The patients were in NYHA group II-IV. The QT_c time was defined as the longest QT_c time measured in any lead of a 12 lead ECG.

A total of 8 patients died from aggravated heart failure, and 44 died suddenly (within one hour after onset of symptoms, including resuscitated patients who did not survive). Seventy-three patients were hospitalised due to heart failure, and altogether 81 patients died or were hospitalized for heart failure.

An univariate analysis demonstrated a significant relationship between QT_c and death or hospitalisation for heart failure ($p=0.0001$; time to first event). There was no relationship to sudden death. The significant relationship between QT_c and heart failure events was confirmed in a multivariate analysis including RR-interval, QRS duration and QT dispersion ($p=0.0038$).

In conclusion, a prolonged QT_c time interval is a risk factor for death or hospitalization for heart failure, but not for sudden death.

P549 Iron metabolism is abnormal in patients with chronic heart failure and associated with immune activation, exercise intolerance and increased mortality



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Background: Defective iron homeostasis linked to erythropoiesis has emerged as a principal cause of anaemia in chronic heart failure (CHF). We studied iron metabolism and its relation to immune activation, exercise capacity and survival across a broader spectrum of patients (pts) with CHF.

Methods: We prospectively recruited 174 consecutive CHF pts (age 71 ± 11 years, NYHA class 2 ± 1 , LVEF $31 \pm 1\%$, Hb 13 ± 1 g/dL) and 21 controls matched for age, sex and ethnicity. Circulating (transferrin saturation [TSAT], soluble transferrin receptor), stored (ferritin), and functional (mean cell haemoglobin concentration [MCHC], % hypochromic cells, reticulocyte Hb content) iron status were quantified. Peak oxygen consumption [pVO₂] was measured. We analysed the relation of the MCHC to survival in a separate cohort of 147 CHF pts (age 63 ± 11 years, NYHA class 2.3 ± 1 , LVEF $31 \pm 1\%$).

Results: There was a progressive reduction in TSAT from controls ($28 \pm 8\%$) to NYHA 1/2 ($n=69$; $26 \pm 7\%$ [mean $\pm$ SD]), NYHA 3 ($n=73$; $19 \pm 8\%$), and NYHA 4 ($n=32$; $15 \pm 6\%$) pts (ANOVA $p < 0.0001$). A similar trend in MCHC (ANOVA $p < 0.0001$) but not ferritin (ANOVA $p=0.45$) levels was seen. Within NYHA 3 and NYHA 4 strata, anaemic pts had lower TSAT and MCHC values than non-anaemic pts (all $p < 0.05$). Soluble transferrin receptor levels and % hypochromic cells were higher in pts than controls, and increased with increasing NYHA class (all $p < 0.01$). A trend towards a reduction in reticulocyte haemoglobin content from controls to NYHA 4 pts was seen (ANOVA $p=0.09$). Interleukin-6 levels re-

lated to TSAT ($n=49$, $r=-0.3$, $p=0.03$) and MCHC ($n=51$, $r=0.3$, $p=0.02$). Levels of TSAT ($r=0.65$, $p=0.01$), but not ferritin ($r=0.53$, $p=0.06$) related to pVO_2 . During follow-up (34 ± 27 months, >6 months in survivors), 54 (37%) pts died. In univariate Cox analysis, LVEF, age, NYHA class, Hb, TNF receptor-1 levels and MCHC ($c\ 2\ 30.5$) predicted survival (all $p<0.03$). In multivariate analysis only MCHC ($p=0.037$), LVEF ($p=0.004$), and TNFR-1 levels ($p<0.001$) independently predicted survival. When subdividing patients by MCHC quartiles (Q1:28.3-30.1g/dL; Q2:30.2-32g/dL; Q3:32.1-33.9g/dL; Q4:34-35.9g/dL) there was a significant difference in survival with each quartile ($p<0.0001$). Survival at 36 months for patients in Q1,Q2,Q3 and Q4 was 43%, 64%, 90% and 92% respectively.

Conclusions: Iron metabolism is abnormal in patients with chronic heart failure and characterised by reduced circulating and functional, but not stored, iron status. Defective iron homeostasis is associated with immune activation, and impaired exercise capacity and survival.

P550 The impact of regular planned home visit by physician in outpatients with chronic heart failure and low literacy and income



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Background: Some studies demonstrated that intervention combining patient education and postdischarge management is effective in patients with chronic heart failure. However, the benefit, contributable to outpatient with chronic heart failure and low literacy and income, is not known, and it is not to compare the effects of optimization of guideline-based medical therapy, patient education and psychosocial support by trained physician with trained nurse. We hypothesized that the planned home visit by physician would prove effective and cost-effective care for these patients in China.

Methods and results: We conducted a randomized controlled of 218 outpatients with chronic heart failure and low literacy and income, and compared the effects of every three month planned home visit by the physician ($n=74$), the nurse ($n=72$), the conventional care ($n=72$). Mean follow up was 24 months (ranged from 20 to 108 months). Subjects randomized to receive the physician home visit had the fewest days hospitalized or lower fatality, and they increased significantly self-care behaviour in the follow-up period. Patients receiving the physician home visit had the lowest risk of rehospitalization or death (RR 0.57 95%CI 0.34 to 0.78 $p<0.01$). In addition, their costs of care were the lowest among the three groups. Subjects randomized to receiving conventional care had more days hospitalization, higher fatality, and higher cost.

Conclusions: The planned, systematic, and tailored home visit by the physician may result in an increase in the patient's self-behaviour and a decrease in the day hospitalization, mortality, and the visit may lower costs of care in outpatients with chronic heart failure and low literacy and income in China.

P551 Usefulness of non-invasive parameters for the identification of patients with left ventricular dysfunction after myocardial infarction at low risk of death: a 11 years follow-up



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Background: Recent trials showed significantly lower mortality in ICD recipients with severe left ventricular dysfunction after myocardial infarction. The potential role of non invasive testing, combined with left ventricular ejection fraction evaluation, in the optimization of the selection criteria for such therapy has not been evaluated, and no data are available on long term prognosis in this setting.

Aim: To evaluate the ability of non-invasive markers in the identification of patients with left ventricular dysfunction after myocardial infarction at low risk of death from any cause.

Materials and methods: Of 278 patients with recent (≤ 30 days) myocardial infarction, 65 (23%) with left ventricular ejection fraction $\leq 40\%$ represent the study group: mean age 56 ± 9 years, thrombolysis 57%, left ventricular ejection fraction $36 \pm 4\%$, anterior myocardial infarction 83%, previous myocardial infarction 17%, left ventricular dyskinesia 51%, QRS duration at signal averaging 105 ± 13 msec, SDNN 106 ± 38 msec, unsustained ventricular tachycardia at Holter monitoring 32%.

Results: At follow-up (11 ± 3 years) 28 deaths (43%) were recorded. Among the above-mentioned variables, the survival Cox analysis identified as independent predictors of death from any cause, besides left ventricular ejection fraction ($p=0.05$), QRS duration at signal averaging ($p=0.007$) and the presence of unsustained ventricular tachycardia at Holter monitoring ($p=0.008$). In the study group 9 patients (14%) had both variables (QRS duration and unsustained ventricular tachycardia) altered (group '2'), 33 (51%) presented only one variable altered (group '1'), and 23 (35%) had no altered variables (group '0'). Mortality rate from

any cause was 67% in group '2', 54% in group '1' and 17% in group '0'. Patients in group '0' showed an average annual mortality of 1.5% during follow-up.

Conclusions: The present analysis suggests that the normality of 2 non-invasive variables identify a subgroup of post-infarction patients with good long term prognosis, despite moderate to severe left ventricular dysfunction. Therefore non invasive tests, together with left ventricular ejection fraction, may result of help in the optimization of selection criteria of patients candidate for ICD therapy after myocardial infarction.

P552 Untreated human immunodeficiency virus (HIV) - infection does not influence outcome in peripartum cardiomyopathy patients



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Introduction: HIV infection occurs in 34% of patients with peripartum cardiomyopathy (PPCM) in South Africa. Both conditions are associated with immune dysregulation. The influence of HIV induced immunosuppression on standard heart failure therapy in PPCM is unknown.

Aim: To describe clinical presentation, echocardiographic parameters and immune plasma parameters in HIV positive and negative PPCM patients and explore effectiveness of standard heart failure therapy.

Methods: Single centre prospective study of 71 newly diagnosed PPCM patients. Patients started on antiretroviral therapy were excluded from this analysis. Parameters were reassessed after 6 months.

Results: (Table) HIV-positive PPCM patients present with lower Hb, CD4, WCC and higher heart rate. Deaths do not differ between groups at 6 months. After 6 months both groups improved left ventricular (LV) parameters ($p<0.001$). Heart rate was still significantly higher in HIV positive patients.

Parameter	Baseline			6 months		
	HIV-positive	HIV-negative	p-value	HIV-positive	HIV-negative	p-value
NYHA FC	3.2±0.6	3.3±0.7	NS	1.6±0.7	1.5±0.6	NS
HR (beats/min)	109.8±17.1	99.4±16.7	0.02	95.9±19.9	79.3±13.5	0.0003
Hb	10.4±2.2	11.8±1.7	0.005	11.6±1.9	12.7±1.5	0.02
LVEDD (cm)	5.6±0.6	5.7±0.6	NS	5.1±0.9	5.2±0.7	NS
LVEDS (cm)	4.8±0.7	4.9±0.6	NS	4.1±0.9	4.0±0.8	NS
Fractional shortening (%)	17.7±16.4	14.0±4.7	NS	21.8±6.6	22.9±6.5	NS
Ejection fraction (%)	29.4±8.7	29.0±9.0	NS	43.2±11.2	45.0±11.3	NS
CD4 (x10 ⁹ /l)	445.1	1023.9	<0.0001	381.0	820.9	<0.0001
	±296.6	±383.7		±280.0	±284.6	
WCC	5.5	7.7±4.3	0.02	5.4±1.5	5.8±1.9	NS
CRP	28.7±54.2	35.7±49.3	NS	32.8±62.5	10.3±31.5	NS

Conclusions: 1. No difference in recovery of LV function was observed between groups, underlining the importance of optimal heart failure therapy for HIV positive PPCM patients even in resource constraint settings. 2. Elevated levels of CRP and inflammatory cytokines in both groups suggest a systemic inflammatory component in the pathogenesis of PPCM. 3. CRP remains elevated in HIV-positive PPCM patients despite improved LV function and is therefore unsuitable to monitor heart failure in these patients. 4. The effect of cardiac therapy on HIV viral load and on CD4 levels is currently under study.

P553 Low levels of free testosterone are only indirectly associated with increased mortality in male chronic heart failure patients



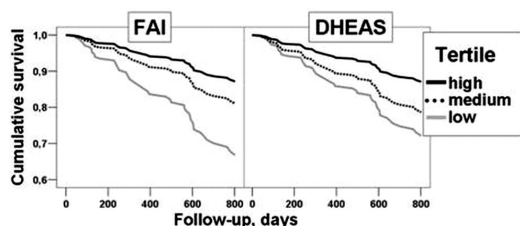
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Background: In chronic heart failure (CHF), levels of anabolic factors as testosterone (T) are depressed, but its prognostic impact is unknown. We estimated the independent prognostic relevance of T in the prediction of all-cause death in CHF.

Methods: Prospective cohort study [median follow-up 708d (IQR 218-1071), event rate 28%] in 194 consecutive males with CHF of any etiology and severity. Patients were characterized in detail at baseline. T, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEAS), and NT-pro brain natriuretic peptide (BNP) were measured. Free androgen index (FAI) was calculated as $[T(nmol/L)*100/SHBG(nmol/L)]$.

Results: Patients were aged 64 ± 13 y; they were in NYHA classes I-II-III-IV in 24-30-34-12%. Median levels of T and FAI were 3.6 ng/ml (IQR 2.7-4.6) and 33 (25-51). NYHA class correlated with FAI (Spearman's $r=0.25$), DHEAS ($r=-0.27$), and NT-proBNP ($r=0.30$; all $p<0.001$). Sex hormones and NT-proBNP correlated strongly with age, but only the latter with fractional shortening. Further, FAI and NT-proBNP were highly correlated ($r=0.41$; $p<0.001$). In Cox analyses (figure), adjusted for age and NYHA class, decreasing tertiles of FAI or DHEAS independently predicted all-cause mortality risk (hazard ratio per tertile of FAI: 1.75, 95%CI 1.3-2.4; hazard ratio per tertile of DHEAS: 1.55, 95%CI 1.14-2.00). Further

adjustment for renal function, anemia, and fractional shortening did not abolish these associations, but adjustment for NT-proBNP did so.



Sex hormones and mortality risk

Conclusions: Low levels of free T and DHEAS relate to the severity of CHF and predict all-cause mortality in males. However, this association depends on NT-proBNP. The contribution of T and DHEAS to the pathophysiology and clinical course of heart failure remains to be determined.

P554 Increased mortality but not increased rate of sudden cardiac death is associated with low haemoglobin levels in chronic heart failure patients



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Background: Low haemoglobin (Hb) levels can be found in patients with chronic heart failure (CHF) frequently and are associated with higher mortality rates. Whether CHF patients with lower Hb have a higher risk for sudden cardiac death is not known.

Methods: We assessed full blood count, mortality, hospitalisation rate and the occurrence of life threatening arrhythmias, i.e. sustained ventricular tachycardia (sVT) and ventricular flutter (VF), in 213 CHF patients who had received an implantable cardioverter-defibrillator (ICD): mean age 61±10 years; 30 (14.5%) female; NYHA I/II/III/IV: n=73/96/42/2; aetiology: 74% coronary artery disease. Death, time to first sVT or VF and all hospitalisations were considered as end-points for Cox proportional hazard analyses.

Results: The mean haemoglobin level at baseline visit was 13.4±1.9mg/dL. Non-survivors had a significant lower Hb level compared to survivors (Hb 12.6±1.9mg/dl vs. Hb 13.6±1.9mg/dl; p=0.027). During a mean follow-up time of 501±127 days 23 deaths occurred, 95 Patients had sVT/VF and 103 hospitalisations were recorded. Haemoglobin was a significant predictor of mortality in univariate analysis (p=0.041; RR 0.76; 95%CI 0.64-0.99). In multivariate analysis (including age, NYHA class, sex and sodium) haemoglobin remained significant (p=0.03; RR 0.78; 95%CI 0.62-0.98) in this cohort. There was no significant impact of a low haemoglobin level on the time to first life threatening arrhythmic event (p=0.7), on the combined endpoint of death and time to first sVT/VF (p=0.8) or on the time to first hospitalisation (p=0.7).

Conclusion: These results show that in CHF patients lower haemoglobin levels are associated with higher total mortality rates but not with a higher risk for sudden cardiac death. We hypothesize that anaemia in CHF more often leads to decompensated heart failure and higher prevalence of progressive pump failure.

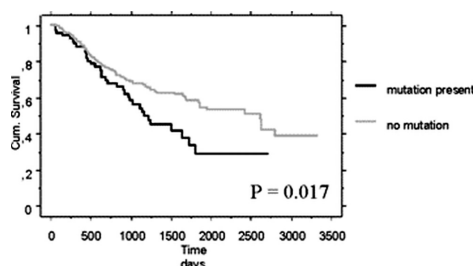
P555 HFE mutations are associated with increased mortality in heart failure patients from different etiologies



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Introduction: the HFE gene has been suggested as a contributing factor in dilated cardiomyopathy (DCM) development. However, results are contradictory and there are no large follow-up studies to date. We have studied the effect of H63D and C282Y mutations in 318 patients with the diagnosis of DCM prospectively followed-up in a tertiary care center. Animal models were developed to study possible mechanistic roles of the HFE gene during DCM development.

Methods and Results: We grouped individuals with at least one mutated allele. Mean follow-up time was 1007 (±701) days. Twenty-one percent of individuals in our sample harbor at least one mutated allele. There were no significant differences in baseline characteristics between groups. However, Kaplan-Meier mortality curves were significant different between individuals with and without HFE mutated alleles (figure). Presence of at least one HFE mutated allele remained significantly associated with increased mortality even after adjustment for other covariates in a Cox hazard model (RR=1.57, CI 1.05-2.36). This difference was present and homogeneous in all etiological subgroups analyzed. RT-PCR experiments demonstrated presence of mRNA HFE transcripts and immunohistochemistry studies demonstrated the presence of the HFE protein in mouse myocardial tissue. Interestingly, a dynamic regulation of HFE gene expression was demonstrated in mice with a ischemic cardiomyopathy model developed with myocardial infarction through LAD ligation (p=0.03). No differences in HFE expression were detected in intestinal segments of the same animals.



Conclusions: we provide further data on the possible association between HFE gene mutations and DCM development in humans. Animal experiments suggest a still unexplored paracrine role of HFE in the ischemic myocardium.

P556 Prognostic significance of location and type of myocardial infarction in the setting of advanced left ventricular dysfunction



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Background: After myocardial infarction, location (anterior) and type (Q-wave) might be considered of prognostic significance when predicting mortality. In this study, we determined the prognostic significance of type and location of MI in patients with severe left ventricular dysfunction.

Methods and Results: Of the 1221 patients participating in MADIT II, 763 (62%) had Q-wave MI, 115 (10%) had non-Q wave MI and 343 (28%) were excluded from ECG categorization of MI due to conduction disturbances or paced rhythm. Among Q wave infarctions, anterior wall MI was present in 430 patients (57%), inferior wall MI in 155 (20%), and combined anterior and inferior MI in 178 (23%). Study endpoints included all cause mortality, hospitalization or death due to worsening congestive heart failure, and episodes of ventricular tachycardia or ventricular fibrillation requiring ICD therapy. In the multivariate Cox proportional hazard model predicting mortality, the following clinical variables entered the predictive model at the p<0.10 level: treatment (ICD vs. conventional therapy), age dichotomized at 65 years, history of angina, ejection fraction dichotomized at 25%, BUN dichotomized at 25 mg/dl, and beta-blocker use. After adjustment for these covariates (Table), the risk of mortality was not significantly different in NQMI vs. QMI. Yet, when analyzing location of MI, inferior MI was associated with significantly (58%; p=0.048) higher risk of mortality than anterior MI. Also, patients excluded from categorization had a 36% higher risk of mortality with borderline significance (p=0.088).

Location and Type of Myocardial Infarct

Variable Tested	HR	95%CI	P value
Type of MI			
Non-Q vs. Q wave	1.011	0.586-1.745	0.968
Excluded vs. Q wave	1.163	0.856-1.581	0.335
Location of MI			
Inferior vs. Anterior	1.582	1.003-2.496	0.048
Combined vs. Anterior	1.094	0.676-1.769	0.715
Excluded vs. Anterior	1.363	0.954-1.947	0.088

Conclusions: In the setting of severely depressed ejection fraction (<= 30%), inferior wall myocardial infarction was associated with a significantly higher risk of mortality than anterior wall myocardial infarction.

P557 Prognostic value of combined dobutamine stress echocardiography and myocardial contrast echocardiography in patients with known or suspected coronary artery disease



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Purpose: This study sought to determine whether the combination of dobutamine stress echocardiography (DSE) and myocardial contrast echo (MCE) can be used to predict morbidity and mortality in patients with known or suspected coronary artery disease.

Methods: Follow-up was performed on 440 patients (mean age: 65 y, 315 men) over a period of 36 months (an average 25 months) after clinically indicated DSE. The DSE-MCE protocol included SonoVue (Bracco) infusion (at a rate of 0.8 ml/min) during the baseline echo study and during the last stage of DSE using power modulation and a low mechanical index (0.1-0.2). Transient high mechanical index (1.7) pulses were used to destroy microbubbles, allowing the assessment of myocardial replenishment. All echo studies were stratified according to either inducible wall motion abnormalities or MCE perfusion defects into 4 responses: negative for ischemia DSE(-) and MCE(-), positive DSE(+) and negative MCE(-), negative DSE(-) and positive MCE(+) as well as positive DSE(+) and MCE(+). The combined end points of cardiac death and/or events were tabulated for the outcome.

Results: Cardiac events occurred in 79 patients (18%). A negative DSE(-)MCE(-) was associated with a statistically lower likelihood of cardiac event compared to other DSE-MCE responses ($p=0.003$). The combination of both positive DSE(+)MCE(+) was associated with a higher likelihood of cardiac events by the multivariate analysis ($p=0.001$). By multiple logistic regression analysis of DSE-MCE response, age, and cardiac risk factors, a positive DSE and/or MCE response was independently associated with the occurrence of a cardiac end point during the follow-up period. In a multivariate Cox proportional hazards model, the likelihood of any cardiac event was increased in the presence of both positive DSE-MCE response (relative risk [RR] 6.6, 95% confidence interval [CI] 4.1 to 9.4, $p<0.01$).

Conclusions: The presence of positive response during DSE-MCE is an independent predictor of cardiac events and therefore it can identify high and low risk subsets of patients with known or suspected coronary artery disease. Long term follow up of these patients would merit major consideration.

P558 Prognostic value of left ventricular mass as a continuous variable



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Left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular (CV) events and a conventional partition value of LV mass (LVM) is used to assess presence/absence of LVH. Few data are available on whether continuous relationships exist between LVM and CV events. We investigated the prognostic value of increasing levels of LVM in a sample of high risk subjects.

Methods: We retrospectively studied 251 patients (51% male, mean age 64 ± 12) with at least one CV risk factor, who had baseline echocardiogram. Hypertension was present in 77% of cases, type 2 diabetes in 20%, hypercholesterolemia in 47% and previous CV disease in 55%. The average 10 years Framingham risk was $31 \pm 27\%$. The mean interval from baseline echocardiogram to the follow-up contact was 68 ± 20 months. The primary end point was fatal and non fatal CV events. Secondary end points were all cause and CV mortality. LVM has been indexed for body height in $\text{metres}^2.7$. Patients was divided in quartiles of baseline LVM (Table 1) and relative risks (RR) among quartiles were calculated. LVM was within the normal limits ($<51 \text{ g/m}^2.7$) in 100% of the patients in the 1st and 2nd quartile, while it was increased in 65% of the patients in the 3rd quartile.

Results: During follow-up ninety four patients had fatal or non fatal CV events. All cause deaths and CV deaths were 41 and 25, respectively. Significant and progressive increases in RR were observed in 2nd, 3rd and 4th quartile compared to 1st quartile for all CV events (RR=2.05, CI 1.08-4.17; RR=3.16, CI 1.64-6.09; RR=4.43, CI 2.63-7.46; respectively), all cause mortality (RR=1.64, CI 0.56-4.63; RR=2.44, CI 0.94-6.34; RR=3.28, CI 1.38-7.81) and CV mortality (RR=4.10, CI 1.12-7.85; RR=6.11, CI 1.02-35.2; RR=12.36, CI 2.73-55.8). Patients in the upper quartile of LVM had higher risk for all CV events (RR=1.41, CI 1.02-1.95) and CV mortality (RR=2.0, CI 1.32-3.08) than patients of the 3rd quartile.

Table 1

	1st q	2nd q	3rd q	4th q
LVM Range	23-38.9	39-48.1	48.2-58.7	58.8-122

q=quartile; MVS=left ventricular mass

Conclusions: Our data suggest that there is a continuum between values of LVM and CV events also within the normal range of LVM. A new classification as normal, high-normal, moderately increased and severely increased LVM might stratify CV risk better than the conventional approach based on presence/absence of LVH.

P559 Low Urotensin II levels predict risk of non-fatal MI in humans



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Background: Urotensin II (Ull) is a potent vasoactive peptide present in human myocardium acting via the Ull receptor. We have previously shown Ull to be raised after an acute myocardial infarction (AMI) suggesting a pathophysiological role for this endogenous peptide. The aim of this study was to see if Ull levels could be used to predict risk of non-fatal MI in post AMI patients.

Methods: We studied 504 patients (383 men, mean age 64.8 ± 12.5 years, 80% STEMI, 20% NSTEMI) with AMI. Serial blood measurements were made at 24 hourly intervals for a median of 5 days after onset of chest pain. Samples were extracted using standard C18 Sep-Pak columns and Ull was assayed using an in-house competitive chemiluminescent immunoassay. Comparison was made with N terminal pro B-type natriuretic peptide (NT-BNP) a peptide which is raised post AMI. There was 100% patient follow-up and reinfarction was defined as readmission to hospital with ECG changes and a troponin rise above the 99th centile for our population. Patients who died were excluded from analysis.

Results: Median follow up was 352 days (range 0-644) and 42 reinfarctions were noted over this time. Peak Ull levels were lower in patients who were admitted with non-fatal MI compared to those who were not (median [range] fmol/ml, $0.77[0.29-$

$11.0]$ vs. $1.6[0.29-34.7]$, $p=0.01$). Using a multivariate binary logistic model peak Ull (OR 0.49, 95% CI: 0.27-0.89, $p=0.018$) and peak NT-BNP (OR 1.71, 95% CI: 1.0-2.96, $p=0.05$) independently predicted non-fatal MI. On the Cox proportional hazards model however the only independent predictor of non-fatal MI was peak Ull (HR 0.51, 95% CI: 0.29-0.89, $p=0.019$). The Kaplan-Meier survival curve revealed a significantly better clinical outcome in patients with peak Ull above the median compared with those with peak Ull below the median (log rank 6.30, $p=0.012$). The receiver operating curve for peak NT-BNP yielded an area under the curve (AUC) of 0.59 (95% CI: 0.51-0.67, $p=0.03$); for peak Ull the AUC was 0.61 (95% CI: 0.53-0.68, $p=0.01$).

Conclusion: Peak Ull but not NT-BNP is better able to independently predict non-fatal MI in patients post AMI. Patients with a poor outcome mount a lower Ull response suggesting a possible cardioprotective role for this peptide and target for future therapy. The role of Ull in affecting plaque stability remains to be established.

P560 The restrictive mitral filling pattern predicts mortality in patients post-acute myocardial infarction independently of LV ejection fraction: results from an individual patient meta-analysis (MeRGE)



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Left ventricular (LV) restrictive filling pattern (RFP), characterised by a short E wave deceleration time, is related to higher filling pressure. Several previous studies have suggested RFP is associated with increased risk of death following acute myocardial infarction (AMI). However, it is uncertain whether RFP is independent of other predictive indices, especially when LV systolic function is preserved. We therefore merged the individual patient data from 12 international prospective studies with the aim of determining whether RFP added independent prognostic information to ejection fraction (EF).

Methods: Individual patient data (demographic, clinical, echocardiographic and all cause death) were collated into a single database. Patients were divided into quartiles on the basis of EF (biplane Simpson's or derived from wall motion index). Each quartile was then stratified by the presence of RFP (DT < 140 ms, or pattern defined) and the hazard ratio for all-cause death was compared between the patients with and without RFP. Kaplan Meier survival analysis and Cox Proportional Hazards multivariate analysis were performed to determine the combined and individual effects upon survival.

Results: 3303 patients were included: 28% female, mean age 63 ± 12 yrs, mean EF $46 \pm 10\%$. RFP was present in 720 patients (22%) at baseline. Average follow-up was 1019 ± 635 days (median 1084, max 1461 days). 526 patients died: 310 deaths in the RFP group and 216 deaths in the non-RFP group (hazard ratio: 3.38 (CI:2.78,4.19). RFP independently predicted outcome in each quartile of EF. In multi-variate analysis, RFP, EF and age were independent predictors of mortality.

All-cause mortality associated with RFP

Quartiles: EF Range	Q1: EF <39%	Q2: EF 39-47%	Q3: 47-53%	Q4: EF >53%
Number at risk	787	852	833	831
RFP: deaths/number at risk (% died)	136/323 (42%)	35/170 (21%)	23/124 (19%)	22/75 (29%)
non-RFP: deaths/number at risk (% died)	93/464 (20%)	85/682 (12%)	67/709 (9%)	65/756 (9%)
Hazard Ratio (95% CI)	2.90 (2.11,3.98)	1.82 (1.18,2.82)	2.18 (1.30,3.66)	4.41 (2.52,7.71)

Abbreviations: CI = confidence interval, EF = ejection fraction, RFP = restrictive filling pattern, Q = quartile.

Conclusion: This large collaborative individual patient meta-analysis demonstrates that RFP is an important and independent prognostic indicator after AMI. It is incremental to LVEF and predicts a high mortality, even in patients with preserved systolic function.

P561 Progressive heart failure, rather than sudden death, accounts for most early deaths in patients with incident heart failure in the general population



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Background: The early prognosis for patients with newly diagnosed heart failure (HF) in the general population is poor, with up to 25% not surviving six months. Clinical trials demonstrate that approximately 50% of chronic HF patients die suddenly. The mode of death for newly diagnosed HF in the general population has not been evaluated.

Aims: To describe the mode of death in a population-based cohort of patients in the first six months after a new diagnosis of HF.

Design: Two-centre UK population-based study (The Hillingdon Hospital, London and The Conquest Hospital, Hastings).

Methods: New cases of HF were identified by daily surveillance of acute hospital admissions and general practitioner referral. A diagnosis of HF was made based on the ESC criteria. A panel of three cardiologists reviewed all deaths occurring within six months and assigned a mode of death, according to pre-specified criteria.

Results: Between Jan 2004 and Oct 2005, 396 patients (61% males) with incident heart failure were identified. Median age was 75.2 (st. dev. 12.3) years. Prior to initial discharge or death, 28% tolerated both a β -blocker and an ACE inhibitor or angiotensin receptor blocker (ARB), 51% an ACE inhibitor or ARB alone and 3% a β -blocker alone. Five (1%) patients underwent successful ICD implantation. There were 59 deaths over a median follow-up of 10 months; 86% (n=51) were cardiovascular (CV) deaths of which 25% (n=13) occurred within 14 days of an acute myocardial infarction. Of the CV deaths, the mode of death was progressive heart failure (PHF) in 61% (n=31), sudden death (SD) in 25% (n=13) and other CV modes of death in 14% (n=7). Dying suddenly (vs. PHF and other modes) was associated with an increased mean left ventricular end diastolic diameter (6.3 (0.7) vs. 5.5 (0.8) cm; $p=0.02$) and left ventricular end systolic diameter (5.4 (0.9) vs. 4.3 (0.9) cm; $p=0.02$) but not with age, gender, NYHA class, aetiology of HF, cardiac rhythm, or QRS duration. Using Cox proportional regression multivariable analysis, both PHF death and SD were independently associated with older age and lower serum sodium at baseline.

Conclusion: Progressive heart failure accounts for the majority of CV deaths in the first six months after a new diagnosis of HF in the general population. Sudden death accounts for one-quarter of CV deaths and is associated with greater left ventricular dilatation at baseline. Although risk factor profiles differ somewhat between the modes of death, identification of those at risk of early sudden death for specific therapy such as ICD implantation is not straightforward.

P562 Holter-Based predictors of cardiovascular and sudden death in Post-MI Heart Failure: results from EPHEsus

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Purpose: Post-AMI and HF pts are at increased risk for ventricular arrhythmias, CV mortality and sudden cardiac death (SCD). Decreased heart rate variability (HRV) and abnormal heart rate turbulence (HRT), reflecting autonomic abnormalities occur post-AMI and in HF. It is not established whether these parameters among patients with post-AMI HF identify increased risk of CV death or SCD.

Methods: In the Holter substudy (N=493) of EPHEsus, arrhythmia frequency, HRV, and HRT were measured at pre-randomization baseline and at 6 months FU. Pts were followed for ≤ 345 days. Two-tier risk scores encompassing clinical and demographic predictors of CV or SCD and pharmacological treatment at AMI were developed. Cox regression determined independent associations of arrhythmia frequency, HRV and HRT with CV or SCD after adjustment for the 2 risk scores.

Results: No differences in demographics, baseline or post-treatment HRV, or medications were observed between groups randomized to eplerenone (E) or placebo. TM with E resulted in a significant decline in % of pts with PVCs >30 /hr or >100 /hr but no change in HRV or HRT. Significant predictors of SCD included: LVEF $<30\%$, Killip class III/IV, pulse >100 bpm, and TM with digoxin or nitrates ($p<0.001$). Additional predictors of CV death included: age >65 , history of HF, sodium >35 mmol/l, creatinine >96 , prior TM with antiplatelets, antiarrhythmics, loop diuretics and anticoagulants but not TM with nitrates. After adjustment, increased HR and more abnormal HRT remained strongly associated with CV death. After adjustment, only PVCs >30 /hr or >100 /hr predicted SCD.

		RR	95% CI	p-value
CV death	24-hr HR (bpm)	1.05	1.03, 1.08	<0.001
	Abnormal HRT	2.30	1.19, 4.43	0.013
SCD	PVC30	3.28	1.21, 8.85	0.019
	PVC100	3.61	1.04, 12.48	0.042

Conclusions: Increased HR and abnormal HRT are associated with CV death, reflecting autonomic abnormalities that predispose patients to higher mortality. The decrease in PVC frequency with E suggests that the reduction in ventricular arrhythmias might explain the reduction in SCD seen in EPHEsus.

P563 No clear benefit in short term but in mid and long term mortality in patients with chronic heart failure and ICD on medication of betablockers

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Background: The prognostic beneficial effect of both betablockers (BB) and ICD-

Therapy in advanced heart failure (CHF) has been clearly demonstrated. The reduction in mortality is in part addicted to a reduction in fatal arrhythmias.

Aim of the study: The benefit of additional BB therapy vs. no BB in P with CHF and ICD

Methods and patients: From the regional, prospective CHF-registry HELUMA (since 1994, 2996 consecutive patients (P), ejection fraction $<40\%$, 90% invasively diagnosed, non-valvular genesis) 342 P with ICD (clinical indication, primary and secondary prophylaxis) at entry in the study were stratified according to therapy with BB.

Results: Differences between groups (CHF and ICD with BB (n=241) vs without BB (n=101)): hyperlipidemia (38% vs. 26%, $p=0.03$), diabetes (29% vs. 14%, $p=0.01$), ACE-Inhibitors and ARB (95% vs. 65%, $p<0.0001$), aldosteronantagonists (56% vs. 11%, $p<0.0001$). No difference was seen between groups for gender, age, ejection fraction, ischemic or dilatativ CMP, NYHA-functional class III-IV, creatinine clearance, other concomitant medication.

Outcome in CHF-patients with ICD, stratified by beta-blocker therapy

Mortality	ICD BB + n=241	ICD BB - n=101	p-values	Odds ratio
1-year, %	11	15	0.35	0.70 (0.33-1.48)
3-year, %	27	44	0.02	0.48 (0.26-0.89)*
5-year, %	42	71	<0.001	0.30 (0.15-0.60)*

*significant after adjustment for hyperlipidemia, diabetes, ACE/ARB therapy, aldosteronantagonist.

Summary and Conclusion: 1. CHF-patient with ICD and BB vs. no BB have more severe concomitant diseases, are better treated in respect to prognostic medication.

2. After adjustment for differences between the groups there is no clear benefit in short term but a clear benefit in mid and long term mortality.

P564 Desmin distribution in cardiomyocytes and left ventricle function of patients with chronic heart failure

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Background: Desmin is the first, basic muscular - specific structural protein, which decides of cardiac muscle cells function. It is supposed that both, down and up - regulation of desmin in cardiomyocytes plays important role in progression of heart failure (HF). Aim: Evaluation of desmin in samples taken from right ventricular during diagnostic endomyocardial biopsy (DMB). Material and methods: The study population consisted of 135 patients (86.7% of males, mean age 49.4 ± 14.1 years) clinical symptoms of HF (LVEF $<45\%$). During DMB four samples were taken from right ventricle. The immunohistochemical studies of the endomyocardial muscle specimens included immunostaining with antibodies to desmin. Study population was divided into three groups: I group - 48 patients with normal expression of desmin, II group - 54 patients with increased accumulation of desmin, III group - 33 patients with low expression of desmin in cardiomyocytes. **Results:** The ejection fraction (EF) was significantly bigger in group I, than group II and III. The size of left ventricle (LV) was statistically smaller in group I than in group II and III (table below).

Echocardiography examination and desmin

Desmin accumulation in cardiomyocytes	EF (%) Value	EFp	LV diameter (mm); Value	LV diameter p
Group I	35.5 ± 12.6	0.009#	61.4 ± 9.7	0.027#
Group II	29.3 ± 10.4	0.67*	65.9 ± 10.1	0.23*
Group III	28.4 ± 8.3	0.003*	69.1 ± 12.0	0.004*

$p<0.05$: # group I vs group II, * group III vs group I, ^ group II vs group III.

Conclusions: Our results have confirmed that either low or high expression of desmin in cardiomyocytes co-exists with HF development. Abnormal expression of desmin in cardiomyocyte in immunohistochemical study is associated with significant enlargement of LV diameter and lower EF of LV.

P565 First results from the HeartNet ventricular support system study in heart failure

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Purpose: The prevention, attenuation or reversal of ventricular remodeling and the prevention of sudden death are major targets in the treatment of heart failure and may be achieved by means of a new ventricular support system. We report on the first clinical results of the Paracor HeartNet, an elastic Nitinol and Silicone net without or with additional defibrillator electrode coils implanted around both ventricles via a minimally invasive lateral thoracotomy.

Methods: 11 patients (pts), 9 males and 2 females, mean age 52 y/o with cardiomyopathy (9 non-ischemic, 3 ischemic) with optimal medical therapy for at

least three months received the HeartNet. In the last two pts the new generation HeartNet with integrated defibrillation electrode coils was implanted and connected with a commercially available ICD generator.

Results: Mean NYHA class prior to implantation of the ventricular support system was 2.45, two pts were listed for heart transplantation. All support systems were implanted without major adverse events. 12-month follow-up data are available in 8/11 pts, no pt died, 2 pts developed temporary small pericardial effusion. There were no clinical or echocardiographic signs of constriction. Unrelated to the HeartNet system three pts developed sustained VT during follow-up and received ICD's thereafter. One pt with atrial fibrillation developed a minor embolic stroke after 7 months. There is a strong trend of clinical, functional and hemodynamic improvement after 12 months (Table).

Clinical parameters (n=8)

	Baseline	12-months follow-up
NYHA-Class	2.45	1.75
EF (Echo) [%]	25 ± 4.9	26.7 ± 8
LVEDD (Echo) [mm]	70.8 ± 7.8	67.2 ± 9.7
6 min walk test [m]	436 ± 115	471 ± 130
VO ₂ max [ml O ₂ /kg/min]	17.5 ± 2.1	18.7 ± 3.5
BNP [pg/ml] (converted US values)	632 ± 284	368 ± 498

Mean values and standard deviation are given

Conclusion: We conclude that the HeartNet support system can be implanted easily without major complications. There is a promising trend of clinical and hemodynamic improvement indicating attenuation of ventricular remodeling. Since most patients who may need a support system are candidates for ICD therapy future HeartNet devices should have integrated defibrillation electrodes.

P566 Effect of combined statin and beta-blocker treatment on one-year morbidity and mortality in refractory end-stage chronic heart failure patients



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Background: Chronic heart failure (CHF) is a common mounting problem associated with frequent admissions to hospital and poor prognosis. Beta-blockers (BB) are associated with substantial survival benefit in CHF, achieving improvements in NYHA class and reduction in mortality, sudden cardiac death and hospitalizations. Currently, only 23%-55% of patients with CHF are treated with lipid-lowering drugs. Furthermore, the benefits of decreasing cholesterol in severe CHF patients have been questioned.

Aim: To investigate whether the initiation of combined BB and statin treatment, compared with none or either drug, in refractory end-stage (Stage D) CHF patients is associated with decreased risk of both cardiovascular and all cause mortality as well as prospective interaction between the drugs.

Methods: We retrospectively analysed all patients admitted to the CHF day care service of Sheba Medical Center over a 5-year period between September 2000 and September 2005.

Results: One-hundred and ninety patients with refractory end-stage (Stage D, NYHA IV) CHF enrolled in the program during this period, with mean age 65 ± 12 years (range 42-82), mean left ventricular ejection fraction (LVEF) 25 ± 11%, mean body mass index of 27.4 ± 4.9 kg/m². Seventy-seven percent had ischemic cardiomyopathy and 23% non-ischemic cardiomyopathy. Of all patients 136/190 (72%) received BB [BB(+)] and 54/190 (28%) did not [BB(-)]; 68/136 (50%) from the BB(+) and 22/54 (41%) from the BB(-) received statins, and 68/136 (50%) from BB(+) and 32/54 (59%) from BB(-) did not. Thus, 68/190 (36%) received BB and statins, 68/190 (36%) only BB, 22/190 (12%) only statins and 32/190 (17%) none. The four groups had comparable baseline characteristics, including LVEF, NYHA class, CAD risk factors, hemoglobin, lipids, concomitant medications and therapy in CHF day care service. During the 5-year follow-up 92 (55%) patients died. The cumulative survival adjusted for baseline differences showed that treatment with statins alone was associated with hazard ratio (HR) 1.59 (0.84,3.00), BB alone HR 1.60 (0.72,3.53), and the combination of BB and statins HR 2.61 (1.31,5.20) compared to none (p<0.001).

Conclusion: Statin therapy or BB alone in severe end-stage CHF patients was associated with improved event-free survival, and the benefits of the combined treatment were additive. Further prospective double-blind studies are needed to evaluate the impact of various treatment strategies on these patient survival and quality of life given these results.

P567 Prognostic role of pro- and anti-inflammatory cytokines and their polymorphisms in acute decompensated heart failure



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Aim: To study the prognostic role of inflammatory cytokines and their gene polymorphisms in the setting of acute decompensated heart failure (ADHF). The cur-

rent study is part of the multicenter Finnish Acute Heart Failure Study (FINN-AKVA), which aims to investigate etiology, triggering factors and modern treatment modalities together with factors affecting morbidity and mortality of acute decompensated heart failure.

Methods: Patients included in the FINN-AKVA study (n = 620) were characterized according to the new acute HF guidelines as having congestive HF (65%), pulmonary oedema (26%), isolated right HF (5%), cardiogenic shock (2%) or hypertensive crisis (2%). In the present study, patients with either pulmonary oedema (n = 128) or congestive HF (n = 343) were included. Circulating concentrations of interleukin (IL)-6, IL-10, and tumor necrosis factor alpha (TNF-alpha) were measured on admission and/or 2-3 days after admission as well as at 4-5 weeks after discharge. In addition, appropriate cytokine gene polymorphisms were screened. Survival was followed up to 12 months.

Results: The survival curves indicated a worse outcome for patients with high levels of IL-6 and TNF-alpha on admission or 2-3 days after admission (1-year mortality, p < 0.001), whereas elevated IL-10 level was predictive only of 6-month mortality (p < 0.05) (Fig). Cytokine levels at 4-5 weeks after discharge were significantly decreased from those of admission. Cytokine gene polymorphisms were not associated with outcome.

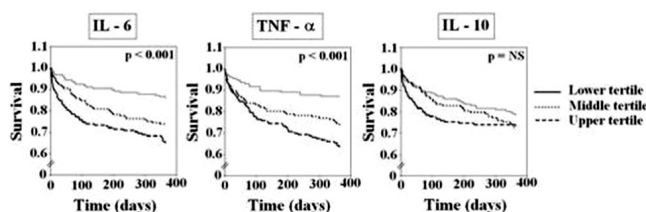


Fig. Survival curves for cytokines

Conclusions: Circulating levels of inflammatory markers, but not their gene polymorphisms, provide novel and important prognostic information in patients with acute decompensated heart failure.

P568 Prognostic significance of plasma levels of interleukin-6 and white blood cells in patients with acute heart failure due to ischemic cardiomyopathy



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Introduction: Persistent inflammation has been recognized to play a significant role in the development, as well as in the progression of heart failure. In this study we sought to evaluate the relationship between circulating cytokine levels and clinical outcome in patients with acute heart failure due to ischemic cardiomyopathy.

Methods: We enrolled 66 consecutive patients with first diagnosed heart failure, who were hospitalized in our institute. Among them 45 had acute heart failure due to ischemic cardiomyopathy (mean age 66 ± 10 years old). We measured plasma levels of interleukin-6 (IL-6), soluble tumor necrosis factor receptor 1, CD-40 and CD-14 and white blood cells counts (WBC) in all patients during their third day of hospitalization. Logistic regression analysis evaluated the association between the short - term (6 weeks) outcome (death or rehospitalization) due to heart failure and cytokines levels, after adjustment for several confounders (age, sex, BMI and smoking habits).

Results: During the first 6 weeks after hospital discharge, 18 out of 45 patients (40%) had a clinical event (5 fatal). We found that 1 mg/dl increase in IL-6 levels and 1,000 WBC increment were associated with 20% and 51%, respectively, higher risk of adverse clinical events during the first 6 weeks after hospital discharge (RR=1.2, p=0.05 & RR = 1.51, p=0.05, respectively). High IL-6 levels and WBC remain significant predictors for adverse clinical outcome even after adjustment for possible confounders (RR = 1.24, p = 0.04 for IL-6 & RR = 2.13, p = 0.03 for WBC).

Conclusion: This study reveals that assessment of IL-6 levels and WBC might provide important prognostic information for the short-term clinical outcome in patients with acute heart failure due to ischemic cardiomyopathy. These results demonstrate the important role of proinflammatory cytokines and increased white blood cells count on the clinical prognosis of those high risk patients.

P569 Circulating levels of tumor necrosis factor-alpha, brain natriuretic peptide and cardiac troponin I upon admission and 31-day mortality in patients with acute decompensated chronic heart failure



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Background: Elevated circulating levels of tumor necrosis factor alpha (TNF-α), brain natriuretic peptide (BNP) and cardiac troponin I (cTnI) have been connected

with adverse prognosis in pts with chronic heart failure (CHF). However there are scant data about the predictive value of these biomarkers in combination.

Methods: A total of 577 consecutive pts (mean age:73±9 yrs), who were hospitalized for acute decompensation of NYHA class III/IV (65.3% of ischemic etiology) low-output (mean LVEF:22±5) CHF, were studied. Biochemical markers were measured upon admission. The incidence of 31-day death was the pre-specified primary endpoint.

Results: The incidence of the primary endpoint was 17.7%. By multivariate Cox analysis, including baseline characteristics and the study biomarkers, elevated circulating levels of TNF- α (RR=2.1; $p<0.001$), BNP (RR=3.5; $p<0.001$ and cTnI (RR=3.8; $p<0.001$) were independently associated with the primary endpoint. When the pts were divided according to the number of positive biomarkers (estimated by ROC analysis) there was a significant gradual increase in the rate of the primary endpoint with increasing of the number of the positive biomarkers (Fig. 1).

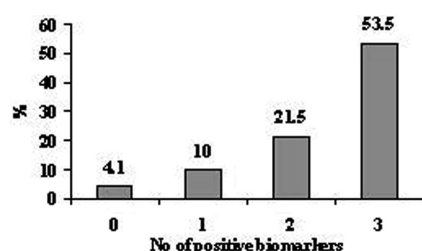


Fig. 1

Conclusions: The present results suggest in patients who hospitalized due to acutely decompensated severe low-output chronic heart failure, serum levels of TNF- α , BNP and cTnI can be used in combination for enhanced early risk stratification.

P570 Serum tumor necrosis-alpha levels upon discharge predicts 180-day mortality in patients hospitalized for acute decompensated chronic heart failure

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Background: To test the hypothesis that elevated serum levels of tumor necrosis factor alpha (TNF- α) upon discharge predict long-term outcome in patients who hospitalized because of acute decompensation of chronic heart failure (CHF).

Methods: A total of 425 consecutive pts (mean age:71±10 yrs), who survived to hospital discharge following hospitalization for acute decompensation of NYHA class III/IV (65.9% of ischemic etiology) low-output (mean LVEF:23±5) CHF, were studied. The incidence of 180-day death was the prespecified primary endpoint. The pts were divided according to the tertiles of serum TNF- α levels upon discharge.

Results: There were not significant differences among the groups, defined by the tertiles of TNF- α , in baseline characteristics and drug therapy during the follow up. The incidence of 180-day mortality was 25.6%. Kaplan Maier analysis had shown that there was an increased risk of 180-day death with increasing of the tertiles of serum TNF- α levels (18.6%, 21.1%, and 37.1% for First, Second and Third tertile respectively; $p<0.001$) (Figure 1).

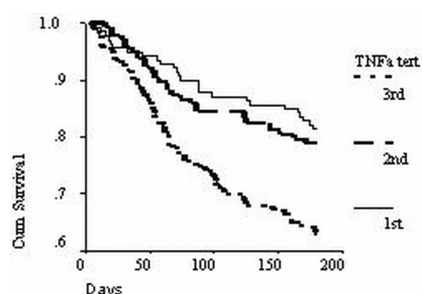


Fig. 1

Conclusions: The present results suggest that in patients who hospitalized due to acutely decompensated of severe low-output chronic heart failure, elevated serum TNF- α levels upon discharge portends an increase risk of 180-day death.

ISCHAEMIA AND REPERFUSION INJURY MODELS AND MECHANISM

P571 Hemodynamic evaluation of two models of coronary artery occlusion in pigs

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Objective: To evaluate the hemodynamic effects of two models of coronary artery occlusion in pigs.

Methods: Experiments were performed in 12 pigs in which left ventricular (LV) function was assessed by the slope (Ees) of ESPVR and stroke work (SW), and systemic arterial properties, including peripheral resistance (R2), compliance (C), and arterial elastance (Ea) with a windkessel model. Ventriculo-arterial (VA) coupling was defined as Ees/Ea, and mechanical efficiency as SW/pressure-volume area (PVA). After baseline, the pigs were randomised in 2 groups: in group LIG (n = 6), the LAD coronary artery was ligated, while in group FeCl3 (n = 6), it was wrapped for 45 minutes with a strip saturated with FeCl3. The animals were followed for three hours.

Results: LAD coronary artery flow dropped immediately to zero in group LIG, but progressively decreased in group FeCl3 (occlusion time 23.2 ± 1.2 min). In group LIG, mean aortic pressure (Pmean) and flow (Qmean) decreased abruptly, between baseline and T60, from 101 ± 3 to 78 ± 6 mmHg and from 56.4 ± 5.4 to 34.9 ± 3.8 ml/sec, respectively, while heart rate (HR) was unchanged; R2 and Ea increased from 1.77 ± 0.33 to 2.33 ± 0.22 mmHg.sec/ml, and from 3.12 ± 0.22 to 4.24 ± 0.28 mmHg/sec, respectively, while Ees dropped from 2.7 ± 0.3 to 1.7 ± 0.4 mmHg/sec. As a consequence, VA coupling failed from 0.90 ± 0.19 to 0.41 ± 0.12. SW and PVA decreased from 4963 ± 596 to 2712 ± 225 mmHg.ml and from 5371 ± 358 to 4553 ± 309 mmH.ml, while SW/PVA dropped from 0.85 ± 0.12 to 0.59 ± 0.06. Most significant hemodynamic changes were observed in the first 30 min after the LAD ligation. In group FeCl3, Pmean remained constant, while Qmean progressively decreased from 57.8 ± 6.6 to 47.3 ± 5.5 ml/sec, and HR increased from 107 ± 10 to 142 ± 13 beats/min, between baseline and T180; R2 and Ea increased from 1.72 ± 0.22 to 1.95 ± 0.28 mmHg.sec/ml, and from 2.99 ± 0.33 to 3.55 ± 0.22 mmHg/sec, respectively, while Ees decreased from 2.7 ± 0.4 to 2.2 ± 0.3 mmHg/sec. As a consequence, VA coupling failed from 0.90 ± 0.16 to 0.63 ± 0.18. SW and PVA decreased from 4903 ± 157 to 3744 ± 299 mmHg.ml and from 5733 ± 366 to 5137 ± 299 mmH.ml, while SW/PVA dropped from 0.85 ± 0.07 to 0.72 ± 0.07. Most hemodynamic changes observed in the FeCl3 were progressive.

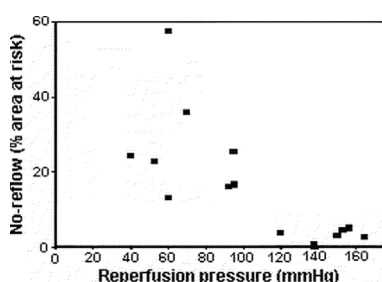
Conclusion: Progressive coronary artery occlusion, as obtained by topical FeCl3 application, is responsible for a less impaired hemodynamic condition. This model, closer to the clinical condition of coronary artery thrombus formation, could be more suitable to assess pharmaceutical or mechanical cardiac support during acute myocardial ischemia.

P572 The ischemia induced no-reflow phenomenon is inversely related to reperfusion pressure. Experimental study

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Studies have shown that microvascular injury and external compression of the myocardial vessels during ischemia result in obstruction of the microcirculation, leading to the no-reflow phenomenon (NR). The structural damage of the microcirculation during the initial hours of ischemia is minimal. Thus we assumed that the obstruction of the microcirculation is not permanent and may be reversed by increased reperfusion pressure (RP).

Methods: In 14 anesthetized, open chest pigs ischemia was induced by ligation of the mid part of the left anterior descending coronary artery (LAD). After one hour the distal part of the LAD was cannulated and thioflavine solution (0.2%), was injected over 20 seconds through the cannula. The infusion pressure was measured and kept constant throughout the infusion. Each animal was randomly assigned to an infusion pressure ranging, in Group I (n=8), between 40 and 100 mmHg and in Group II (n=6), between 100 and 180mmHg. Immediately after



thioflavine infusion, gentian violet solution was injected in the left atrium, the heart was arrested and excised, the left ventricle was transversely sectioned and the extent of the NRP was measured and expressed as percentage of the area at risk.

Results: There was a significant negative correlation between RP and the extent of the NR ($r=-0.732$, $p=0.003$). Reperfusion pressures higher than 100mmHg in Group II, resulted in a significantly smaller extent of the NR (mean RP=147±16mmHg, NR=3.2±1.8%) than in Group I with pressures lower than 100mmHg (mean RP=71±21mmHg, NR=26.3±14.5%, $p=0.002$).

Conclusions: Our results in a swine ischemia-reperfusion model suggest that microvascular obstruction caused by ischemia is reversible and high reperfusion pressures could result in abolishment of the early no-reflow phenomenon.

P573 ADMA as a critical regulator of myocardial ischemia reperfusion injury



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Introduction: Endothelial dysfunction characterized by the loss of endothelium derived nitric oxide (NO) is a critical event during reperfusion of ischemic myocardium. Reduced NO availability signals important pathophysiological changes, such as leukocyte adherence and transmigration of mononuclear cells, leading to myocardial reperfusion injury.

We have recently shown that NO biosynthesis can be impaired by the endogenous NOS inhibitor asymmetric dimethylarginine (ADMA) by inhibition of its metabolizing enzyme DDAH in animal models and humans at risk for atherosclerosis. We therefore analyzed the possible role of ADMA and DDAH in the setting of myocardial ischemia and reperfusion.

Methods: In an in vivo model C57-bl6 (WT) mice were subjected to 30min of myocardial ischemia following reperfusion for 0 to 72hrs. After surgery myocardial tissue of the left ventricle was homogenized and determinants of the NOS pathway were analyzed. Furthermore WT mice were compared to transgenic (TR) mice overexpressing DDAH (who have low ADMA plasma and tissue concentrations) and to mice fed with L-NAME or L-arginine for reperfusion injury after 30min of ischemia and subsequent 4 hrs of reperfusion.

Results: NOx tissue concentrations significantly decreased to a minimum at 8hrs of reperfusion compared to sham operated mice. However, no differences were found in protein concentrations of constitutive NOS isoforms, suggesting that NO biosynthesis in ml/R is due to reduction of NOS activity. Interestingly, 4-fold elevations of tissue ADMA were shown in ml/R with a maximum at 4hrs. The increases of ADMA and reductions of NO metabolites were associated with significant reductions of DDAH activity. Reduction of tissue ADMA by over-expression of DDAH in a transgenic mouse strain markedly reduced infarct size, serum troponin T and histologic damage score. These effects were mimicked by L-arginine in the drinking water of WT mice and could be blunted by L-NAME in TR mice. Finally the observed changes between WT and TR mice were found to be accompanied by alterations of cellular adhesion molecules and leukocyte activity.

Conclusion: We found a significant decrement of NO and a marked elevation of ADMA tissue levels in our mouse model of myocardial ischemia/reperfusion. These changes seem to be patho-physiologically relevant, since reduction of ADMA by genetic modification significantly reduced reperfusion injury. Our results indicate that ADMA could be a potential new target for the treatment of myocardial ischemia/reperfusion injury.

P574 Catheter-based transcatheter myocardial hypothermia, initiated late during ischemia preserves coronary flow reserve through antioxidant process



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We previously reported that regional myocardial hypothermia, induced early during ischemia (15min after coronary occlusion) reduced myocardial necrosis using a new method of catheter-based transcatheter myocardial hypothermia (CTMH) in pigs with acute myocardial infarction (MI). However, we needed complete coronary flow obstruction to reduce the myocardial temperature by 3±?. Thus, in this study, to examine the clinical feasibility of CTMH, CTMH with coronary reperfusion, which was induced after longer period of coronary occlusion (60min after coronary occlusion), was compared to simple immediate reperfusion-therapy in pigs with MI.

Methods: Anesthetized pigs underwent 60min of coronary occlusion with an infusion balloon (Helios[®], Avantec, USA), which enables us to infuse larger amount of cold saline than conventional over-the-wire type percutaneous transluminal coronary angiography balloon. They were randomly assigned to Hypothermia-reperfusion (H: n=5) or Reperfusion (R: n=5) groups. After 60min of coronary occlusion, in animals assigned to H group, cold saline (4%) was started to infuse into ischemic myocardium through the completely deflated infusion balloon at a rate of 8 ml/min and the cooling was continued for 30min. In pigs assigned to R, only simple reperfusion was applied. Reperfusion was then observed for 180min in both groups. Myocardial and systemic temperature, hemodynamic variables, coronary

flow reserve (CFR) assessed by intra-coronary Doppler-tipped guidewire, blood samples, ischemic risk and necrosis were evaluated.

Result: In H group, the ischemic myocardial temperature started to decrease after the initiation of cooling and reached a minimum (33.1±0.4°C: 3.4°C absolute reduction) with a stable rectal temperature. The levels of CFR in H group were significantly higher than that in R group at 60 min after reperfusion (2.14±0.06 vs. 1.49±0.12, $P=0.03$). For blood sample analysis, the oxidative stress assessed by $\Delta 8$ -iso-PGF2 α in H group was significantly smaller than that in R group (-1.20±1.24pg/ml vs. 3.50±0.87; $P=0.02$). Although the ischemic risk area was the same for both groups (13±3% vs. 12±1%; $P=0.72$), the necrotic area for the H group had a tendency to be smaller than that for the R group without statistical significance (33±2% vs. 45±5%; $P=0.08$). There were no differences in hemodynamic variables, histopathologic findings of edema or bleeding in the myocardium between the two groups.

Conclusion: CTMH, initiated late during ischemia with reperfusion preserved CFR and reduced oxidative stress without apparent side effect in acute MI.

P575 Forty milligrams atorvastatin improves myocardial perfusion in hypercholesterolemic coronary patients



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In coronary patients statins treatment reduces coronary events in the middle and long term. There is some evidence that high doses could improve coronary flow in the short term. Sixty two patients who met the following criteria were included, a reversible myocardial perfusion defect in a Technetium 99 sestamibi SPECT stress test, and an LDL cholesterol higher than 100 mg/dL. Patients were excluded if they had had an acute coronary event in the last 3 months, if a PTCA or CABG was performed in the previous year, if a coronary intervention was planned in the next 3 months or if they were stratified as high ischemic risk in the stress test. Current smokers and those patients on statins therapy were also excluded. Patients were randomly allocated either to atorvastatin 40 mg daily or 5 mg daily during 3 months. After that, a Technetium 99 sestamibi SPECT stress and cholesterol levels test were repeated. SPECT initial results were compared with final results by an observer blinded to the allocation group. Quantification of ischemic area was performed using O'Connors technique. An area was considered ischemic when low stress uptake in one area was reversed at rest. A patient was considered improved when the ischemic area of final study was smaller than initial study.

Results: Both treatment groups were similar at baseline. Eight patients (26%) out of 30 in the 5 mg group improved myocardial perfusion, while 17 (53%) of the 32 patients in the 40 mg group showed an improvement in myocardial perfusion ($p=0.033$). In the 5 mg group LDL cholesterol values were 144 ± 34 mg/dL (initial) and 99 ± 24 mg/dL (final). In the 40 mg group they were 155 ± 46 mg/dL (initial) and 93 ± 37 mg/dL (final). Differences were not significant.

Conclusions: Three months treatment with 40 mg atorvastatin induces an improvement in myocardial perfusion compared to 5 mg. Partial correction of endothelial function could be a possible explanation. Improvement seems to be not associated to LDL cholesterol changes.

P576 The cardioprotective potential of erythropoietin is not due to an increased angiogenesis



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Background and purpose: Besides its well known effect of stimulating the erythropoiesis, erythropoietin (EPO) demonstrates an angiogenic and anti-apoptotic potential. These cellular protective effects could be shown in brain ischemia as well as in acute myocardial infarction models. In contrast, we here investigated the effect of EPO in a porcine model of chronic progressive myocardial ischemia.

Methods: A circumflex ameroid constrictor was placed off pump by minimal invasive surgery in 11 swines. Constrictor occlusion was documented angiographically after 2 weeks and verified morphologically after experiments. At week 2 and 6 endocardial NOGA mapping of the left ventricle, coronary and ventricular angiogram and echocardiography were done. After blinded randomisation 6 pigs received 10.000 U Epo at 10 injection sites in the ischemic region using a computer guided percutaneous endocardial injection catheter. Five pigs received placebo solution. After 6 weeks histology (Elastica-van-Gieson, Wright-Giemsa) and immunohistochemistry (smooth muscle actin antibody) of ischemic as well as and non-ischemic regions were performed.

Results and conclusion: The analysis of the endocardial mapping showed an increase of the median value of the unipolar voltage (UV = 8.84 to 10.57mV) within the ischemic segments in the Epo treated animals. In contrast, in the placebo group UV was reduced from 8.87 to 8.30mV. In addition, a significant reduction of interstitial fibrosis as well as a 50% reduction of inflammatory cells in the Epo area could be demonstrated. When comparing the number and the cross-section area of functionally relevant vessels in the "area of interest" no measurable differences were found in both groups. These findings indicate a reduction of ischemia caused by the cardioprotective effect of Epo, which is not due to an increased angiogenesis.

P577 Human failing myocardium is resistant to hydroxyl radical-induced contractile dysfunction - involvement of ATP-sensitive potassium channels



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Background: Reactive oxygen species (ROS) from various intracellular sources are involved in signaling pathways of cardiac hypertrophy and apoptosis. Furthermore, ROS are important mediators of ischemic preconditioning, which involves the activation of KATP channels. Since ROS are elevated in failing myocardium, and ROS impair excitation-contraction coupling, we hypothesized that failing myocardium may adapt to chronic oxidative stress to be protected from ROS-induced contractile dysfunction by mechanisms involving mitochondrial (mito) and/or sarcolemmal (sarc) KATP channels.

Methods: Functional experiments were performed on right atrial (RA, n=253) and left ventricular (LV, n=61) trabeculae from patients with terminal heart failure (CHF) and nonfailing controls (NF). We used diazoxide (100 μ M/L) or P-1075 (0.3-30 μ M/L) to activate mito- or sarcKATP channels, respectively, and 5-HD (500 μ M/L) and HMR-1098 (30 μ M/L) to block these, respectively. Hydroxyl radicals (OH) were produced by Fe3+-nitrotriacetic acid (0.1 μ M) and H₂O₂ (1-3 mM). Western blot analysis of Kir6.1, Kir6.2, SUR1, SUR2 and cytochrome c was performed on LV myocardium of CHF (n=16) and NF (n=8) after differential centrifugation.

Results: In RA trabeculae, P-1075, but neither diazoxide, 5-HD nor HMR-1098 reduced force of contraction (FOC) by 95 $\pm$ 2%. This was antagonized only by HMR-1098. In RA trabeculae exposed to hypoxia and reoxygenation (90/120 min), diazoxide, but not P-1075 improved posthypoxic recovery of FOC (p<0.05). This was antagonized by 5-HD, but not HMR-1098. In LV and RA trabeculae from NF myocardium, OH (15 min) decreased systolic FOC and increased diastolic tension (p<0.01). After wash-out of OH, maximal Ca²⁺-induced FOC (F_{max}Ca) remained reduced compared to control (p<0.05). Pretreatment with either diazoxide or P-1075 improved F_{max}Ca after OH. In contrast, LV trabeculae from patients with CHF were resistant to OH-induced impairment of systolic FOC. However, when blocking either sarc- or mitoKATP with 5-HD or HMR-1098 in LV-CHF trabeculae, F_{max}Ca was reduced after OH exposure (p<0.05). Sarcolemmal expression of SUR2 and Kir6.2 as components of the sarcKATP were ~2-fold upregulated in CHF. Mitochondrial expression of cytochrome C was reduced, of Kir6.1 unchanged and of SUR1 ~2-fold upregulated in CHF (p<0.05, respectively).

Conclusions: Failing human myocardium is resistant to OH-induced contractile dysfunction. Increased expression and/or activity of KATP channels may contribute to the functional protection of excitation-contraction coupling against OH in failing myocardium.

P578 IL6 deficiency has no effect on neutrophil recruitment and myocardial apoptosis, despite increased ICAM-1 expression during myocardial ischemia and reperfusion in mice



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Interleukin 6 (IL6) is a prototypic pleiotropic cytokine possessing both inflammatory and anti-inflammatory properties. It regulates expression of adhesion molecules and may affect migration of leukocytes. On the other hand, it is involved in preconditioning and may exert cytoprotection.

The aim of the study was to evaluate the effects of interleukin 6 deficiency on the expression of ICAM-1 and its consequences on myocardial ischemia and reperfusion injury in mice.

Methods: All experiments were performed on 12-14 week old male C57BL/6J IL6^{-/-} mice (IL6KO) and C57BL/6J animals (WT), which were subjected to 30 minutes of reversible myocardial ischemia or sham operation. The transient ligation of left anterior descending artery was performed from lateral thoracotomy access in ketamine/xylazine anesthesia. After 5 hours of reperfusion mice were sacrificed, LV was dissected, embedded in OCT and frozen in liquid nitrogen. ICAM-1 expression and neutrophil infiltration were examined using immunohistochemistry. At the same time apoptosis in the area at risk was assessed by TUNEL-FITC staining. Expression of Bcl-2 and Bax was investigated using western blotting. Other mice were sacrificed 24 hours after reperfusion, hearts were stained using Evans blue and tetrazolium chloride (TTC) to reveal ischemic and infarcted regions. A ratio of infarct to area at risk was used as a parameter describing the extent of ischemia and reperfusion injury.

Results: Mice from both groups presented similar body and LV weight. Ischemic

	Body weight (g)	LV weight (mg)	Area at risk/LV (%)	Infarct/area at risk (%)	ICAM-1 (semi-quantitative score)	ICAM-1 (% of area stained)	Neutrophils (no. of cells/total no. of nuclei) %	Apoptosis (TUNEL positive/all nuclei) %
C57BL6/J	27.8 $\pm$ 2.1	69.8 $\pm$ 11.2	39.2 $\pm$ 10.2	36.7 $\pm$ 17.4	1.9 $\pm$ 0.5	2.99 $\pm$ 0.9	1.8 (iq 1.5-3.3)	11.3 $\pm$ 7.8
IL6 KO	27.9 $\pm$ 2.1	74.1 $\pm$ 9.2	44.9 $\pm$ 9.6	31.7 $\pm$ 13.3	2.7 $\pm$ 0.7*	4.2 $\pm$ 0.7*	1.5 (iq 1-2.2)	12.5 $\pm$ 8.5

* p<0.01 vs C57BL6/J group

and reperfused myocardium of IL6KO presented higher expression of ICAM-1 protein in comparison with WT. Surprisingly, this disparity did not translate into different neutrophil infiltration. Also apoptosis was similar in area at risk in both groups. Evans blue and TTC staining revealed similar the area at risk size as well as infarct/area at risk ratio indicating no significant differences in injury between the IL6KO and WT animals.

Conclusion: IL6 deficiency was associated with increased ICAM-1 expression in ischemic and reperfused myocardium. This, however, did not translate into different extent of injury and leukocyte recruitment in the mouse model.

P579 Amelioration of ischemia reperfusion injury by the novel endothelial nitric oxide synthase transcription enhancer AVE 9488



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Background: Endothelial nitric oxide synthase (eNOS) is cardioprotective in ischemia/reperfusion injury: Ischemia/reperfusion injury is aggravated in eNOS knockout mice and reduced in mice overexpressing eNOS. Novel pharmacological substances, so called eNOS enhancers, have been designed to selectively upregulate eNOS expression and thereby increase NO production. We tested the effects of the eNOS enhancer AVE 9488 on cardiac ischemia/reperfusion injury in vivo in mice.

Methods and Results: Mice were treated with the eNOS enhancer AVE 9488 (30 mg/kg/day) or placebo for one week and subsequently underwent 30 minutes of coronary artery ligation and 24 hours of reperfusion in vivo. Ischemia-reperfusion damage was significantly reduced in the eNOS-enhancer treated when compared to placebo treated mice (infarct/area at risk 65.4 $\pm$ 4.1 vs. 36.9 $\pm$ 4.0%, placebo vs. eNOS-enhancer, p=0.0002). The protective effect was blunted in eNOS KO mice treated with the eNOS enhancer (infarct/area at risk 64.1 $\pm$ 6.2%). Reactive oxygen species were significantly reduced in mice treated with the eNOS enhancer as indicated by significant lower MDA levels (3.2 $\pm$ 0.5 vs. 0.8 $\pm$ 0.07 μ mol/l, p=0.0003 wild type placebo vs. wild type eNOS-enhancer).

Conclusion: Treatment with the eNOS enhancer AVE 9488 significantly reduces ischemia/reperfusion injury. eNOS enhancer is an interesting novel approach for the treatment of cardiovascular diseases.

P580 Geranylgeranyl pyrophosphate blocks cardioprotective effect of rosuvastatin in vivo



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Background: HMG-CoA reductase inhibitors (statins) protect the myocardium against ischaemia/reperfusion injury via a mechanism unrelated to cholesterol-lowering effects. Statins may via inhibition of geranylgeranyl pyrophosphate (GGPP) attenuate posttranslational prenylation and membrane localization of proteins including Rho A. We hypothesized that statins protect the myocardium against ischaemia/reperfusion injury by lowering the levels of GGPP in vivo.

Methods: Five groups of SD-rats were given either the HMG-CoA reductase inhibitor rosuvastatin (RVA) 10 mg/kg bid (n=8), GGPP 1 mg/kg in methanol (n=8), the combination of RVA and GGPP (RVA+GGPP) (n=7), RVA and methanol (RVA+methanol) (n=7) or distilled water (control) (n=9) by i.p. injection for 2 days before ischaemia/reperfusion. In experimental protocol I animals from all five groups were anaesthetized and subjected to 30 min of coronary artery occlusion followed by 2 h of reperfusion. Infarct size (IS) was determined. In experimental protocol II animals from control, RVA and RVA+GGPP groups were anaesthetized, hearts were excised. The expression of Rho A protein was determined in cytosolic and membrane fractions by ultracentrifugation and subsequent western blotting.

Results: There were no significant differences in haemodynamics between the groups before ischaemia or during ischaemia and reperfusion. The IS was 80 $\pm$ 3% of the area at risk in the control group. RVA reduced the IS to 64 $\pm$ 2% (p<0.001 vs. control). Addition of GGPP but not methanol abolished the cardioprotective effect of RVA (IS 77 $\pm$ 2% in RVA+GGPP group, p<0.01 vs. RVA and 65 $\pm$ 2% in RVA+methanol group, NS vs. RVA). GGPP did not affect IS per se (84 $\pm$ 2%). RVA increased Rho A protein expression in the cytosolic fraction and cytosol/membrane ratio of Rho A protein in the myocardium (p<0.05 vs. control). These changes were abolished by addition of GGPP (p<0.01 vs. RVA; NS vs. control).

Conclusions: This study demonstrates that cardioprotection and the increase in cytosol/membrane ratio of Rho A induced by RVA in vivo are blocked by GGPP. The results suggest that inhibition of GGPP formation and subsequent prenylation of RhoA is of importance for the protective effect of statins during myocardial ischaemia/reperfusion injury.

P581 Apoptosis and MPK phosphorylation are inhibited in the ischemic myocardium from Daxx-DN transgenic mice subjected to myocardial ischemia-reperfusion



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Apoptosis contributes to myocardial cell death after cardiac ischemia and reperfusion. Daxx, a Fas-associated protein, is involved in apoptotic cell death in vitro. To analyze the role of Daxx in vivo, 10 transgenic mice that over-express a dominant negative form of Daxx (Daxx-DN) and 14 littermate wild-type mice underwent an IR (ischemia reperfusion) protocol corresponding to 40 minutes of left coronary artery occlusion followed by 60 minutes of reperfusion. Left ventricle tissues from transgenic mice expressed Daxx-DN at the protein level. After the surgical protocol, left ventricle were allowed to infarct size determination (after dual staining by triphenyltetrazolium chloride - phtalocyanine blue dye and planimetry) or apoptosis analysis (DNA fragmentation assessed by ELISA and western blotting). Comparison between groups were assessed by one-way ANOVA with post hoc analysis using the Newman-Keuls test for multiple comparison. Statistical significance was defined as a value $P < 0.05$.

Area at risk and VG/body mass index were comparable among groups. Interestingly, infarct size/area at risk was 45%- reduced in IR Daxx-DN compared to IR wild-type animals ($p < 0.05$). DNA fragmentation in the ischemic area compared to the non-ischemic control part of the left ventricle was significantly inhibited in IR Daxx-DN. Moreover, activation of caspase-3, -8 and -9 was almost completely prevented in the ischemic regions of left ventricle obtained from transgenic mice. Phosphorylation of p38, JNK 1/2 and ERK 1/2 is also inhibited in those animals. Our study clearly indicates that the Daxx pathway is critical for myocardial damage due to ischemia/reperfusion in vivo.

P582 ACE inhibition does not block apoptosis in the remote myocardium after infarction in diabetes mellitus



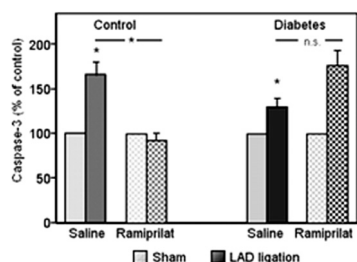
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Background: Patients with diabetes mellitus are subjected to increased remodeling of the left ventricle after infarction than those without diabetes. Previous data showed an activation of apoptosis in the remote myocardium after infarction in normoglycemia

that could be reversed by ACE inhibition. Aim of this study was to clarify the regulation of apoptosis in the remote myocardium in diabetes mellitus and the effects of ACE inhibition.

Methods: Rats with streptozotocin-induced diabetes mellitus (DIA) or normoglycemic controls (NORM) were subjected to LAD ligation (LIG) or sham operation (SHAM). After 6-24 hours, apoptotic signal transduction molecules (Caspase-3, bcl-2/bax-Quotient, Akt, bad, GSK3 β) and DNA fragmentation were determined remote from the infarction.

Results: Rats with DIA had increased markers of apoptosis at baseline (Caspase-3: + 30%, DNA-laddering +40%). After LIG, caspase-3 and DNA laddering were increased compared to SHAM both in DIA and NORM. In contrast, a shift of the bcl-2/bax-ratio after LIG, was observed only in NORM, but not in DIA. Anti-apoptotic molecules (GSK3 β , Akt, bad) were unchanged under any condition. ACE inhibition with ramiprilat (10 μ g/kg/d) completely blocked the activation of apoptosis in NORM. In DIA, however, ramiprilat was unable to block the activation of caspase-3 (figure) and DNA fragmentation in the remote myocardium after LIG.



Conclusion: Activation of apoptosis in the remote myocardium after infarction in DIA is mainly caspase-dependent, but not regulated by the mitochondrial apoptosis pathway, and was not reversible by ACE inhibition. This could in part explain the increased remodeling after infarction in DIA despite the use of ACE inhibitors.

P583 The 26S-proteasome is released in myocardial infarction



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The 26S proteasome is responsible for most non-lysosomal protein degradation in eukaryotes. The ubiquitin-proteasome system is involved in a number of physiological and pathophysiological processes including myocardial hypertrophy, cell cycle regulation and processing of intracellular antigens for MHC class I presentation. Circulating proteasomes are markers of cell damage and can be found in autoimmune diseases, malignant diseases and hepatitis. Antibodies against the C9-subunit of the 20S-proteasome occur among patients with myositis. Little is known about levels of proteasome in acute myocardial infarction (AMI), therefore we performed a pilot study in such patients. The study included 19 patients after myocardial infarction (mean age 64 years). 7 patients undergoing diagnostic heart catheterisation served as control (mean age 65 years). Over a period of 72 hours we measured serum concentration of the 26S proteasome, creatine kinase, troponin T and myoglobin. We applied a custom made ELISA technique for proteasome measurement. Time to needle in the group of AMI patients was 4 hours. Proteasome was detected in the serum of controls (704 μ g/dl, SD: 223) and after myocardial infarction (1405 μ g/dl, SD: 685). The AUC of the serum proteasome correlated closely with that of troponin T ($p < 0.001$), CK ($p = 0.008$) and CK-MB ($p = 0.036$). The proteasome level peaked 48h after myocardial infarction. This study shows for the first time, that the 26S proteasome is released via cellular necrosis during myocardial infarction. The serum concentration correlates with the size of the infarction. Future studies will show the diagnostic impact of this release and changes in proteolytic activity in the ubiquitin-proteasome-system under conditions of myocardial ischemia.

P584 Ephrin-B2 influences angiogenesis in ischemic myocardium in mice



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Background: The ephrin receptor kinases (Eph) and their ligands, the ephrins are involved in embryogenesis, vascular morphogenesis and have been shown to control cell migration and adhesion in the brain.

Aims: To explore if these signalling pathways are important in ischemic heart disease and to study if pharmacologic modulation stimulates angiogenesis.

Methods: Myocardial infarction was induced by ligation of the left anterior descending artery (LAD) in C57BL/6 mice (n=5-6 in each group). The hearts were harvested between 24 h and 28 days after myocardial infarction. Sham operated (thoracotomy) mice were used as controls. The whole heart was used for the preparation of cDNA libraries and expression of Eph/ephrins was examined by rtPCR. 24 h after LAD ligation, mice were randomised to treatment with the fusion protein Ephrin-B2-Ig or control Ig. In order to detect cell proliferation, the mice were treated with BrdU on days 7-12 after myocardial infarction. Hearts were harvested after 28 days, BrdU and vessel density (lectin staining) was determined in ischemic and non-ischemic myocardium. Nonparametric statistics were used.

Results: Eph-B4/ephrin-B2 were present in abundance in all the myocardial specimens as well as the Eph receptors A1, A3, A4 and the ephrin ligands A1, A2, A5. Initially there was a down regulation of ephrin-B2 and upregulation of Eph-B4. 2-4 days after infarction expression of ephrin-B2 increased and Eph-B4 decreased. After administration of Ephrin-B2-Ig, capillary density in the peri-infarct myocardium differed between the groups (median 442 vs 296/viewing field, $p < 0.06$) while in the non-infarcted myocardium no significant differences was observed (393 vs 390/viewing field). Capillary density in the peri-infarct region compared to the non-infarcted region was lower ($p < 0.06$) in the control-Ig treated group and higher in the Ephrin-B2-Ig treated group. BrdU staining followed the vessels and was not present in cardiomyocytes.

Conclusions: Several ephrin-Eph are expressed in the myocardium, ephrin-B2 and Eph-B4 have a relatively high level of expression and are influenced by ischemia. Capillary density is depressed in the peri-infarct myocardium in untreated mice. Modulation of the Eph/ephrin signalling with Ephrin-B2-Ig increases angiogenesis in the infarcted area to a degree which supercedes vascularity in the non-infarcted regions. These observations infer that manipulation of ephrin signalling maybe important in promoting angiogenesis in heart disease.

P585 Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE)



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Purpose: Few trials have specifically investigated the effects of lipid-lowering therapy with statins in older patients. The Study Assessing Goals in the Elderly (SAGE) investigated statin therapy as a novel approach to the treatment of my-

ocardial ischemia in elderly patients with stable coronary artery disease (CAD) and evidence of myocardial ischemia during daily life.

Methods: SAGE was a prospective, 12-month, double-blind randomized study conducted at 192 sites worldwide. Qualifying patients were men and women with stable CAD (aged 65-85 years; LDL-C between 100 and 250 mg/dL) who had at least 1 episode of myocardial ischemia with total ischemia duration ≥ 3 mins on baseline 48-hour ambulatory ECG (AECG) monitoring. The AECG was performed while patients conducted routine daily activities and continued their usual prescribed anti-anginal medications. In total, 893 patients were randomized to either atorvastatin 80 mg/day (aggressive lipid lowering; A) or pravastatin 40 mg/day (moderate lipid lowering; P). The primary efficacy parameter was the absolute change in the total duration of myocardial ischemia from baseline to Month 12. Secondary efficacy parameters included the proportion of patients who were totally free of ischemia.

Results: A significantly greater reduction in LDL-C from baseline to Month 12 was achieved with A (55% vs. 32% for P; $p < 0.0001$). There was a significant reduction from baseline to Month 12 for both the primary and secondary parameters ($p < 0.001$) within each treatment group. There was, however, no difference between treatment groups in ischemia reduction (absolute change in duration, 48 mins for A vs. 46 mins for P; proportion of patients free of ischemia, 46% for A vs. 45% for P). Although SAGE was neither designed nor powered to assess Major Adverse Cardiac Events (MACE), there was a favourable trend for A (HR=0.74, A vs. P; $p=0.16$). The proportions of patients in the 2 treatment groups having serious adverse events and non-serious adverse events were similar. Withdrawal rates were also similar.

Conclusion: SAGE is the first large, multi-center international trial to demonstrate the efficacy of lipid-lowering therapy in reducing myocardial ischemia in older patients with stable CAD who were already receiving standard antianginal drug therapy. The anti-ischemic effects observed in this study further demonstrate evidence in support of the pleiotropic effects of statins.

P586 Strong upregulation of Tissue Factor occurs in the remote and the border zone after myocardial infarction, and is limited by bFGF treatment



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Introduction: Tissue Factor (TF), the main initiator of blood coagulation, is expressed in cardiomyocytes, and recent data suggest that TF inhibition might limit the necrosis area after myocardial infarction (MI). However, the regulation of TF after MI, and its possible modulation by angiogenic growth factors is not known. We aimed to analyze TF expression in infarcted myocardium, and the effects of bFGF, an angiogenic factor which also limits the necrosis area, on TF expression. **Methods:** MI was induced in 37 New Zealand male rabbits by permanent coronary occlusion. Then, bFGF (n=20) or placebo (n=16) was intravenously administered twice weekly during 3-weeks. After sacrifice, left ventricle scars were examined through histology, and TF activity was measured on protein extracts from the left ventricles. TF expression was localized through immunohistological analysis. In addition, VEGF, an angiogenic factor induced by hypoxia, and a possible inducer for TF expression was measured on protein extract.

Results: Coronary ligation induced a 180 fold-increase in myocardial TF activity (as compared to normal myocardium levels) and a 1.5-fold increase in VEGF antigen. TF and VEGF levels were closely correlated to each other ($r=0.85$, $p < 0.0001$). TF overexpression was observed in the remote zone, and was especially strong in the border zone. As compared to the placebo group, bFGF treatment tended to reduce the necrotic area (36% versus 33% of left ventricle, ns), the TF increase (3107 vs 2585 mU/mg, ns), and the VEGF increase (49 vs 41 pg/mg, $p=0.05$).

Conclusion: These results demonstrate that TF is strongly upregulated in the border zone after MI. Angiogenic factor such as bFGF reduce TF overexpression. Since TF upregulation could increase the thrombotic process, TF might be a potential therapeutic target after MI. Whether bFGF regulates TF by angiogenesis enhancement remains to be assessed.

P587 Candesartan blocks activation of apoptosis in the remote myocardium after infarction both by inhibition of caspase-3 and activation of anti-apoptotic pathways



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Background: It could be shown that an activation of apoptotic processes, as one trigger of the process of remodeling of the infarcted heart, occurs in the remote myocardium as soon as 3 hours after after regional myocardial infarction. Recent data suggest that angiotensin AT1 receptors are involved in this activation of apoptosis. The influence of this receptor on distinct pro- and anti-apoptotic pathways, however, was unresolved. Goal of this study was therefore to test the effects of an angiotensin AT1 receptor antagonist on pro- and antiapoptotic pathways in the remote myocardium after infarction.

Methods: Rats were pretreated with Candesartan (2 mg/kg) or saline for 7 days and were then subjected to ligation of the left anterior descending coronary artery in situ (LIG) or sham operation (SHAM). After 24 hours, biopsies were taken from the myocardium remote from the infarction. In the biopsies, pro- and anti-apoptotic

signal transduction molecules (Caspase-3, bcl-2/bax-Quotient, GSK-3 β) were determined.

Results: In the saline-treated animals subjected to LIG, a significant activation of the pro-apoptotic Caspase-3 (128% of sham, $p < 0.05$) could be observed. Bcl-2/bax was unchanged. Phosphorylation of the anti-apoptotic GSK-3 after LIG was at the level of sham (101%). Pretreatment with Candesartan completely blocked the activation of Caspase-3 after LIG (90% of sham). In those animals, however, LIG lead to a significant increase of GSK-3 β phosphorylation (117% of sham, $p=0.03$).

Conclusion: Pretreatment with the angiotensin AT1-receptor antagonist Candesartan blocks the activation of apoptosis in the remote myocardium 24 hours after regional myocardial infarction. This anti-apoptotic effect is mediated both by the blockade of pro-apoptotic pathways and by the activation of anti-apoptotic pathways. This dual mechanism leads to a robust anti-apoptotic effect that may contribute to the favorable actions of angiotensin receptor blockade in the remote myocardium after infarction

P588 Post-conditioning restores pre-ischemic receptor coupling



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Background: Pre-conditioning and post-conditioning are known to reduce infarct sizes in the post-ischemic hearts. Unfortunately, a strong improvement of post-ischemic recovery in terms of heart function could often not be demonstrated, irrespectively of the strong infarct size reduction. This leads to the open question, whether the post-ischemic myocardium responds to inotropic stimulation of endogenously released factors and exogenous application of pro-inotropic agonists. The present study was aimed to investigate whether the post-ischemic heart responses to isoprenaline (100 nmol/l) or parathyroid hormone-related protein (PTHrP, 100 nmol/l) a natural released peptide that improves post-ischemic recovery.

Methods: Hearts from 96 rats were used and subdivided into four groups: Non-ischemic control, ischemia-reperfusion (I/R; 45 min/2 h), pre-conditioning (IPC), and post-conditioning (IPoC). The hearts were perfused in a Langendorff mode under flow constant conditions with an initial perfusion pressure of 50 mmHg. This allows the hearts to beat stable for nearly 3 h under non-ischemic conditions. 30 min after reperfusion the agonists were given to each of the four groups.

Results: No significant differences were observed between I/R, IPC, and IPoC in respect to post-ischemic recovery (read outs: LVDP, HR, LVDPxHR, and coronary resistance (CR)). However, IPC and IPoC significantly conserved the structure of the myocardium (connexin staining) and lowered LDH-release. Both parameters can be considered as a read out for cardioprotection achieved by IPC and IPoC. All four groups responded similar to isoprenaline (+LVDP, +HR, +LVDPxHR, -CR). The effect of isoprenaline was transient in all cases and rapidly gone once isoprenaline was washed out. However, PTHrP exerted a negative effect on LVDP in normoxic and IPoC but not in I/R and IPC, less positive chronotropy in I/R and IPC compared to control and IPoC, and a reduction of CR in controls and IPoC, but not in I/R and IPC. The effect on CR was stable once PTHrP was washed out. In a separate ischemia group, inhibition of endogeneous release of PTHrP during ischemia blocked the I/R-dependent loss of responsiveness.

Conclusion: This study shows that signal transduction pathways activated by IPoC restore rapidly a normal responsiveness to PTHrP in the post-ischemic heart. The data indicate that post-conditioning-derived pathways not only reduce infarct sizes but also interact with receptor-coupling and that these pathways are different compared to IPC.

P589 Effect of calpain inhibition on myocardial infarction following local ischemia and reperfusion



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Introduction: This study was performed to test the protective effectiveness of a novel water-soluble and cell-permeable calpain inhibitor when administered before or after local ischemia. **Material and Methods:** Isolated rabbit hearts were perfused in an open working Langendorff heart system at constant pressure (80 mmHg) and temperature (37°C) with Krebs-Henseleit buffer solution. After a steady state period of 20 min, the ramus interventricularis of the left coronary artery was blocked just below the origin of the first diagonal branch by means of a Tourniquet for 60 min, and subsequently reperfused for 120 min. The calpain inhibitor A-705253 ($K_i = 27 \pm 2.5$ nM) from Abbott/Ludwigshafen/Germany was added to the perfusion fluid in various final concentrations in one series (A) of experiments before the closure and in an other series (B) after the reopening of the coronary vessel. Hearts without inhibitor or with the administration of the Na⁺/H⁺-exchange inhibitor cariporide[®] served as controls. Hemodynamic monitoring and biochemical analysis of perfusion fluid from the coronary outflow were performed. Myocardial infarct size was determined by microscopic evaluation of left ventricular slices after a special staining procedure with Evans blue and 2,3,5 triphenyltetrazoliumchloride.

Results: The area of necrosis/infarction was $77.9 \pm 2.3\%$ of the area at risk in controls without calpain inhibition of series A ($n=12$), respectively $72.7 \pm 4.0\%$ of series B ($n=8$). Preischemic administration of A-705253 ($n=8$) reduced the area of infarction most effectively ($p<0.001$) to $49.3 \pm 3.9\%$ ($n=8$) with an inhibitor concentration of 10^{-8} mol/l. Even with postischemic inhibitor application ($n=8$) area of infarction could be reduced significantly ($p<0.01$) to $48.3 \pm 2.3\%$ using an inhibitor concentration of 10^{-6} mol/l. Administration of cariporide® ($n=8$; 10^{-6} mol/l) resulted in a comparable reduction ($p<0.01$) to $50.2 \pm 3.4\%$ of the area at risk. The protective effect of calpain inhibition on myocardial infarction was dose dependant in relation to the time point of administration.

Conclusion: The experiments imply a major role of calpains in myocardial ischemia and reperfusion injury which can be attenuated as well by preischemic as by postischemic calpain inhibition. The protective effect of Na^+/H^+ -exchange inhibition seems to be mediated by the inhibition of calpain activation.

P590 44AANA47-RANTES: New anti-inflammatory molecule to reduce reperfusion injuries in mice



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Background: 44AANA47-RANTES is a specific inhibitor of the chemokine RANTES and we have previously shown that the anti-inflammatory effects of RANTES antagonism leads to a reduction of atherosclerosis progression. Myocardial ischemia is the major consequence of atherosclerosis and animal models of sustained ischemia have shown exacerbation of myocardial injury early during reperfusion, mediated largely by an inflammatory process. Thus, the aim of the present study was to investigate the effect of 44AANA47-RANTES in a mouse model of ischemia and reperfusion in vivo.

Methods and Results: After 10 weeks high cholesterol diet, ApoE^{-/-} mice were submitted to 30 min ischemia, by ligation of the left coronary artery, followed by 24 h reperfusion, in vivo. Infarct size (as percentage of ischemic risk zone) was determined by Evans' blue and tetrazolium double staining. Intraperitoneal injection of $10 \mu\text{g}$ 44AANA47-RANTES, 5 min prior reperfusion, significantly reduced infarct size ($9.1 \pm 1.1\%$ in 44AANA47-RANTES group versus $18.2 \pm 2.0\%$ in PBS group, $P=0.01$). Ongoing experiments will now show whether 44AANA47-RANTES treatment could reduce neutrophil infiltration in myocardium after the ischemia-reperfusion sequence, as well as the expression of chemokines and chemokine receptors, which are known to be increased by ischemia and reperfusion.

Conclusions: This study provides the first evidence that 44AANA47-RANTES exerts a cytoprotective effect specifically during early reperfusion, through its anti-inflammatory properties. Our findings indicate that blockade of chemokine receptor/ligand interactions might become a novel therapeutic strategy to reduce reperfusion injuries in patients undergoing angioplasty.

P591 Peroxynitrite mediates the antiapoptotic effect of postconditioning in myocardial ischemia-reperfusion



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Objects: To elucidate the effect of postconditioning on post-ischemic cardiac apoptotic ratio in vivo and the signaling pathway involved in the pro/antiapoptotic effect of postconditioning.

Methods: Male Sprague-Dawley rats were subjected to 30 minutes of myocardial ischemia and 4 hours of reperfusion. Rats were randomized to receive vehicle, GSH ($100 \mu\text{mol kg}^{-1} \text{h}^{-1}$), postconditioning (three cycles of 30 s reperfusion and 30 s LAD reocclusion preceded the 4 h of reperfusion), or postconditioning plus SIN-1 ($1 \text{ mmol kg}^{-1} \text{h}^{-1}$). Myocardial apoptosis (TUNEL and caspase-3 activity assay), nitrotyrosine formation (immunohistochemical detection), plasma cTnI and CK-MB concentration were determined.

Results: Compared with vehicle rats, postconditioning exerted a significant antiapoptotic effect (TUNEL staining: $12.3 \pm 2.5\%$ vs $18.1 \pm 2.2\%$, $P<0.01$; caspase-3 activity: 552.1 ± 78.4 vs 857.7 ± 113.9 , $P<0.01$). SIN-1 inhibited the antiapoptotic effect of postconditioning significantly (TUNEL staining: $17.3 \pm 2.1\%$ vs

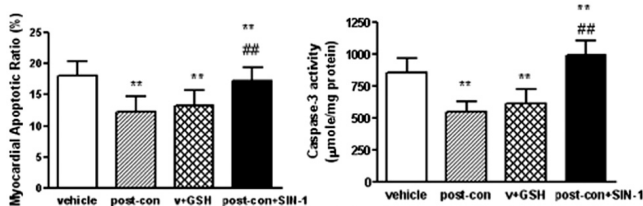


Fig. 1. The anti-apoptotic effect of postconditioning. Left figure indicates TUNEL staining result, right, caspase-3 activity assay. Post-con indicates postconditioning; v+GSH, vehicle plus GSH; post-con+SIN-1, postconditioning plus SIN-1. All data were expressed as mean $\pm$ SD, $n=12$. ** $P<0.01$, vs vehicle, ## $P<0.01$, vs post-con.

$12.3 \pm 2.5\%$, $P<0.01$; caspase-3 activity: 992.3 ± 118.6 vs 552.1 ± 78.4 , $P<0.01$). In addition, GSH exerted a similar anti-apoptotic effect as postconditioning (fig.). Immunohistochemical staining indicated postconditioning depressed I/R-induced peroxynitrite increase, but the effect of postconditioning was counteracted by SIN-1.

Conclusion: These results demonstrated that postconditioning reduced postischemic myocardial apoptotic death and the concurrent decrease of peroxynitrite production contribute significantly to the antiapoptotic effect of postconditioning.

P592 EPO administration reduces mortality and improves cardiac function after induced myocardial infarction in mice



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Objective: Recent reports have shown additional effects of EPO beside its classical function in erythropoiesis, like antiapoptotic effects and stem cell mobilization. These effects are known to improve myocardial regeneration after myocardial infarction (MI). We aimed to define survival, functional parameters as well as cell proliferation and stem cell mobilization in a murine model of surgically induced MI after treatment with EPO.

Methods: Immediately after ligation of the left anterior descendens (LAD) 3000 IE/kg human EPO and 1000 IE/kg on the two consecutive days were injected intraperitoneally. 6 days after application different subpopulations of mobilized stem cells were determined by flow cytometry. 30 days after MI pressure volume relationships were investigated in vivo using conductance catheters.

Results: FACS analysis 6 days after EPO application demonstrated a significant increase of different CD34⁺ stem cell populations (CD31⁺, c-kit⁺, Sca-1⁺). EPO treated animals showed a significant improvement of survival post MI (62% vs. 36%). Comparison of pressure-volume loops between sham operated and infarcted mice revealed a pronounced difference of cardiac function (EF: $22.9 \pm 2.7\%$ vs. $15.0 \pm 2.0\%$). This effect was associated with a reduced infarct size. In addition elasticity demonstrated a less degree of infarct remodelling (Elasticity: 21.0 ± 3.4 vs. $8.1 \pm 0.9 \text{ mmHg}/\mu\text{l}$).

Conclusion: EPO administration after myocardial infarction is associated with a pronounced stem cell mobilization, an improved rate of survival as well as remodelling and demonstrated a beneficial role on long term myocardial function up to 4 weeks after MI. Therefore, mobilization of autologous bone marrow derived cells presents a promising non-invasive approach to ameliorate heart failure post MI.

P593 Effects of acute vagal nerve stimulation on electrotonic uncoupling induced by myocardial ischemia



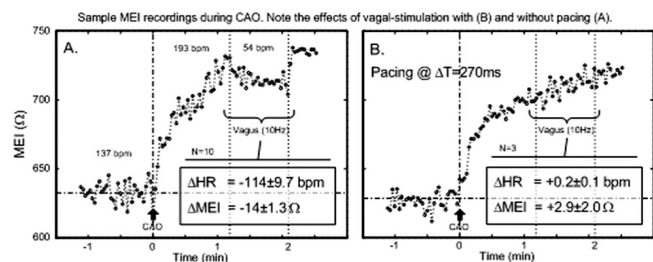
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Introduction: Electrotonic uncoupling and cell-swelling occurring early during ischemia have been shown to modulate myocardial-repolarization currents, being correlated with 1A-arrhythmias¹. Vagal nerve stimulation (VNS) is known to be anti-arrhythmic and prevents the ischemic loss of connexin43 (cell-to-cell electrical coupling)¹. Thus, we sought to study the effects of acute VNS on electrotonic uncoupling, as measured by myocardial electrical impedance (MEI)² early during coronary artery occlusion (CAO).

Methods: Twelve mongrel dogs were anesthetized with morphine, alpha-chloralose and urethane³. The dogs were instrumented with MEI electrodes² in the LCX distribution and underwent bilateral vagotomy. Subsequently, CAO was performed (proximal LCX tie), followed ($4 \pm 0.8 \text{ min}$) by VNS (10 Hz, 15V). In a subset of animals, heart rate (HR) was maintained constant by AV-pacing (220 bpm). MEI and HR values are presented as mean $\pm$ SEM and were analyzed using RM one-way ANOVA (w/Tukey test, $P<0.05$).

Results: MEI increased significantly after CAO in both paced ($+78 \pm 5.1 \Omega$ from $616 \pm 24.1 \Omega$, $N=7$), and non-paced ($+86 \pm 15.1 \Omega$ from $655 \pm 21.1 \Omega$, $N=3$) hearts, indicating early electrotonic uncoupling. Acute VNS after the onset of ischemia abruptly decreased MEI ($-14 \pm 1.3 \Omega$, $P<0.05$) and HR ($-114 \pm 9.7 \text{ bpm}$) only in non-paced hearts ($N=10$). In other words, such effects were absent when HR was held constant (MEI: $2.9 \pm 2.0 \Omega$, HR: $0.2 \pm 0.1 \text{ bpm}$). See fig.

Conclusion: Acute VNS during myocardial ischemia exerts negative chronotropic



effects, limiting early electrotonic coupling and ischemic cell-swelling. As such, it may play a role limiting 1A-arrhythmias.

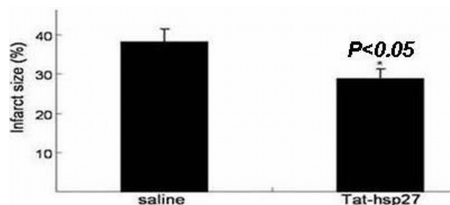
- References:** 1. J Physiol; 568; 423-43, Am J Physiol Heart Circ Physiol; 286: H1901-9, Circulation; 92:3051-60, Circulation; 112:164-70
2. J Appl Physiol; 99:1576-81.
3. Am J Physiol; 262:H1719-24

P594 Myocardial protective effects of Heat Shock Protein 27 using Protein Transduction Domain-mediated delivery after Ischemia/Reperfusion injury



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Heat shock proteins (HSPs) provide one kind of defense against stresses such as high temperature, hypoxia/ischemia and oxidative stress in all mammalian cells. One such protein which is highly induced during the stress response is hsp27, and its expression is correlated with the cellular survival in response to cytotoxic insults. Recent studies have been established that the overexpression of hsp27 protects against cell death triggered by a variety of stimuli including ischemia, hyperthermia, and various cytotoxic agents. Therefore, it can be used as a potential therapeutic strategy for the treatment of critically ill patients. In this study, using protein delivery approach, we studied the potential cardiac protective effects of hsp27 as a therapeutic protein in rat cardiac myoblast H9c2 cells and rat LAD ligation model of ischemia/reperfusion. Human hsp27 cDNA was cloned and fused with a gene fragment encoding the basic domain from HIV-1 Tat protein called the protein transduction domain (PTD). Then, the efficiency of transduction of the resulting Tat-hsp27 fusion protein into H9c2 cells was analyzed. The Tat-hsp27 fusion protein was efficiently delivered to H9c2 cells, and its transduction showed cytoprotective effect against the hypoxic stress.



Effects of Tat-hsp27 on infarct size

Moreover, transduction of Tat-hsp27 also attenuated hypoxia-induced apoptosis, which was accompanied by reduced caspase-3 activity. In addition, intraperitoneal injection of Tat-hsp27 into rat resulted in efficient protein transduction in heart tissues within 2 h, and decreased infarcted myocardium (H-E stain; control vs Tat-hsp27, 39.1% vs 29.5%, $p < 0.05$) and preserved heart function (fractional shortening and 2D strain of myocardium, 15.6% vs 33.4%, 4.83 vs 9.59, $p < 0.05$), as determined at 7 days after ischemia/reperfusion.

P595 Low-frequency ultrasound increases activity and tissue content of nitric oxide synthase in acute limb ischemia in rabbits

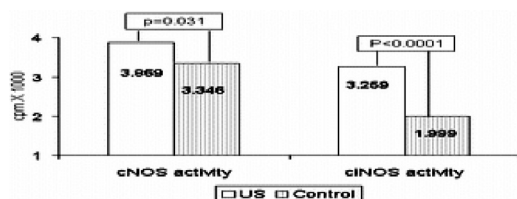


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Background: Low-frequency ultrasound (US) preserves myocardial and skeletal muscle viability in ischemic models by inducing vasodilatation through nitric oxide (NO)-dependent mechanisms that has not been defined yet. We examined the effect of US on the expression and activity of the 3 NO synthase (NOS) isoforms.

Methods: The two femoral arteries of 4 New Zealand rabbits were ligated for a total of 120 minutes. After 60 minutes of ligation, transcutaneous US (27 kHz, 0.5 W/cm²) was applied for 60 minutes to one femoral artery, while the contralateral artery served as control. We examined the effect of US on the activity of calcium-dependent (cNOS) and independent (iNOS) NOS, and the expression of endothelial (eNOS), inducible (iNOS), neuronal (nNOS), and phosphorylated eNOS (PeNOS) in the ischemic muscle.

Results: As shown in the Figure, compared to control, US application significantly increased both cNOS and iNOS activity. Western immunoblotting showed



Figure

that US increased the expression of total eNOS ($104.5 \pm 0.6\%$; $p = 0.001$), and to a greater extent of PeNOS ($381.5 \pm 2.5\%$; $p < 0.001$), and iNOS ($184.0 \pm 1.1\%$; $p < 0.001$), whereas it had only a small effect on nNOS expression ($102.5 \pm 0.6\%$; $p = 0.023$).

Conclusions: Application of transcutaneous US to ischemic muscular tissue significantly increases cNOS and iNOS activity by increasing the expression of PeNOS and iNOS. This effect should be further studied as a possible treatment of acute and chronic ischemic syndromes.

P596 The use of human heart-type fatty acid binding protein as an early diagnostic biochemical marker of myocardial necrosis in patients with acute coronary syndrome



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Background: Heart-type fatty acid binding protein (H-FABP), a new biochemical marker of sarcolemmal injury due to acute myocardial ischemia can be used as a tool in early diagnosis of patients with high risk. Our aim was to determine the early diagnostic value of H-FABP in acute coronary syndrome (ACS) and to compare it with troponin-T (TnT) and creatine kinase-myocardial band (CK-MB) accuracy. **Patients and Methods:** The study consisted of 40 consecutive patients with chest pain admitted to the coronary care unit with diagnosis of ACS. 26 patients admitted within 6 hours of chest pain and 14 patients admitted within 6 to 24 hours of chest pain. Blood samples for H-FABP, TnT and CK-MB were obtained at admittance, 6th and 24th hours for the first and at admittance and 24th hours for the second group. Statistical analysis was performed among the 26 patients for the first 6 hours values and among the whole 40 patients for the values obtained within 6-24 hours and at the 24th hour. The patients were divided into unstable angina pectoris (USAP), non-ST elevation myocardial infarction (MI) and ST-elevation MI according to changes in the ECG and cardiac enzymes.

Results: Sensitivity of TnT, CK-MB and H-FABP in the first group (within 6 hours of chest pain) were 38%, 76% and 95% respectively. The sensitivity of H-FABP was significantly higher than TnT ($p = 0.014$). Within 6 to 24 hours of chest pain, sensitivity of TnT, CK-MB and H-FABP tests were 100%, 90% and 91% respectively. In this time period, the sensitivity of TnT was higher than H-FABP, but it was statistically insignificant. At the 24th hour, sensitivity of TnT was 100%, CK-MB 90% and H-FABP 27.3% and TnT and CK-MB were more sensitive than H-FABP for the whole group ($p = 0.002$). Within the first 6 hours of chest pain, H-FABP had significantly greater positive results than TnT serum levels for the patients with non ST-elevation MI ($p = 0.017$). However, positiveness of H-FABP gradually decreased and at the 6 to 24th hours and lost its significance ($p = 0.306$). H-FABP was negative in patients with USAP both within the first 6 hours and 6-24 hours of chest pain. Similarly, TnT levels were below 0.01ng/mL in all patients with USAP within the first 6 hours while higher than 0.01ng/mL in 3 of them within 6-12 hours.

Conclusion: We conclude that within the 6 hours of ACS, H-FABP seems to be a more sensitive biochemical marker than TnT in the early detection of ischemic myocardial necrosis. But after the first 6 hours, the sensitivity of H-FABP decreases and this marker should not be used alone in patients admitted 24 hours after the onset of chest pain.

P597 Leukocytes as prognostic markers in patients with non ST segment elevation acute coronary syndromes



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Purpose: Leukocytes are the part of inflammatory mechanisms that underline initiation and progression of atherosclerosis. The aim of our study was to determine whether leukocyte count might be used as a prognostic marker in patients with non ST segment elevation acute coronary syndromes (ACS)

Methods: The prospective study included 546 patients with non ST segment elevation ACS (mean age 58 years, 61% males) admitted to our Coronary Care Unit from January 2001 to January 2005. We evaluated clinical history, ECG and leukocytes count and several troponin I measurements. Mortality and new events were noted in the follow up period of 1 year.

Results: Leukocytes were higher in subgroup with troponin I elevation ($p < 0.001$) compared to patients with no events. Distribution showed that leukocytes count was related to mortality ($p = 0.002$) in the group with elevated troponin I levels, but not in the group without. When adjusted for other risk factors for coronary artery diseases, leukocytes were independent predictors of new event ($p < 0.001$) and death.

Conclusion: Leukocytes count predict worse prognosis in patients with non ST segment elevation ACS and minor myocardial damage (troponin I positive patients) and can be routinely performed in all communities.

P598 Effect of Trimetazidin on myocardial ischemic parameters in early postinfarction period

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Purpose: Trimetazidine (TMZ) is a metabolic agent that has no haemodynamic or negative inotropic properties. This study aimed at estimating the effectiveness of TMZ in early postinfarction period and its effects on clinical parameters.

Methods: The study involved 78 patients with initial myocardial infarction (MI) aged from 38 to 67. All patients received a standard treatment. Beginning with the 2nd day, 60 mg/day TMZ was added to the standard treatment regimen of 40 patients (TMZ group), the remaining 38 patients kept the initial treatment (Control group). Above groups were identical concerning clinical variables. Follow-up was performed in the 2nd week of the treatment- EchoCG, treadmill-test (TT), 24-hour Holter-monitoring (HM) ECG. Total duration of exercise (TDE), total workload (TWL), time to 1mm ST-segment depression (TSTD), time to onset of angina (TOA) on TT, daily number of ischemic episodes (DNIE), daily duration of ischemia (DDI) on HM and ejection fraction (EF) of left ventricle (LV) on EchoCG were analyzed.

Results: As it is presented in the table, apart from EF LV, all other variables were favorable in the TMZ group, particularly, tolerance of exercise; TDE was greater by 64 sec (8.4%); TWL: 8.9 ± 1.8 METs vs 8.0 ± 2.1 METs, $p < 0.05$. TSTD and TOA were significantly greater in the TMZ group, too. The HM parameters were also better in the TMZ group: DNIE and DDI were significantly lower in the TMZ group than in the Control group (1.8 ± 1.4 vs. 2.6 ± 1.6 , $p < 0.001$ and 608 ± 144 sec vs. 726 ± 215 sec, $p < 0.01$, correspondingly).

Parameters	TMZ	Contr.	P
LV EF (%)	48.4 ± 4.9	47 ± 5.7	NS
TDE (sec)	830 ± 133	766 ± 102	< 0.05
TWL (METs)	8.9 ± 1.8	8.0 ± 2.1	< 0.05
TSTD (sec)	790 ± 108	708 ± 88	< 0.001
TOA (sec)	816 ± 138	738 ± 114	< 0.01
DNIE	1.8 ± 1.4	2.6 ± 2.15	< 0.01
DDI (sec)	608 ± 144	726 ± 215	< 0.01

NS-no significant

Conclusion: TMZ improves tolerance to of exercise, increases threshold of myocardial ischemia and effort angina, decreases frequency and duration of daily myocardial ischemia in early postinfarction period.

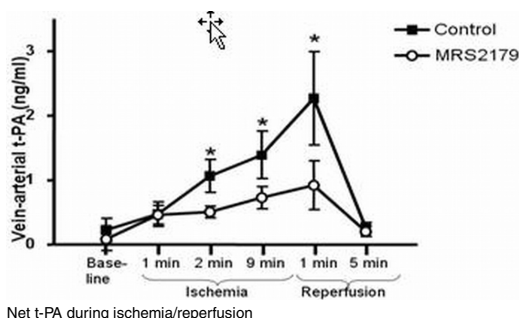
P599 P2Y₁ receptors mediates release of tissue plasminogen activator (t-PA) in response to reactive coronary hyperemia in a pig model

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Introduction: The endothelial P2Y₁ receptor is responsible for a large part of the reactive hyperemia following cardiac ischemia. Tissue plasminogen activator (t-PA) increases during reactive hyperemia. We postulated that the release of t-PA during reactive hyperemia could be mitigated through blocking the coronary endothelial P2Y₁ receptor.

Methods: t-PA was measured in peripheral arterial blood and locally in the venous blood from the coronary sinus (CS) in a porcine model. 2-MeSADP (10-5M), alone or as co-infusion with a selective P2Y₁ receptor blocker, MRS 2179 (10-3M) was locally delivered in the left anterior descending artery (LAD) through the tip of a coronary angioplasty balloon. In separate pigs the coronary artery was occluded with the balloon for ten min. During the first and tenth min of coronary ischemia, 2.5 ml of MRS 2179 (10-3M) was delivered distal to the occlusion in 8 pigs, 10 pigs were used as controls.

Results: 2-MeSADP increased levels of t-PA in the CS by 85% which could completely be inhibited by co-infusion with MRS 2179. During cardiac ischemia and reperfusion t-PA increased significantly, an effect that could be significantly inhibited by MRS 2179.



Net-t-PA during ischemia/reperfusion

Conclusion: Intra coronary administered MRS 2179, a selective P2Y₁ receptor blocker, significantly reduces the increased levels of t-PA caused by both 2-MeSADP and cardiac ischemia + reperfusion in coronary arteries. Thus, ADP acting on the endothelial P2Y₁ receptor may play a major role in the release of t-PA during post- ischemic hyperemia.

EXPERIMENTAL ISCHAEMIA PRECONDITIONING AND POSTCONDITIONING**P600 Cardioprotection of ischemic postconditioning and ATP-postconditioning in rabbits is associated with the activation of adenosine receptors**

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Objective: Recent experimental studies indicate that application of short, repetitive ischemia only during the onset of reperfusion, i.e. ischemic postconditioning, attenuates myocardial reperfusion injury. This study was designed to examine if adenosine triphosphate (ATP) had the same cardioprotective effects when administered at the onset of reperfusion, and investigate the role of adenosine receptors in the protection by postconditioning.

Methods: Thirty anesthetized open-chest rabbits were subjected to 40 min ischemia of the left anterior descending artery and 180 min reperfusion, and assigned to the following five groups: (1)Control(CON): 40 min ischemia/180 min reperfusion only without other intervention; (2)Post-con: At the first three minutes of reperfusion, three cycles of 30s reperfusion/30s ischemia preceded 180 min reperfusion; (3)ATP-Post: ATP (3mg/kg, i.v) was used for 20 min starting 5 min before reperfusion; (4)Post + SPT: Besides the treatment of Post-con, the non-selective adenosine receptor antagonist 8-p-sulphophenyl theophylline (SPT, 5.3mg/kg,i.v) was given for 20 min starting 5 min before reperfusion; (5)CON+SPT: Only SPT was given. Infarct size (TTC staining), the plasma MB isoenzymes of creatine kinase(CK-MB), superoxide dismutase(SOD), and lipid peroxidation product malondialdehyde (MDA) were measured at the end of ischemia.

Results: Myocardial infarct size was limited in Post-con($12.6 \pm 2.6\%$) and in ATP-Post($13.3 \pm 4.8\%$) compared to CON($17.9 \pm 3.5\%$, $p < 0.05$, respectively), consistent with CK-MB(218 ± 47 U/L in Post-con, 252 ± 37 U/L in ATP-Post vs 340 ± 29 U/L in CON, $p < 0.05$, respectively). SPT alone had no effect on infarct size($20.3 \pm 3.1\%$ in CON+SPT vs $17.9 \pm 3.5\%$ in CON, $p = \text{NS}$), however, SPT abrogated the myocardial infarct size reduction in postconditioning($18.4 \pm 2.8\%$ in Post+SPT vs $12.6 \pm 2.6\%$ in Post-con, $p < 0.05$; $18.4 \pm 2.8\%$ in Post+SPT vs $17.9 \pm 3.5\%$ in CON, $p = \text{NS}$). MDA was lower and SOD higher in Post-con (3.9 ± 0.7 nmol/ml, 234 ± 29 U/ml) and ATP-Post(3.3 ± 0.8 nmol/ml, 218 ± 35 U/ml) than CON(4.9 ± 0.6 nmol/ml, 176 ± 17 U/ml, $p < 0.05$ respectively). Similarly, SPT abolished these protective effects in postconditioning.

Conclusions: Our results suggest that ATP can protect the heart from myocardial ischemia/reperfusion injury when administered at the onset of reperfusion and is as effective as mechanical postconditioning. The mechanism of postconditioning's protection may be associated with the activation of adenosine receptors. ATP induced postconditioning may have potential utility in coronary interventions, thrombolysis, coronary artery bypass grafting.

P601 Enhanced efficiency of superoxide dismutase-induced cardioprotection by retrograde intracoronary administration prior to reperfusion

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Superoxide dismutase (SOD) is a promising reagent to attenuate myocardial reperfusion injury; however, its efficacy has not been fully established in experimental or clinical reports. We hypothesized that priming the ischaemic myocardium with SOD before reperfusion may induce the maximum effect of this type of therapy, as superoxides are generated within seconds after reperfusion. However, the routes previously examined, intravenous and arterial intracoronary infusion, can deliver SOD into the ischaemic myocardium only after reperfusion. In contrast, retrograde intracoronary infusion would enable such a timely delivery and might therefore enhance the efficiency of SOD-induced cardioprotection.

Methods and Results: Lewis rats underwent 30-min left coronary artery occlusion. Just before reperfusion, CuZn-SOD was administered intravenously ($15,000$ U/kg, V-SOD group) or by retrograde intracoronary infusion ($1,500$ U/kg, R-SOD group) through a catheter inserted into the left cardiac vein. This method perfused the whole left ventricular free walls of the heart whose left coronary artery was occluded. Controls for each group were injected with PBS only by either route (V-PBS or R-PBS group). Hearts were then reperused for 24 hours. R-SOD group demonstrated the most improved left ventricular ejection fraction (LVEF) assessed by echocardiography and the smallest infarct size (% infarct area of total ischaemic area; Evans blue and TTC staining) amongst all the groups. In addition, these improved effects in RIC group were associated with the most preserved regional myocardial blood flow in the ischaemic area measured

using colored-microspheres (RMBF, % of the flow in the non-ischaemic area) and the most reduced acute inflammation evaluated by neutrophil infiltration into the ischaemic area.

Protective effects by SOD-treatment

	Infarct Area (%)	LVEF (%)	RMBF (%)	Neutrophil Number ($10^3/\text{mm}^2$)
R-SOD	23.3±2.3*	77.5±1.6*	69.8±2.3*	11.8±0.4*
R-PBS	48.9±2.8	52.4±2.3	54.4±2.4	18.0±0.6
V-SOD	42.3±3.4	60.8±2.3	64.3±2.1 [†]	14.8±1 [†]
V-PBS	47.4±3.4	54.7±2.9	53.4±2.4	16.8±0.7

* $p < 0.05$ vs R-PBS, V-PBS, and V-SOD; [†] $p < 0.05$ vs V-PBS and R-PBS, $n > 5$ in each group

Conclusion: Retrograde intracoronary infusion prior to reperfusion enhanced the efficacy of SOD-induced myocardial protection against ischaemia-reperfusion injury.

P602 Preconditioning and postconditioning in anesthetized female rabbits in relation to hormonal status



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Preconditioning (prec) and postconditioning (postc) protect ischemic myocardium. However, most studies have been done in male animal models and therefore, the effectiveness of these protective mechanisms is questionable in females. Purpose: To test the hypothesis that both prec and postc are effective in limiting infarct size in female rabbits without (intact) or with ovariectomy (ovx).

Methods: Anesthetized female rabbits were subjected to 30min ischemia and 3h reperfusion with the following additional interventions: control group no intervention, prec group in two cycles of 5min ischemia - 10min reperfusion before the sustained ischemia and postc group in six cycles of 10sec ischemia - 10sec reperfusion immediately after sustained ischemia. In a second series of experiments three respective to the first series groups were subjected to ovx and three weeks later to the same interventions as the first series groups. The infarct to risk ratio (I/R) was determined in % with the aid of fluorescent particles and TTC staining.

Results: In intact female groups: control $43.2 \pm 2.6\%$, prec $10.6 \pm 1.4\%$, ($P < 0.01$ vs control) postc $55.1 \pm 6.6\%$ ($P < 0.01$ vs prec and NS vs control). In ovx groups: control $50.9 \pm 6.7\%$, prec $18.5 \pm 2.3\%$, ($P < 0.05$ vs control), postc $27.3 \pm 2.9\%$ ($P < 0.05$ vs control).

Conclusion: There is significant difference in the protection of prec and postc between intact and ovx animals. Prec preserves its effectiveness in intact as well as in ovx female rabbits whereas postc is effective only after ovx.

P603 Vascular pre-conditioning like effect of TIP39 in long-term ischemia



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Background: Parathyroid hormone-related peptide (PTHrP) and Tuberoindole peptide of 39 amino acids (TIP39) are expressed in endothelial cells and potential modifiers of the coronary perfusion pressure. While the mechanism by which PTHrP exerts its vasodilating effect has been investigated in great detail it is completely unclear under which conditions TIP39 may alter coronary perfusion. Recent studies on renal perfusion suggest a cross talk between the PTH type 1-receptor (PTH-1R), that is activated by PTHrP, and the PTH type 2-receptor (PTH-2R), that is activated by TIP39. The aim of this study was to investigate whether down-regulation of PTH-1R damasks an effect of TIP39 on the coronary perfusion.

Methods: Isolated rat hearts were perfused at a constant flow and the coronary resistance was calculated by the determination of the perfusion pressure. Hearts were perfused in the Langendorff mode.

Results: Under basal conditions, TIP39 (100 nmol/l) did not influence coronary perfusion alone. Pre-treatment of PTH-1R with PTHrP attenuated the responsiveness of the hearts to PTHrP but induced a vasodilating effect evoked by TIP39 (-22%). The TIP39 effect was attenuated in the co-presence of a PTH-2R antagonist and L-nitro arginine (L-NA), that was used to block NO-formation. In the next set of experiments, hearts underwent a 30 min null-flow-ischemia. Hearts were treated just before the onset of ischemia with TIP39 (100 nmol/l). Under these conditions the vascular endothelial cells release PTHrP. This endogenous release of PTHrP was sufficient to allow TIP39 to reduce post-ischemic vascular stunning by 28%. Again, the effect was inhibited by an NO-antagonist, an PTH-2R antagonist and by inhibition of endogenously released PTHrP. When given at the beginning of reperfusion, however, TIP39 did not reduce coronary resistance.

Conclusion: Endogenous release of PTHrP during ischemia is sufficient to damask PTH-2R to respond to TIP39, the natural agonist of the receptor. The mechanisms by which TIP39 stably reduces the post-ischemic coronary resistance is similar to that of NO-dependent vascular pre-conditioning and seems to represent a similar mechanism.

P604 In Senescence Accelerated Mouse (SAM) heart, the protective effect of postconditioning is associated with a decrease in oxidative stress



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The senescent heart susceptibility to ischemia (I) triggers multiple processes especially oxidative stress but precise mechanisms remain unclear. New animal's models such as "Senescence Accelerated Mouse" Prone 8 (SAM-P8) and their control (SAM-R1) can be useful for a better understanding of aging process. We studied heart adaptation of these mice to I/reperfusion (R) sequence and a putative cardioprotector effect of post-conditioning (PC). Isolated working mice (8 months) hearts were subjected to a global total ischemia (20 minutes at 38°C), followed by 40 minutes of reperfusion. 4 groups of hearts were constituted: 1) SAM-R1 (n=8), 2) SAM-P8 (n=9), brief ischemia applied during the onset of reperfusion 3 times I: 10 sec, R: 10 sec for PC groups, 3) SAM-R1 PC (n=7) and 4) SAM-P8 PC (n=8). Myocardial functions (left ventricular end systolic/diastolic pressures, contractility, relaxation, aortic flow, coronary flow and heart rate) were recorded throughout the protocol. Hearts were then frozen and superoxide anion ($O_2^{\cdot-}$) production has been evaluated on cryosections using a fluorescent probe Dihydroethidium (DHE). During pre-I period, cardiac functional parameters were comparable in all groups. SAM-P8 heart showed the worst reperfusion parameters compare to SAM-R1; for instance cardiac output (0.60 ± 0.33 ml/min vs. 1.84 ± 0.64 ml/min, $p < 0.05$). PC induced a significant better functional recovery on both group (3.96 ± 0.68 ml/min SAM-R1 PC vs. 3.20 ± 0.78 ml/min SAM-P8 PC; $p < 0.05$). Furthermore PC is associated with a significant reduction of superoxide production on heart slice has been observed ($p < 0.05$). These results indicate that SAM-P8 mice, a murine model of aging, present a susceptibility to reversible I and are still sensitive to PC. This cardioprotection is associated with a decrease of free radicals production. These results demonstrate a role of the oxidative stress in the process of myocardial adaptation to I/R sequences.

P605 The effect of the phytoestrogen genistein on myocardial protection and preconditioning in hypercholesterolemia



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Purpose: We have previously shown that estrogen reduce myocardial infarct size in normocholesterolemic and hypercholesterolemic ovariectomized female rabbits whereas raloxifene has no protective effect. As genistein, a phytoestrogen derived from soy can be administered in both sexes, we now evaluated its effect on myocardial ischemia and preconditioning, in both male and female hypercholesterolemic rabbits.

Methods: We studied 40 hypercholesterolemic-fed with cholesterol enriched diet for 8 weeks-sexually mature New Zealand rabbits, 21 males and 19 ovariectomized females, treated with genistein (0.2 mg/kg/day subcutaneously) for 4 weeks (groups A and C) or placebo (groups B and D). Subsequently all animals underwent 30 minutes of ischemia and 120 minutes of reperfusion, with (subgroup I) or without (subgroup II) preconditioning (PC) with two cycles of 5 minutes of ischemia and 10 minutes of reperfusion. Infarct and risk areas were delineated by Zn-Cd fluorescent particles and tetrazolium chloride staining. The infarct size was expressed as a percentage of the risk zone (I/R%). We analyzed our results with factorial ANOVA and the LSD test was applied for post-hoc analysis.

Results: Results are expressed as mean±SEM. There were significant differences between the groups ($p=0.01$). Genistein did not decrease infarct size in either males (AII vs BII, $p=NS$) or females (CII vs DII, $p=NS$). All groups with preconditioning had significant smaller infarcts compared to those without (AI vs AII, BI vs BII, CI vs CII, DI vs DII, $p=0.01$). There were no gender differences between our groups (AI vs BI, CI vs DI, AII vs BII, CII vs DII, $p=NS$).

	AI	AII	BI	BII	CI	CII	DI	DII
I/R %	11.96 ±5.76*	51.17 ±13.06	26.49 ±7.45*	66.71 ±2.4	12.87 ±2.74*	41.89 ±13.25	17.88 ±4.23*	54.86 ±7.23

* $p=0.01$ vs non-PC groups

Conclusion: Genistein, at this dose, does not reduce infarct size per se nor abolishes the protective effect of preconditioning, in hypercholesterolemic rabbits of either gender. Preconditioning induces myocardial protection in hypercholesterolemic rabbits, both males and females, whether genistein treated or not. We observed no gender differences in the effects of genistein and preconditioning in hypercholesterolemic animals, nor there was difference in infarct size between male and female animals.

P606 Protection from postconditioning depends on the number of the short ischemic insults in anesthetized pigs

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Postconditioning (postC) in the early reperfusion (rep) period confers protection to the heart after a potentially lethal episode of prolonged ischemia (isch). This novel endogenous mechanism has been documented in several animal models but there are still questions regarding the number and duration of the isch/rep cycles required to cause effective salvage. Furthermore, very few postC studies have used large animal species that should be more relevant to humans. Purpose: To test whether an effective postC protocol can be identified that limits infarct size in anesthetized pigs.

Methods: Domestic Landrace pigs weighing 25-29 kg were fasted for 24h, anesthetized with ketamine 15mg/kg i.m. and midazolam 0.5 mg/kg i.m. as premedication, intubated and mechanically ventilated. Then iv injection of propofol 3mg/kg, pancuronium 0.15 mg/kg and fentanyl 17.5 µg/kg were given and supplemented as necessary. After midsternal thoracotomy and pericardiotomy the anterior descending coronary artery was ligated and the animals were subjected to 60min isch and 3 hours rep with the following additional interventions: Control group (n=5) no other intervention, 4-30 postC group (n=5) to 4 cycles of 30sec isch-30sec rep and 8-30 postC (n=6) to 8 cycles of 30sec isch-30sec rep both starting 30sec after the release of prolonged isch. The infarct size (I) and the area at risk (R) were delineated with the aid of TTC staining and monastral blue, respectively. **Results:** 33.5 ± 7.6% of the R infarcted in control, 36.7 ± 3.7% in 4-30 postC group (P=NS) and 10.5 ± 0.5% in 8-30 postC group (P<0.01vs the other 2 groups).

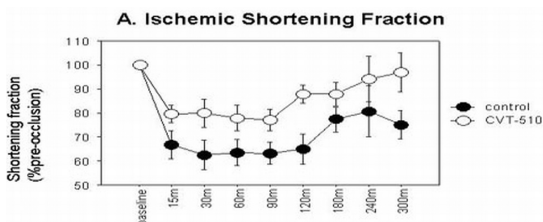
Conclusion: Postconditioning confers protection in anesthetized pigs but requires more than 4 isch/rep cycles.

P607 Protective effect of the selective A1 adenosine receptor agonist CVT-510 (Tecadenoson) on recovery from myocardial stunning

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Pharmacological activation of A1 adenosine receptors on cardiac myocytes enhances tolerance to ischemia reducing the extent of necrosis. We determined the effects of CVT-510, a selective A1 adenosine receptor agonist, on post ischemia/reperfusion (I/R) stunning. Fifteen anesthetized pigs underwent cycles of I/R consisting of 10 consecutive 2-min occlusions of the left circumflex, interspersed by 2-min reperfusion. Animals were monitored for 5 hours. Pigs were treated with an i.v. infusion of either vehicle (V; n=5) or CVT-510 0.5 microg/kg/min for 45 min, starting 5 min before the first occlusion (CVT; n=10). Systemic and left ventricular pressure, LVdP/dt and regional segmental shortening (SF) were recorded every hour during pacing at 120 b/min. The deficit of SF after reperfusion was calculated by measuring the difference of the AUC between the SF and the baseline line (100%) during recovery starting at 15 min up to 300 min.

Results: The baseline hemodynamic values before I/R were not different between V and CVT groups and no significant difference was observed at any time point. A significant difference (p=0.047 ANOVA RM) was observed in the time course of the SF of the ischemic region. The SF had fallen to 63% of baseline value in the control group up to 120 minutes, whereas it was up to 75% in the CVT treated group at 90 minutes. SF deficit AUC was significantly lower in CVT (3865±949) than in V (7409±1151) (p=0.042)



Conclusion CVT-510 attenuates myocardial stunning following repetitive I/R independently of hemodynamic unloading of the left ventricle.

VENTRICULAR REMODELLING AFTER INFARCTION**P608 The role of CD44 signaling in infarct healing and left ventricular remodeling**

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Purpose: CD44 is a transmembrane adhesion molecule with a role in inflammatory processes, mediated in part through interactions with hyaluronan. CD44 modulates leukocyte trafficking, promotes resolution of inflammation through removal of dead cells and debris, and regulates fibroblast behavior. We hypothesized that CD44 may be important in post-infarction cardiac repair and left ventricular remodeling by modulating inflammation and fibrous tissue deposition.

Methods: In order to study the role of CD44 signaling on the post-infarction inflammatory response, fibrous tissue deposition, and left ventricular remodeling, we performed reperfusion infarction protocols using wildtype (WT) and CD44 -/- mice. We also examined CD44 expression by isolated mouse cardiac fibroblasts.

Results: WT animals showed marked upregulation of CD44 mRNA expression after 6h of reperfusion. CD44 was expressed on infiltrating leukocytes, and wound myofibroblasts in the infarcted myocardium. CD44 -/- animals showed enhanced expression of pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-6) in the infarcted heart, and increased neutrophil (p<0.05) and macrophage (p<0.05) infiltration during the early stages of reperfusion when compared to their WT littermates. During the proliferative phase of healing, fibroblast infiltration was diminished in CD44 -/- animals (p<0.05) and the amount of collagen in the scar was significantly reduced (p<0.05). CD44 null infarcts exhibited diminished proliferative activity and decreased smad2 phosphorylation suggesting impaired activation of the TGF-beta signaling pathway. In CD44 -/- mice, decreased collagen content was associated with a trend towards enhanced adverse remodeling (LVEDV -/-: 47.5 ± 5.9 vs. WT: 36.6 ± 2.2 mm³, p=0.09), whereas infarct size was similar in both groups. In vitro experiments demonstrated that TNF-alpha and bFGF markedly induced CD44 mRNA synthesis by isolated cardiac fibroblasts.

Conclusions: CD44 critically regulates inflammation and fibrous tissue deposition in healing infarcts. CD44 gene disruption results in enhanced inflammation, possibly through defective clearance of hyaluronan fragments and debris from the infarcted myocardium. In addition, CD44 deficiency decreases fibroblast infiltration in the infarct, probably by decreasing fibroblast proliferation and by disrupting cellular interactions with newly deposited hyaluronan-based matrix. These effects enhance adverse remodeling.

P609 The possible role of oxidative stress caused by uncoupled eNOS in left ventricular remodeling after myocardial infarction in rats

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Reactive oxygen species (ROS) plays an important role in the process of ventricular remodeling. Under oxidative stress, endothelial NO synthase (eNOS) can be converted to a ROS generator, because deprivation of tetrahydrobiopterin (BH4), an essential cofactor for NO synthesis, leads to eNOS uncoupling. The uncoupled eNOS generates superoxide rather than NO. We investigated the possible role of ROS generated by eNOS in ventricular remodeling after myocardial infarction (MI) produced by ligation of the left coronary artery. We treated rats with oral BH4 supplementation (10mg/kg/day started at 3 days before the surgery, MI+BH4 group). At 4 weeks after MI, myocardial ROS generation was increased and BH4 contents in the heart were reduced. BH4 treatment maintained BH4 contents and retarded LV remodeling process compared with MI rats without BH4 treatment (MI group) (LVDd; MI 11.1±0.1 MI+BH4 10.4±0.2 mm, posterior wall thickness; MI 1.65±0.04, MI+BH4 1.37±0.06 mm). Cardiac function was also preserved in MI+BH4 group (LVEDP; MI 19.6±1.0 MI+BH4 12.3±2.4 mmHg, dP/dtmax; MI 4885±305 MI+BH4 7838±559 mmHg/s). The myocyte size in non-infarcted LV was more than 25% smaller in MI+BH4 group compared with those in MI group. Our study suggested that ventricular remodeling process after MI lead to BH4 reduction, which likely resulted in uncoupled eNOS-derived ROS generation. The restoration of eNOS function by BH4 could be a therapeutic target for heart failure.

P610 Mechano-growth factor decreases the area of 'at-risk' tissue post-myocardial infarction and improves cardiac function

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Background: We have previously reported that the E domain of mechano-growth factor (MGF), a splice-variant of insulin-like growth factor -I, increases left ventricular ejection fraction post-myocardial infarction (MI). At present, it is unclear how

MGF acts. In this study we assess 'at-risk' tissue in the peri-infarct zone using a novel method of staining 'at-risk' tissue with Evans blue dye (EBD) and the effects of MGF on this region.

Methods: MI was induced by injecting microspheres (0.6ml of 45mm) directly into the left anterior descending coronary artery of sheep. Animals were randomised to receive 200 mM MGF or sterile saline (controls) 10 min post-MI directly into the coronary artery. Groups (n=8) in each cohort were killed at 0.5 or 8 d post-MI, with an intravenous injection of EBD (2 mg/kg bodyweight of a 2% solution) administered 1.5 hours before death. 'At-risk' tissue was assessed by planimetry and left ventricular function pre-and post MI by echocardiography. Fractional shortening (FS) was used as an assessment of LV contractility.

Results: There was no difference in the percent of 'at-risk' myocardium in MGF-treated sheep compared to controls at 0.5 d. However, at 8 d, the area of 'at-risk' myocardium in the treated group was 35% less than that in controls ($p < 0.001$). In addition, FS was not altered in MGF-treated sheep over eight days, but was reduced in controls at d 1 ($p < 0.05$).

Conclusion: The E domain of MGF appears to preserve cardiac function post MI by a reduction in the area of 'at-risk' myocardium.

P611 Time delay to reperfusion and left ventricular remodeling after successful angioplasty for acute myocardial infarction



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Background: The ability of primary percutaneous coronary intervention (PCI) to salvage ischemic myocardium and to prevent left ventricular (LV) remodeling in patients (pts) with acute myocardial infarction (AMI) presenting late after symptom onset is questioned. Aim: To assess the relationship between time delay to reperfusion and LV remodeling after successful PCI for AMI.

Methods: A series of 430 consecutive pts with AMI successfully treated with primary PCI underwent serial 2D echocardiography from admission to 1 and 6 months, and 6-month angiography. LV volumes, global and regional systolic function were measured. According to the time delay from symptom onset to reperfusion pts were classified into three groups: early reperfusion (<2 hours, group 1: 65 pts), intermediate reperfusion (2-4 hours, group 2: 240 pts), and late reperfusion (≥4 hours, group 3: 125 pts). From baseline to 6-months, an increase >20% in end-diastolic volume index was considered LV remodeling.

Results: At baseline group 3 pts were older ($p = .0008$) and showed a not significant higher infarct size (measured as peak creatine kinase, $p = .314$) compared to the other 2 groups. With similar rate of 6-month restenosis/reocclusion, LV remodeling rate was higher in group 3 pts compared to group 1 and 2 pts (34% vs 22% and 23% respectively, $p = .018$ for both), and a lower recovery of global ($p < .001$) and regional ($p = .003$) systolic function was observed in group 3 pts (ANOVA analysis). A significant correlation was found between time to reperfusion and LV remodeling ($p < .0001$). By stepwise multivariate logistic regression analysis the independent predictors of LV remodeling were regional systolic function (OR 4.74, 95% CI 2.4 to 9.0, $p < .0001$), infarct size (OR 1.4, 95% CI 1.25 to 1.58, $p < .0001$), and LV end diastolic volume (OR 0.97, 95% CI 0.97 to 0.98, $p < .0001$), whereas the time delay from symptom onset to reperfusion was not ($p = .185$).

Conclusions: A higher rate of LV remodeling along with a less recovery of systolic function was observed after late optimal reperfusion in AMI. However, after controlling for enzymatic infarct size and LV function, time delay to reperfusion was not an independent predictor of LV remodeling.

P612 Impact of early mitral regurgitation on left ventricular remodeling after successful primary percutaneous coronary intervention in acute myocardial infarction



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Background: The mechanisms by which mitral regurgitation (MR) may increase mortality after reperfused acute myocardial infarction (AMI) is not yet fully investigated. We sought to test the impact of early MR on left ventricular (LV) remodeling and on global and regional LV function in AMI patients.

Methods and results: A series of 184 patients with AMI successfully treated with primary percutaneous coronary intervention (PCI) underwent serial 2-D echocardiography from admission to 1 and 6 months, and 6-month angiography. On the basis of color Doppler, MR was graded from 0 (none) to 4 (severe). Patients were divided into two groups: those with MR grade ≤1 (group 1, n=146) and those with grade ≥2 (group 2, n=38). The regurgitant volume and the effective regurgitant orifice (ERO) area of MR were significantly higher in group 2 than in group 1 pts (36.7 ± 12.9 mL/beat vs 4.7 ± 3.1 mL/beat, $p < .0001$; 22.5 ± 7.6 mm² vs 5.8 ± 5.6 mm², $p < .0001$, respectively). No significant difference was found between the two groups regarding enzymatic infarct size, baseline angiographic and echocardiographic characteristics, 6-month patency/restenosis in the infarct vessel. LV end diastolic volume (EDV) progressively increased in group 2 and was significantly higher in group 1 at 6 months (113.8 ± 31.8 mL vs 96.8 ± 34 mL, $p = .00002$), with a higher rate of LV remodeling (66% vs 22%, $p < .0001$), and a lower recovery

of LV global ($p = .0002$), and regional systolic function ($p = .0002$). A significant correlation was found between ERO area of MR and baseline to 6-month change of LV EDV ($r = .53$, $p = .0005$). By stepwise multivariate logistic regression analysis including clinical, angiographic, and echocardiographic variables, ERO area of MR was an independent predictor of LV remodeling (OR: 1.16, 95% CI 1.09-1.23; $p < .0001$).

Conclusion: Our data suggest that early MR is an independent predictor of LV remodeling after successful primary PCI in AMI. Furthermore, a lower recovery of LV function over time was observed in pts with higher degree MR, indicating a less compensatory nature of LV remodeling.

P613 Severe cardiac dyssynchrony does not allow viable myocardium to improve left ventricular contractile function after surgical myocardial revascularization



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Background: Dyssynchrony of cardiac contractions is associated with deterioration of left ventricular (LV) contractile function. The aim of the present study was to investigate the relationship between baseline cardiac dyssynchrony and LV functional recovery in patients with ischemic cardiomyopathy and severe cardiac dyssynchrony undergoing surgical myocardial revascularization (CABG).

Methods: The study consisted of 60 consecutive patients with ischemic cardiomyopathy and severe cardiac dyssynchrony (age 65 ± 7 years; 85% males, LV ejection fraction $30 \pm 6\%$) undergoing CABG. Cardiac dyssynchrony was calculated by tissue-Doppler imaging (TDI) from measurements of regional electromechanical coupling times in basal segments of the right and left ventricle (DYS). In healthy individuals, mean value of DYS is 10 ± 8 ms. Significant dyssynchrony (the study inclusion criterion) was defined as $DYS \geq 100$ ms. LV ejection fraction was assessed by echocardiography (biapical Simpsons method) before and 12 months after revascularization.

Results: Mean pre-CABG DYS was 227 ± 86 ms. Thirty-three patients had large extent of viable myocardium (≥ 5 dysfunctional but viable segments) at delayed contrast-enhanced magnetic resonance imaging (16-segment model). At follow-up, twenty out of 33 (61%) patients with viable myocardium showed marked ($\geq 10\%$ units) increase in LV ejection fraction (responders). The pre-CABG DYS value of 220 ms had the highest accuracy (AUC=0.80) to identify responders with sensitivity and specificity of 90% and 77%, respectively (Table 1). Extent of ejection fraction improvement significantly correlated with decrease in DYS between baseline and follow-up ($r = -0.73$, $p < 0.0001$).

Table 1.

	≥10% EF improvement (n=20)	<10% EF change (n=13)
DYS < 220 ms (n=21)	18	3
DYS ≥ 220 ms (n=12)	2	10

Conclusions: Significant baseline dyssynchrony does not allow viable myocardium to improve LV contractile function after CABG. Hence, implantation of biventricular pacemaker during CABG should be considered in patients with ischemic cardiomyopathy and severe cardiac dyssynchrony undergoing CABG.

THROMBOSIS. MECHANISMS AND INFARCTIONS

P614 Monocyte/Macrophages play a critical role in organized thrombi: lessons from the natural history of thrombus formation and aging



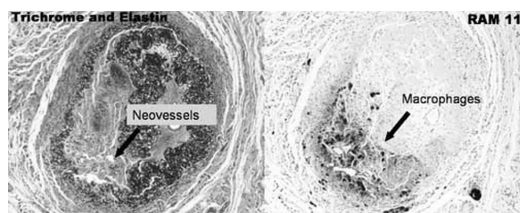
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Background: Arterial thrombosis plays a critical role in clinical manifestation of cardiovascular diseases. Thrombolytic therapy fails in particular in chronic thrombi. A better understanding of thrombus organization through time will provide insights in the pathophysiology of thrombus formation and aging, and therefore will help improve therapy. We sought to investigate the role played by Monocyte/Macrophages in chronic or organized thrombus in an experimental model of carotid thrombosis.

Methods: Carotid artery thrombus was induced by external injury and stasis in 20 rabbits. Two animals were sacrificed at different time points after thrombus induction: Day 1, 2, 3, 4, 6, and week 1, 2, 4, 6, 8. All thrombus components were identified by H&E, CME staining and RAM 11 for macrophages.

Results: Thrombosis was successfully induced in all animals. Acute thrombi (i.e., < 1-week old) were composed of red-blood-cells, platelets and fibrin meshes, associated with an acute inflammatory response of polynuclei. Macrophages started to appear within the thrombus in the four-week old thrombi (Figure). A good correlation was observed between the presence of macrophages and recanalized

neovessels formation within chronic thrombi ($r = 0.82$; $P < 0.01$). Thrombi recanalization appeared to be related to areas of rupture of the internal elastic lamellae.



Conclusion: Macrophages play a critical role in chronic thrombi recanalisation with increased neovascularization in areas of high macrophage density.

P615 The association between factor XIII Val34Leu polymorphism and early myocardial infarction



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Background: Activated factor XIII cross-links between fibrin monomers, thus increases the clot stability and resistance to fibrinolysis. Congenital factor XIII deficiency causes severe bleeding diathesis. Recently, a common polymorphism of the factor XIII A subunit (factor XIII Val34Leu) has been identified as a protective factor against both arterial and venous thrombosis. In this study, we aimed to investigate the role of factor XIII Val34Leu polymorphism in coronary artery thrombosis, especially in young patients. **Patients and Methods:** One hundred and thirty patients younger than 60 years-old with a history of myocardial infarction and 130 healthy control subjects in the same age group were included to our study. Genomic DNA had been extracted from venous blood samples and polymerase chain reaction (PCR) method was used to genotype factor XIII Val34Leu polymorphism. Coronary risk factors such as obesity, diabetes mellitus, hyperlipidemia and smoking were compared between the groups with chi square test and logistic regression analysis.

Results: The allele and genotype frequencies were shown in the table. The Leu allele frequency was significantly lower in patient group compared to control group (7.69% versus 19.23%, $p=0.0001$, x^2). This difference was extremely significant in patients younger than 50 years-old (5.26% versus 19.64%, $p<0.0001$, x^2). In logistic regression model, it was detected that smoking, hypertension and hyperlipidemia were found as independent risk factors while factor XIII Val34Leu polymorphism was a protective factor ($p=0.012$, $OR=0.31$, 95% $CI\ 0.12<OR<0.77$) for myocardial infarction.

Table

	Patient Group (n=130)	Healthy Controls (n=130)
V allele (%)	92.3	80.8
L allele (%)	7.7	19.2
VV genotype (%)	84.6	63.1
VL genotype (%)	15.4	35.4
LL genotype (%)	0	1.5

Allele frequencies and genotype distributions in patient and control group.

Conclusions: Our findings support the hypothesis that VL polymorphism in factor XIII gene has a protective effect against myocardial infarction.

P616 Altered fibrin clot structure in patients with coronary artery disease: a role of C-reactive protein, lipoprotein(a) and homocysteine



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Fibrin clot composed of thin fibers with small pores and the resulting reduced fibrinolysis efficacy is implicated in advanced coronary artery disease (CAD). It has been postulated that apart from genetic polymorphisms of the fibrinogen and factor XIII genes, metabolic factors may affect clot properties. The aim of the study was to evaluate the impact of C-reactive protein [CRP], lipoprotein(a) [Lp(a)] and homocysteine [Hcy] on clot permeability and susceptibility to lysis. We studied 80 male patients with documented stable angina, aged 40 to 65 years. Patients with diabetes, acute infections, renal or hepatic insufficiency were excluded. Thirty healthy age-matched subjects served as controls. Plasma fibrin clot permeability (expressed as Darcy constant, a measure of the pore size) in a pressure-driven system according to Mills et al. and susceptibility to fibrinolysis (expressed as lysis time) in a turbidimetric assay according to Williams et al. were evaluated. Patients with CAD had higher cholesterol, fibrinogen, and CRP levels than healthy subjects. Fibrin clot permeability was reduced by 20% ($p<0.05$) and clot lysis was slower in patients as compared to controls. The median CRP (2.86 vs 1.1 mg/L), Lp(a) (32.3 vs 13.2 mg/L) and total Hcy concentrations (19.1 vs 12.4 μ mol/L) were higher in patients than in healthy subjects ($p<0.05$). CRP showed correlations with permeability and lysis time in controls ($r=-0.56$; $p<0.001$ and $r=-0.53$;

$p=0.002$, respectively) and in patients ($r=-0.64$; $p=0.001$ and $r=-0.49$; $p=0.007$, respectively). Plasma Lp(a) showed associations with clot permeability ($r=-0.67$; $p<0.0001$) and lysis time ($r=0.63$; $p<0.0001$). Similar correlations were noted for plasma total Hcy. In regression analysis after adjusting for confounding factors, including age, fibrinogen, Hcy, and Lp(a), CRP represented an independent predictor of clot permeability ($r=0.52$, $p<0.0001$ and $r=0.46$, $p<0.0001$, respectively) and clot susceptibility to lysis ($r=0.44$, $p=0.002$ and $r=0.48$, $p=0.003$, respectively) in healthy individuals and CAD patients. Our results suggest that adverse effects of CRP, Lp(a) and Hcy in CAD patients might be at least in part attributed to unfavourable alterations in fibrin clot structure. The strongest impact of CRP on fibrin clot properties indicates a novel prothrombotic action of CRP in vivo.

P617 Insulin resistance is a major contributor to thromboxane-dependent platelet activation in obese women



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Purpose: Obesity is associated with persistent platelet activation in otherwise healthy women. We tested the hypothesis that insulin resistance per se contributes to increased platelet activation in this setting.

Methods: We performed a cross-sectional study in 40 obese and 20 non-obese women using urinary thromboxane (TX) metabolite excretion as a non-invasive index of platelet activation. An index of insulin sensitivity, SI, was calculated and plasma adiponectin, C-reactive protein (CRP) and CD40 ligand (CD40L) levels were measured as potential determinants of increased platelet activation.

Results: Obese women had significantly higher 11-dehydro-TXB2 excretion rate ($p<0.0001$), CRP ($p<0.0001$) and CD40L levels ($p<0.0001$) and lower SI ($p<0.002$) and adiponectin ($p<0.01$) than controls. On multiple regression analysis waist-to-hip ratio ($p<0.05$) and SI ($p<0.04$) predicted 11-dehydro-TXB2 excretion, independently of adiponectin, inflammatory and lipid patterns. To investigate the cause-effect relationship of these associations, we examined the effects of a 12-week weight loss program on urinary 11-dehydro-TXB2 in 10 obese women with impaired SI and visceral obesity. Successful weight loss achieved in 5 subjects was associated with an increase in SI (+92%) and a decrease in CD40L (-27%), CRP (-37%) and 11-dehydro-TXB2 (-53%), ($p<0.05$).

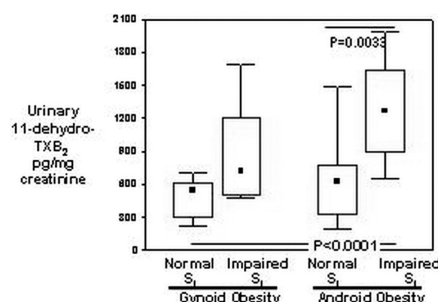


Fig. 1

Conclusions: insulin resistance is a major determinant of platelet activation in female obesity.

P618 Determination of the phosphorylation status of vasodilator-stimulated phosphoprotein: a reliable assay to assess the risk of stent thrombosis



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Background: Several clinical studies revealed a considerable individual variability in platelet responses to the P2Y12 adenosine diphosphate (ADP)-receptor antagonist clopidogrel. Low-response to clopidogrel was suggested to correspond to a higher incidence of stent thrombosis after coronary stent placement. Aim of this prospective study was to assess the capability of two platelet function assays, e.g. direct measurement of the phosphorylation status of vasodilator-stimulated phosphoprotein (VASP) and ADP-induced platelet aggregation, to determine low-response to clopidogrel and the corresponding risk to develop a stent thrombosis.

Methods: 70 patients with a pre-defined high risk to develop stent thrombosis (bifurcation, stent length > 25 mm, poor distal run off) were consecutively enrolled. All patients received a dual antiplatelet therapy consisting of 100-mg ASA and 75-mg clopidogrel during an observation period of 6 months. Blood samples were drawn at day 5-7 after stent placement. Platelet function was monitored by two different assays: flow cytometry phosphorylation of VASP and densitometrically-determined measurement of ADP-induced platelet aggregation. Values for VASP-phosphorylation are reported as platelet reactivity indices defined as mean fluorescence intensity [(MFI_[PGE1] - MFI_[PGE1+ADP]) / MFI_[PGE1]] × 100.

Results: The baseline clinical and procedural characteristics as well as the rate of use of medications were similar between all patients. Eight patients suffered from an angiographically confirmed stent thrombosis (11.4%) during the observation period. In this group, ADP-induced platelet aggregation was higher ($57.5 \pm 17.4\%$) compared to patients without stent thrombosis ($51.7 \pm 14.8\%$), but the difference was not significant ($P=0.3621$). In contrast, the mean PRI in patients with a stent thrombosis was significantly higher ($58.7 \pm 13.5\%$) compared to patients without stent thrombosis ($45.9 \pm 17.6\%$, $P=0.0384$). These data indicate an insufficient inhibition of platelet aggregation by clopidogrel. In consequence, there was only a poor correlation between both methods using non-linear regression analysis ($r^2=0.1786$).

Conclusions: Determination of VASP phosphorylation is superior to conventional platelet aggregatometry for assessing the risk to develop a stent thrombosis. According to prior in vitro data, our data suggest that a PRI between 0.5 and 1 indicates a weak response to clopidogrel. These patients seem to have a significantly increased risk to develop stent thrombosis.

P619 Acute systemic inflammation upregulates endogenous fibrinolysis: a counterbalancing mechanism?

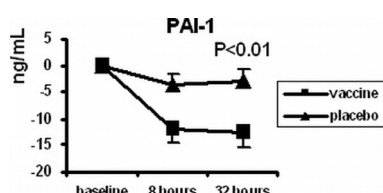


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Purpose: Recent data suggest that acute inflammatory stimuli transiently impair vascular function and can increase the risk of cardiovascular events. The relationship between inflammation and prothrombotic markers such as plasminogen activator-inhibitor-1 (PAI-1) has not been investigated.

Methods: Twenty-six healthy individuals (mean age 36.2 years, 14 men) were studied according to a randomized, double-blind, sham procedure-controlled design. The study consisted of two treatment arms, one with Salmonella Typhi vaccination that produces a mild, systemic, acute and temporary inflammation, and one with sham-vaccination. PAI-1 was measured in venous blood at baseline and at 8 and 32 hours after vaccination.

Results: Differences of PAI-1 from baseline (responses) for each time point are shown in the Figure. Compared with sham-vaccine, Salmonella Typhi vaccination led to a significant decrease in PAI-1 both at 8 and 32 hours (by 8.1 and by 9.5 ng/mL respectively, $P<0.01$ by 2-way repeated-measures ANOVA), indicating an increase in plasma fibrinolytic potential.



Conclusion: Although it is established that acute inflammation transiently augments cardiovascular risk, it may increase the fibrinolytic capacity of young healthy adults, as expressed by the decrease of PAI-1. This may represent an adaptive response, and further research is needed in order to investigate the clinical relevance of this effect and whether this mechanism is activated in individuals with cardiovascular risk factors or disease as well.

P620 Natural history of newly diagnosed patients with venous thromboembolism



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Background: Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a frequent disease with an annual reported incidence ranging from 0.2 to 1.4 per 1000. Objectives: To study the complete clinical spectrum of major venous thromboembolism, to assess the incidence in the general population, to identify risk factors associated with the occurrence of VTE, DVT and PE, and to estimate their magnitude.

Methods: Prospective cohort study with nested case-control analysis using the GPRD. All patients 20-79 years old were followed from 1994 until the first-time recorded diagnosis for PE, DVT, death or 31 December 2000. After manual review of computerized patient profiles, we sent a questionnaire to the GPs in a 5% random sample of DVT/PE patients and the confirmation rate was 95%. Finally 6,550 patients were confirmed and a nested case-control analysis was performed using all of them together with a random sample of 10,000 controls frequency-matched by age, sex and calendar year.

Results: The overall IR of VTE in the cohort was 74.5 per 100,000 person-years increasing markedly with age. Overweight, varicose vein, inflammatory bowel disease (IBD) and cancer were associated with a greater risk of VTE. HF and cerebrovascular diseases were associated with an increased risk of PE but not with DVT. Patients with diabetes were 20% less likely to develop VTE. Fractures were

strongly associated with VTE (20.7;11.8-36.4). Surgery was also a strong predictor of an increased risk of VTE and the increased risk was found with musculoskeletal (13.2;9.7-18.1) and neurosurgery (5.3;1.7-16.0). Results on drug use shown that the OR among users of statins was 0.8 (0.6-1.0). In women the risk of hormone replacement therapy (HRT) associated with VTE was 1.4(1.2-1.6) and the corresponding one in users of oral contraceptives (OC) was 1.9(1.4-2.4). Restricting the analysis to fatal and non fatal cases (one month fatality rate was 1.4% after DVT and 22.6% after PE), HF and cerebrovascular diseases presented a greater relative risk of fatal VTE than non fatal.

Conclusions: Our results confirm the association between DVT and cancer, surgery, fractures, varicose vein and among women with HRT and OC. Also our results suggest that the magnitude of the association of a number of risk factors was different between DVT and PE as well as between fatal and non fatal cases.

RENAL IMPAIRMENT IN CORONARY ARTERY DISEASE

P621 Chronic renal failure is associated with poor coronary collateral development



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The potential of individuals to develop coronary collateral circulation is often neglected but is of potential major importance in myocardial vulnerability. Likewise, the effect of chronic kidney disease (CKD) on collateral vessel development is not known. The purpose of this study was to evaluate the effect of CKD on collateral development in patients with advanced coronary artery disease. A total of 171 uraemic patients (serum creatinine >1.5 mg/dl, creatinine clearance <80 mL/min) who underwent coronary angiography were evaluated in this study. A total of 134 patients met the criteria for uraemic group and 134 consecutive non-uraemic patients who constituted the control group. The collateral score (CS) was graded according to Rentrop classification and the collateral score was calculated by summing the Rentrop numbers of every patient. Collateral vessels have also been categorized according to their anatomic locations and collateral connection grades (CC). CC2 collaterals were observed less frequently in uraemic patients than in control subjects (11% versus 26%, $p=0.03$) and CC0 more frequently (31% versus 22%, $p<0.05$). Epicardial pathway was detected more frequently in control subjects than in uraemic patients (31% versus 12%, $p=0.03$) and septal pathway less frequently (37% versus 54%). There was a significant negative correlation between CS and creatinine ($r=-0.68$, $p<0.01$). The mean CS in the uraemic group was significantly lower than the nonuraemic group (1.29 ± 0.88 versus 2.18 ± 1.3 , $p<0.001$).

These results altogether showed that besides the quantity, quality (functional, haemodynamic and anatomic features) of the uraemic collaterals and a network that they constitute is also impaired and different from the collaterals of the patient with normal renal function.

P622 Renal insufficiency is a stronger independent risk factor than any other known comorbidities for adverse outcome in acute coronary syndromes



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Background: Renal insufficiency has been proven an independent risk factor for death and adverse outcome in patients with acute coronary syndromes (ACS). The measurement of renal function based on creatinine clearance may become additional independent risk factor. The aim of this study was to assess the influence of renal insufficiency along with other known comorbidities in ACS.

Methods: 29 non PCI centres participated in the Registry of Acute Coronary Syndromes. Data on 2471 patients with ACS were gathered. Creatinine clearance (CrCl) was calculated according to the Cockcroft-Gault formula. Impaired renal function was defined as CrCl less than 60 ml/min.

Results: 900 (36%) patients were assigned to group with CrCl <60 ml/min, whereas 1571 to patients had preserved renal function. Patients with impaired renal function were more often older (78 ± 8.7 vs 62.7 ± 10.7 $p=0.001$) and women (59% vs 35% $p<0.0001$) with past medical history of myocardial infarction (39% vs 28% $p<0.001$), diabetes mellitus (29% vs 19% $p<0.001$) and stroke (8% vs 5% $p<0.001$). Patients with CrCl <60 ml/min received less aggressive pharmacotherapy in terms of thienopyridines (31% vs 43% $p<0.05$) and statins (48% vs 80% $p<0.001$). Transfer for invasive treatment to the PCI centre was more frequent in patients with normal renal function (10% vs 18% $p<0.001$). In-hospital mortality for patients remaining for conservative treatment was (8% vs 3% $p<0.001$) in renal insufficiency and normal renal function groups respectively. Logistic regression of multivariate analysis revealed independent risk factors for death: CrCl <60 ml/min OR 4.3 (95%CI 1.3 - 14.3, $p=0.02$); stroke OR 4.8 (95%CI 1.5 - 15.7, $p=0.009$); left ventricular ejection fraction (LVEF) $<40\%$ OR 10.6 (95%CI 3.7 - 30, $p<0.0001$). Combined independent risk factors of decreased LVEF and creatinine clearance increased the risk of death by 46 times (OR 46 95%CI 7.8-270; $p<0.0001$).

Conclusions: Over one third of patients with ACS have impaired renal function on admission. These patients are usually older women with a past medical history of coronary artery disease risk factors. Modern antiplatelet and statin therapy as well as aggressive invasive approach is less frequently used in patients with impaired creatinine clearance. Creatinine clearance is an independent risk factor for death in ACS and a helpful tool for risk stratification.

P623 Effect of individual hemodialysis sessions, coronary artery disease and diabetes on serum cardiac troponin T in unselected chronic renal failure patients over one year



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Introduction: Cardiac Troponin T (cTnT) is a marker of myocardial cell damage and higher cardiovascular risk. It remains a predictor of cardiovascular events even in chronic renal failure. Limited data is available about the short and longer-term effects of hemodialysis sessions, coronary artery disease (CAD), and diabetes on cTnT serum levels.

Hypothesis: We tested the hypothesis that the hemodynamic stress associated with an individual dialysis session would be associated with a short term increase in serum cTnT concentration. We also tested the hypothesis of higher cTnT levels in patients with CAD or diabetes.

Methods: We offered enrollment to all hemodialysis patients at a tertiary hospital. Those who gave consent (107 patients) had blood drawn to measure the serum cTnT levels immediately before and after dialysis three times over one year (0, 6, and 12 months). A third generation test (Troponin T STAT, Roche Diagnostics) was used to measure the cTnT. Patients were interviewed and hospital records were reviewed for clinical data.

Results: Mean age was 58.2 years; 37% had diabetes, and 35% had CAD. We obtained a total of 283 pre-dialysis cTnT and 275 post-dialysis cTnT measurements. The means (standard deviation (SD)) for pre-dialysis cTnT were 0.07 (0.12), 0.06 (0.07), and 0.07 (0.08) mcg/L at 0, 6, and 12 months, respectively. The means (SD) post-dialysis cTnT were 0.06 (0.08), 0.06 (0.07), and 0.07 (0.08) mcg/L. We observed no significant difference between pre and post-dialysis means at time 0 ($p = 0.17$), at 6 months ($p = 0.40$), and at 12 months ($p = 0.50$). Among 274 samples with cTnT measured before and after dialysis, 88 (32%) showed a small decrease (mean -0.04, SD 0.07 mcg/L), 99 (36%) showed a small rise in serum cTnT (mean + 0.02, SD 0.02 mcg/L), and 87 (32%) showed no change in serum cTnT following dialysis, suggesting random variation of pre and post dialysis values. At inclusion, mean cTnT was higher in CAD (0.11 mcg/L) than in non-CAD patients (0.05 mcg/L, $p < 0.05$). This tendency was maintained during the one year follow-up, either before or after dialysis. We observed no significant difference in mean cTnT in patients with or without diabetes.

Conclusions: cTnT levels are not affected by individual hemodialysis sessions, and remain stable around 0.07 mcg/L over a one-year follow-up period in this population. However, random cTnT levels are higher in stable CAD patients undergoing hemodialysis. Therefore, borderline-high cTnT levels (0.05-0.15 mcg/L), documented at any time prior or following a dialysis session, need to be interpreted with caution.

P624 Association of chronic kidney disease with clinical outcomes in mass II trial (medical, angioplasty surgery study): 5 years of follow-up



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Introduction: Chronic kidney disease (CKD) is associated with adverse outcomes after coronary artery bypass graft surgery (CABG) and percutaneous coronary interventions (PCI), but it is unclear which of these revascularization strategies is associated with lower risk for morbidity and mortality in this population. In MASS II trial, we compared long-term clinical outcomes after CABG, PCI or only medical treatment in CKD patients.

Methods: The MASS II trial randomly assigned 611 participants with and without CKD to the three forms of treatment in CAD. We defined minor or equal 60 ml/min estimated by the Cockcroft-Gault equation. The primary outcome was the composite of death, myocardial infarction (MI), or angina requiring revascularization. Participants were followed for a mean of 5 years. We evaluated if randomization to CABG, PCI or medical treatment was associated with different outcomes among participant with CKD.

Results: One hundred fifty five participants (25.4%) had CKD, at entry into MASS II. Fifty three received PCI, forty six CABG and fifty six medical treatments. We observed difference in primary end point and cardiac death among CKD participants ($p = 0.003$ and $p = 0.04$). When we analyzed endpoint primary and death in three forms of treatment in PCI and medical treatment no difference was observed in CKD participants. In the CABG group with CKD we observed more events and death ($p < 0.001$ and $p = 0.001$).

Conclusions: In patients with multivessel CAD and preserved ventricular function and CKD in MASS II we observed more events and death comparing with participants with clearance higher 60ml/min. When we analyze by form of treatment we observed more events and death in CABG group with CKD.

P625 Clinical predictors of significant coronary artery disease and cardiovascular events in patients with end-stage renal disease



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Background: Patients (pt) with end-stage renal disease (ESRD) are at high-risk for major adverse cardiovascular events (MACE), mainly due to coronary artery disease (CAD).

Objective: To identify clinical predictors of significant CAD and MACE in pt with ESRD referred for cardiovascular risk assessment before inclusion on renal transplant waiting lists.

Methods: 329 pt (56±8 years-old, 72% men, 41% with diabetes) with ESRD on dialysis (median=33 months) underwent clinical evaluation and coronary angiography regardless of symptoms or results of non-invasive tests. Significant CAD (S) was defined by luminal reduction ≥70%. Pt were followed-up from 1 to 90 months (median=20 months). Logistic regression and Cox proportional hazards models were used to identify clinical variables significantly associated ($P < 0.05$) with S-CAD and the composite incidence of fatal/non-fatal MACE.

Results: 137 pt (44%) had S-CAD. In the univariate analysis, variables associated with S-CAD were Caucasian ethnicity (OR=2.27, 95%CI=1.32-3.97; $P=0.003$), diabetes (OR=2.70, 95%CI=1.70-4.33; $P<0.0001$), peripheral vascular disease (OR=3.25, 95%CI=1.97-5.42; $P<0.0001$), or previous myocardial infarction (OR=5.38, 95%CI=2.25-15.00; $P<0.0001$). In the multivariate model, the same variables were still significantly associated with S-CAD: Caucasian ethnicity (OR=2.21, 95%CI=1.24-4.05; $P=0.007$), diabetes (OR=1.81, 95%CI=1.06-3.10; $P=0.03$), peripheral vascular disease (OR=2.60, 95%CI=1.48-4.61; $P=0.0009$), or previous myocardial infarction (OR=5.74, 95%CI=2.16-18.18; $P=0.0003$). Age, sex, dyslipidemia, smoking, hypertension, and history of angina, heart failure or stroke were not associated with S-CAD. There were 80 MACE during follow-up. In the univariate analysis, variables significantly associated with fatal/non-fatal MACE were Caucasian ethnicity (RR=1.38, 95%CI=1.04-1.91; $P=0.02$), peripheral vascular disease (RR=1.40, 95%CI=1.11-1.75; $P=0.004$), previous myocardial infarction (RR=1.49, 95%CI=1.09-1.96; $P=0.01$), diabetes (RR=1.51, 95%CI=1.21-1.89; $P=0.0003$), and heart failure (RR=1.68, 95%CI=1.17-2.30; $P=0.007$). In the multivariate model, only diabetes (RR=1.33, 95%CI=1.03-1.72; $P=0.03$) and heart failure (RR=1.63, 95%CI=1.10-2.27; $P=0.02$) were still associated with MACE.

Conclusions: In pt with ESRD referred for cardiovascular risk assessment before inclusion on renal transplant waiting lists, the prevalence of S-CAD is high. Moreover, clinical stratification is a powerful tool to help identify pt at higher risk for S-CAD and MACE, in whom additional workup and aggressive management may be needed.

P626 Acute Coronary Syndromes: Treatment and Outcomes of patients with unknown renal impairment



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Introduction: Serum creatinine is dependent on factors such as age, ethnic origin and body mass. We sought to determine whether patients with impaired renal function, but a normal serum creatinine had a worse outcome than those with normal function. We calculated the creatinine clearance (CrCl) in patients admitted with acute coronary syndromes (ACS).

Methods: This was a prospective observational study of an unselected group of patients admitted over a 1 - year period to a single cardiac tertiary centre with a diagnosis of Acute Coronary Syndrome. All patients had cardiac biomarker evidence of myocardial necrosis. The creatinine clearance was calculated using the admission creatinine and the Modification of Diet in Renal Disease Study Group Formula (MDRD). Comparison was made between patients with no significant renal impairment (Group A, Cr < 120 mg/dl, CrCl > 60 ml/min) and patients with renal impairment but normal SCr (Group B, Cr < 120, CrCl ≤ 59). Survival status, length of hospital stay, in hospital mortality, the proportion receiving coronary angiography and coronary revascularisation was assessed in all groups.

Results: 565 patients with ACS and a serum creatinine less than 120 were admitted over a one year period. The mean follow up was 421 days. There were 438 patients in group A and 131 (23%) in group B. The mean age was significantly different (62.1 ± 12.1 vs 76 ± 9.9 years, respectively).

In hospital death was significantly lower in group A (3%) vs group B (11.5%, $p < 0.01$). Death at follow up was significantly lower in group A (7.8%) vs group B (18.3%, $p < 0.001$). Length of stay did not differ significantly (8.5 ± 8.3 vs 10 ± 10.3 days respectively, $p = ns$).

There was no significant difference in the numbers of patients undergoing coronary angiography (66% vs 61%, $p = ns$). There was no significant difference in the rates of revascularisation. Percutaneous Coronary Revascularisation was undertaken in group A (48%) vs group B (37%, $p = ns$). Coronary artery bypass rates did not differ significantly (7% vs 5%, $p = ns$).

Conclusions: Estimated creatinine clearance detects a large proportion of patients who have undisclosed impaired renal function. Patients with a normal

serum creatinine and renal impairment are older and have a higher mortality than patients with normal renal function, despite similar levels of revascularisation.

P627 Treatment after myocardial infarction in patients with renal insufficiency dependent on diagnostic methods of its recognition



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Background: Patients (pts) with history of myocardial infarction (MI) with renal insufficiency (RI) are at the supreme priority for preventive cardiology. The aim of this study was to determine, in pts after MI with RI, whether the European Society of Cardiology (ESC) recommendations of treatment were being followed in primary care practice.

Methods: Data from representative sample of 1545 general practitioners, on 8972 pts (mean age 63.22 ± 10.3 years; 33.48% women) with history of MI were selected from 31,116 out-patients charts database of POLKARD-SPOK survey. Creatinine clearance was calculated with Cockcroft-Gault (C-G) formula. The incidence of diagnosed RI (based on serum creatinine concentration) was low and estimated at the level of 3.95% pts after MI. Decreased creatinine clearance below 90 ml/min, according to C-G formula, was calculated in 66.36% of pts after MI.

Results: Aspirin was applied on the same level in both groups ($p=NS$). The other drugs such as beta-blockers, ACE inhibitors and statins were prescribed statistically significantly frequently in pts after MI with RI calculated with C-G formula than in pts after MI with RI reported by family doctor (respectively for beta-blockers 77.43% vs 70.42%; $p<0.05$, for ACE inhibitors 75.59% vs 70.99%; $p<0.05$, for statins 81.86% vs 74.08%; $p<0.001$).

Management of MI dependent on RI

Medications	Renal insufficiency		p-level
	Reported by family doctor	Calculated with C-G formula	
Aspirin	81.41%	84.50%	NS
Beta-blockers	70.42%	77.43%	$p<0.05$
ACE inhibitors	70.99%	75.59%	$p<0.05$
Statins	74.08%	81.86%	$p<0.001$

Conclusions: In primary care practice medications with proven efficacy in reducing mortality after MI such as beta-blockers, ACE inhibitors and statins were applied statistically significantly rarely in pts with reported by family doctor RI than in pts with RI calculated with C-G formula.

P628 Five years follow-up of patients aged over 65 years submitted to medical therapy, coronary angioplasty and bypass surgery (MASS I I)



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Introduction: There are many patients aged over 65 years among patients with coronary artery disease. Despite routine use of Coronary Artery Bypass Graft surgery (CABG) and Percutaneous Coronary Intervention (PCI), there is no conclusive evidence, that either one is superior to Medical Therapy (MT) alone for the treatment of multivessel CAD with preserved ventricular function in patients aged over 65 years.

Methods: The primary end point was defined as cardiac mortality, Myocardial Infarction (MI) or refractory angina requiring revascularization in patients aged over 65 years. All data were analyzed to the intention-to-treat principle.

Results: A total of 200 patients were randomly assigned to either a CABG ($n=64$), PCI ($n=68$) or MT ($n=68$). The rates of five-year survival rates were 84.4% for CABG 82.4% for PCI and 82.4% for MT. The rates for five year survival free of events were 76.6% for CABG, 55.9% for PCI and 60.3% for MT ($p=0.034$).

Conclusion: Coronary Artery Bypass Graft (CABG) was associated with a lower incidence of events compared with PCI and MT in elderly patients of MASS I I study. All three therapeutic regimens yielded relatively low rates of cardiac related death.

P629 Cystatin c predicts atherosclerotic burden severity and extent



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Background: Cystatin C, a sensitive marker of renal failure, has been recently proposed as an important predictor of future events in acute coronary syndromes, independently of systemic inflammation assessed by C-reactive protein (CRP). However, mechanisms mediating this prognostic role are unknown. The atherosclerotic burden, necessary substrate for plaque destabilization, might mediate this effect. We wanted to assess the association of cystatin C with severity and extent of coronary atherosclerosis. Furthermore we evaluated if this association is independent of baseline systemic inflammation.

Methods: 70 consecutive ischemic heart disease patients (age 62 ± 12 , male sex 87%) admitted to our Cardiovascular department for stable (17) or unstable (53) angina were included in the present study. All patients underwent coronary angiography which was evaluated by two angiographer assessing disease severity, extent and number of complex or smooth lesions according to Sullivan's scoring system. On admission, cystatin C and CRP serum levels have been assessed. A cut-off value of 1.26 mg/L for cystatin C has been used to identify patients with low or high levels of cystatin C, whereas a cut off of 3 mg/L has been used for CRP. Univariate predictors of disease severity (evaluated by a stenosis score), disease extent (evaluated by an extent score) and disease complexity (evaluated by the number of smooth and complex lesions) were evaluated among risk factors, demographics and laboratory data. Variables showing a p value < 0.1 at univariate analysis were included in the multiple regression model to identify independent predictors.

Results: Independent predictors of disease severity were: diabetes [B (CI) 4.2 (1.06-7.4), $p=0.01$] and cystatin C [B (CI) 5 (1.3-8.7), $p=0.009$]. Independent predictors of disease extent were diabetes [B (CI) 8 (1-15), $p=0.02$] and cystatin C [B (CI) 7 (1-15), $p=0.05$]. Independent predictors of smooth lesions were diabetes [B (CI) 2.5 (1.1-3.8), $p=0.0001$] and cystatin C [B (CI) 2.7 (1.2-4.2), $p=0.001$]. No variable predicted complex lesions. CRP serum levels did not predict disease severity/extent ($p=ns$). No correlation was found between cystatin C and CRP serum levels ($p=ns$).

Conclusion: In this study we demonstrate that cystatin C is a marker of coronary atherosclerosis severity/extent, independently of systemic inflammation, and it is associated with a predominant stable plaque phenotype. The long term prognostic role of cystatin C might be linked to an increase of the atherosclerotic burden, necessary substrate for plaque destabilization.

P630 Incomplete revascularization in diabetic patients with multivessel coronary artery disease- long term follow-up study



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Aim: To evaluate the impact of the completeness of revascularization achieved with angioplasty on the long-term outcome of diabetic patients (pts) with multivessel coronary artery disease (MVD).

Material and methods: Out of 908 consecutive pts treated for MVD with plain balloon angioplasty between 1988 and 1997, one hundred and forty pts with diabetes (75% males, aged 31-80 years) were studied. Pts were followed-up for median 11 years (8-16 years). Complete revascularization (CR) was defined as successful (residual stenosis $<50\%$) angioplasty of all the significant (% diameter stenosis $>70\%$) lesions. Incomplete revascularization (IR) was recognized in case of unsuccessful (residual stenosis $\geq 50\%$) or not attempted angioplasty in any of the significant lesions. Left ventricle (LV) dysfunction was defined as ejection fraction below 40%. Information regarding vital status and cardiovascular events was obtained in 98.5% pts.

Results: The CR was achieved in 86 pts (61%). Pts with CR compared to IR did not differ with regard to majority of clinical and demographic data. However, pts with IR were older (58.8 vs 53.5 years, $p<0.005$), more frequently had family history of coronary artery disease (45.3 vs 27.1% , $p<0.0001$), more often had at least one chronic coronary occlusion (61.1 vs 20.9% , $p<0.0001$) and LV dysfunction (60.4 vs 9.3% , $p<0.0001$). In contrast, there were more smokers in CR-subgroup (59.5 vs 32.1% , $p<0.005$).

Although pts with IR required more re-PTCA (28.4 vs 15.9% , $p<0.05$) and re-hospitalizations during the follow-up period (53.3 vs 32.6% , $p<0.0005$), the completeness of revascularization had no impact on total (16.7% in CR and 24.1% in IR-subgroup, $p=ns$) or cardiovascular mortality (13.1 vs 16.7% respectively, $p=ns$). Furthermore, it did not modify the myocardial infarction prevalence (23.8 in CR vs 34.0% in IR subgroup, $p=ns$).

Conclusions: Incomplete revascularization was associated with higher rate of re-PTCA and re-hospitalization. Interestingly, the completeness of revascularization achieved with angioplasty did not determine the long-term prognosis of diabetic patients treated for multivessel coronary artery disease.

P631 Is diabetes a stronger predictor of recurrent cardiovascular events than the angiographic severity of coronary artery disease?



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Background: Both the presence of diabetes mellitus (DM) and the presence and severity of coronary artery disease (CAD) predict recurrent major adverse cardiovascular events (MACE). We examined the correlation between DM, coronary angiographic findings and the risk of MACE among patients with established CAD.

Methods: We prospectively followed 347 males with CAD undergoing coronary angiography for 4 years. The combined endpoint was the occurrence of MACE, in-

cluding myocardial infarction, unstable angina, stroke, coronary revascularization and death.

Results: DM was the strongest predictor of MACE as judged by the area under the receiver-operator characteristic curve (AU-ROC) (Table). The number of coronary territories involved with hemodynamically significant CAD tended to predict MACE, particularly after adjusting for whether coronary artery bypass surgery (CABG) was needed as a result of the findings on the index angiography. Diabetes remained the strongest predictor of MACE in multivariate models. The best model constructed with multiple angiography-related variables (number of vessels with significant CAD, history of previous CABG, need for CABG or percutaneous coronary intervention from findings during index angiography, and presence left main stenosis) had an AU-ROC of 0.58. This was inferior to the AU-ROC for DM alone (0.60).

Multivariate Predictors of MACE

	Odds Ratio (95%CI)	P value	AU-ROC
Diabetes Mellitus	2.36 (1.49-3.74)	<0.001	0.60
Ejection Fraction (per 10% increase)	0.77 (0.66-0.90)	0.001	0.60
Congestive Heart Failure	2.33 (1.30-4.17)	0.004	0.56
Number of Vessels with significant CAD	1.19 (0.96-1.47)	0.10	0.56
Number of Vessels with significant CAD *	1.24 (0.99-1.55)	0.05	0.57
Peripheral Vascular Disease	2.10 (1.23-3.57)	0.006	0.56
Serum Creatinine (per mg/dL increase)	1.32 (1.02-1.71)	0.03	0.56

* Adjusted for whether CABG was needed as a result of the findings on the index angiography.

Conclusions: DM is a stronger predictor of recurrent MACE than the angiographic severity of CAD. DM is associated with continuous exposure to a pro-atherogenic milieu and extracardiac atherosclerotic disease, explaining its strong ability to predict cardiovascular events beyond the angiographic presence or severity of CAD. Multivariate predictors of MACE

P632 The impact of drug eluting stents on clinical outcomes in renal insufficiency patients undergoing Percutaneous Coronary Intervention



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Background: Chronic renal insufficiency (CRI) is associated with an increased risk of adverse events following coronary revascularization. Coronary artery bypass grafting (CABG) has been shown to result in less target lesion and vessel revascularization (TLR) rates than bare metal stenting (BMS). The effect of newer drug eluting stents (DES) on revascularization rates in renal failure patients is largely unknown.

Methods: In this single center, retrospective study, mortality, TLR and myocardial infarction rates following intracoronary stenting were analyzed in 633 consecutive PCI patients, of whom 158 had baseline CRI, defined as glomerular filtration rate (GFR) < 60 mL/min/1.73 m² as calculated using the Modification of Diet in Renal Disease (MDRD) equation.

Results: Of the 475 patients with normal renal function, 258 received a BMS and 217 received a DES. Of the 158 patients with CRI, 89 received a BMS and 69 received a DES. The mean age was 60.4 years, 64% were male, 18% were black, 69% had hypertension, 65% had a history of tobacco use, 61% had hypercholesterolemia and 69% had diabetes. Among patients with CRI, treatment with DES was associated with a decreased risk of the composite endpoint of death, MI and TLR at 9 months (8.7% vs. 21.4%, $p=0.03$) compared with treatment with a BMS (Relative Risk Reduction (RRR): 0.41, 95% CI: 0.17, 0.96). In comparison, treatment with DES among patients with normal renal function was associated with a RRR of 0.48 (95% CI: 0.27, 0.85) for the same composite endpoint. The use of drug eluting stents was associated with significantly lower TLR rates (1.2% vs. 10.4%, $p<0.001$) but no difference in mortality (1.4 vs. 0.8%, $p=0.52$) or MI (5.1% vs. 5.1%, $p=1.00$) in normal renal function patients compared with a similarly low TLR (0% vs. 11.3%, $p=0.004$), mortality (7.3% vs. 10.1%, $p=0.53$) and MI (2.9 vs. 4.5%, $p=0.62$) rates among CRI patients.

Conclusion: The short-term mortality rate is elevated in patients with CRI who undergo PCI. The use of DES is associated with a significant reduction in TLR but does not reduce the rate of MI or death compared to BMS in patients with and without CRI.

P633 Renal artery stenosis in patients with suspected coronary artery disease



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An increasing body of evidence indicates that renal status is an important factor influencing cardiovascular mortality. Renal artery stenosis (RAS) may contribute to arterial hypertension and the deterioration of renal function. Study aimed to determine the coexistence of coronary artery disease (CAD) or carotid stenosis (CS) with various grade of RAS.

Methods: We performed renal angiography in 659 (433 M) consecutive patients, aged 62.3±9.7 (ranging 25-84) referred to coronary or extracranial angiography.

Results: Significant CAD (at least one stenosis >50% in main coronary branch) was found in 54.7% of patients: 26.5% one-vessel, 13.7% 2-vessel, and 14.4% 3-vessel disease. 16.7% of patients had coronary artery stenosis not exceeding 50% lumen reduction. RAS was found in 33.7% of all patients, including 11.5% bilateral stenosis. The grade of RAS was as follows: RAS < 30% in 17% of patients, between 30-49% in 8.6%, between 50-69% in 5.1%, and RAS exceeding 70% in 3.0% of patients. RAS frequency increased with number of stenosed coronary arteries, accounting for 25.4% in non-significant CAD, 35.4% in 1-vessel, 40.2% in 2 vessel and 54.5% in 3-vessel CAD ($p<0.001$). RAS was similarly often observed in men and women (34.4% vs. 32.4%; $p=0.608$). Prevalence of RAS in patients with confirmed significant CAD was 42.1%, as compared to 22.5% in patients without significant coronary lesions ($p<0.001$). Similarly, frequency of any RAS was higher in patients with hypertension as compared to non-hypertensive ones (36.7% vs. 18.5%; $p=0.001$). The positive correlation between presence of any RAS and age was found ($r=0.160$, $p<0.001$). The multiple regression analysis revealed that independent predictors of RAS were advancing CAD ($p<0.001$), hypertension ($p=0.007$), age ($p=0.009$), creatinine level ($p=0.034$), and diabetes ($p=0.102$).

Conclusions: RAS is a frequent finding in patients with CAD. The frequency of RAS is strongly dependent on the number of stenosed coronary arteries accounting for 54% in patients with 3-vessel CAD. Independent predictors of RAS appeared advancing CAD, arterial hypertension, age and serum creatinine level.

P634 The influence of different types of renal dysfunction on survival in diabetic patients with acute myocardial infarction



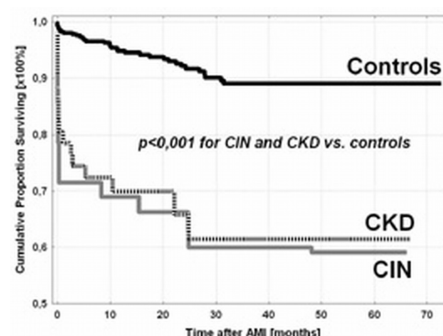
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Background: Impaired renal function (IRF) and diabetes mellitus (DM) are associated with poor prognosis in patients (pts) with coronary artery disease.

The aim of the study: to determine impact of different types of IRF on remote outcome in DM-pts with acute myocardial infarction (AMI), who underwent percutaneous coronary intervention (PCI).

Methods: Prospective single-center study evaluated 2172 consecutive AMI-pts admitted between 2000-2005 and treated with urgent PCI. Among 658 (30.3%) DM-pts two groups of IRF were selected: contrast induced nephropathy (CIN; $n=58$), defined as a serum creatinine (SCr) < 133 $\mu\text{mol/L}$ on admission and its 25% increase, with value > 133 $\mu\text{mol/L}$ within 24-48 hours after PCI and chronic kidney disease (CKD; $n=61$) identified when SCr on admission was above 133 $\mu\text{mol/L}$. 50 IRF-pts were excluded from analysis because they did not match criteria for CIN or CKD and had other forms of IRF. Control group encompassed 489 DM-pts without IRF. Cumulative survival during mean 28 months follow-up was compared using log-rank tests. Independent predictors of death were identified with multivariate Cox regression.

Results: Both CIN and CKD pts were older, more likely to have cardiogenic shock on admission, lower ejection fraction and glomerular filtration rate, longer duration of stenocardia, compared to controls. Remote mortality in CIN pts (51.7%) and in CKD (42.6%) was higher than in controls (11.2%; both $p<0.001$). When incorporating the significant parameters into multivariate analysis, CIN but not CKD was shown to be an independent predictor for death in DM-pts (HR 2.75; 95% CI 2.38 - 3.12; $p<0.05$).



Impact of CIN and CKD on DM-pts Survival

Conclusions: CIN and CKD are associated with excessive mortality in DM-pts after AMI treated with PCI, but only CIN is an independent risk factor of death in this population.

PERCUTANEOUS CORONARY INTERVENTION. COMPLICATIONS

P635 Activated clotting time measurements during percutaneous coronary interventions in clinical practice. Results of the ALKK PCI registry

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Background: Measurement of the activated clotting time (ACT) allows an individualized antithrombotic therapy during percutaneous coronary interventions (PCI) if unfractionated heparin (UFH) is used. However ACT measurement is not routinely used in large parts of Europe.

Methods: We analysed the data from the German ALKK PCI registry of the year 2003.

Results: In 2003 30877 PCI were performed at 78 hospitals. Out of them, 23540 (76.2%) PCI were done with UFH. Out of these interventions 3949 (16.8%) were done with ACT controls, with a range in the use of ACT measurements at the participating hospitals of 0% to 99% (Median 4.4%, Quartiles: 1-21%). Patient characteristics as well as clinical event rates in patients with and without ACT measurements are given in the table.

ACT measurement during PCI with UFH was no independent predictor of death/myocardial infarction or stroke during hospital stay: OR = 1.01, 95%CI: 0.79 - 1.29; p= 0.96.

	ACTn=3949 (100%)	no ACTn=19591 (100%)	p-value
Age (years, Median)	67	67	ns
Men	72.1%	72.7%	ns
Diabetes mellitus	18.8%	18.3%	ns
Renal insufficiency	9.9%	8.7%	0.018
Indication = STEMI	33.3%	22.5%	<0.001
Cardiogenic shock	4.1%	2.4%	<0.001
3-vessel disease	30.4%	29.7%	ns
IIb/IIIa antagonist	47%	29.9%	<0.001
Fluoroscopy time (minutes)	7.0	5.7	<0.001
Death	1.8%	1.4%	0.045
Non-fatal myocardial infarction	0.7%	0.6%	ns
Death/myocardial infarction/stroke	2.9%	2.3%	0.040

Conclusions: In clinical practice in Germany only 16.8% of PCI with UFH were done under controls of the ACT. The range in the use of ACT measurements at the hospitals was 0-99%. We found no differences in clinical event rates whether PCI were performed with or without ACT controls (p=ns).

P636 Incidence and clinical outcome of iatrogenic femoral arteriovenous fistulas and pseudoaneurysms-results from the prospective bad berka registry

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Background: Arteriovenous fistulas (AVF) and arterial pseudoaneurysms (AP) are potentially harmful complications of diagnostic and interventional cardiac catheterization. Incidence, risk factors and clinical outcome are not well defined yet, although important for stratification and treatment.

Methods: A total of 18165 consecutive Patients (P) undergoing cardiac catheterization were enrolled in our prospective registry. For the diagnosis of AVF and AP a clinical examination and a Duplex scan were performed in every patient. The impact of the following risk factors were assessed: body-mass-index (BMI), puncture of left vs right groin, gender, hypertension (HT), sheath size, peripheral artery disease (PAD), glycoprotein IIb/IIIa-inhibitor, and emergency procedure (EP).

Age	63 ± 9.3 (23-90)
BMI	26 ± 5.5 (18.5-39)
HT	45%
GPIIb/IIIa	6%
PAD	8%
EP	13%

Results: Within 3 years a total of 332 complications were found (1.83%). The incidence of AVF and AP was 0.59% (n=107) and 1.24% (n=225), respectively. The majority of procedures were diagnostic (n=13624=75%) with sheath size <6 French (F). 4541 coronary interventions were performed, with sheath size >5 F <9 F. 157 AP (69.8%) were successfully treated by ultrasound-guided manual compression with a mean compression time of 24.5 ± 14 min (range 5 to 90 min). 36 AP (16%) were closed by thrombin injection, 32 AP (14.2%) had to be operated, 4 of them because of failed compression or thrombin injection. 1 P died after surgery (0.4%). 10 AVF (9.4%) had to be operated, 5 AVF (4.7%) closed spontaneously and 92 AVF (86.9%) were managed conservatively. None of the prespecified risk factors showed a significant influence on the incidence of AVF/AP.

Conclusion: Almost 2% of patients undergoing cardiac catheterization acquire femoral AVF or AP, for which patient- or procedure-related risk factors could not

be identified. Most of them could be managed conservatively or without any treatment. The overall mortality of iatrogenic AVF/AP is low.

P637 Detection of coronary microembolization by Doppler ultrasound in patients with stable angina pectoris undergoing elective percutaneous coronary interventions

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Background: Intracoronary Doppler guide wires can be used for real time detection and quantification of microembolism during percutaneous coronary interventions (PCI). We investigated, whether the frequency of Doppler-detected microembolism is related to periprocedural non ST-elevation myocardial infarctions (NSTEMI) during elective PCI.

Methods: The study population included 42 consecutive patients (age 62 ± 10 years; 31 men, 11 women) with coronary artery disease who underwent elective PCI of a single vessel stenosis, including intracoronary Doppler flow analysis during PCI. Creatine kinase (CK), CK-MB, Troponin I (cTNI), and high sensitivity C-reactive protein (CRP) were analyzed before and after PCI. The cTNI threshold of at least one value exceeding the 99th percentile of the lower limit of detection (0.04 ng/mL) in a reference population was used to determinate periprocedural NSTEMI. Using intracoronary Doppler ultrasound, we compared the frequency of microembolism during PCI in the two groups: 19 patients with periprocedural NSTEMI and 23 patients without periprocedural NSTEMI. The two groups were comparable regarding their clinical and procedural characteristics.

Results: In the group with NSTEMI the total number of coronary microemboli (26 ± 10 vs. 18 ± 8, P=0.011) and high sensitivity CRP plasma levels after PCI (18.3 ± 15.1 vs. 7.3 ± 5.3, P=0.025) were significantly higher than in the group without NSTEMI. There was a significant correlation (r=0.562, P<0.001) between the number of coronary microemboli and postprocedural cTNI elevation. In the logistic regression analysis to determine predictors of coronary microembolization, we included postprocedural CK, CK-MB, and cTNI as parameters. Microembolic count was the only independent predictor of postprocedural cTNI elevation (19.415 [9.396 to 29.434], P<0.001). By receiver operating characteristics curve analysis (AUC 0.714 [0.533-0.874], P=0.018), a number of 20 microemboli was identified as the best discriminating value between positive and negative postprocedural cTNI status. Thus, for a number of more than 20 microemboli, the sensitivity, specificity, positive predictive value, and negative predictive value for a positive cTNI test result were 63%, 65%, 60% and 68%, respectively.

Conclusions: Patients with periprocedural NSTEMI had a significantly higher frequency of coronary microembolization during PCI. The inflammatory response after PCI was more pronounced. Intracoronary Doppler ultrasound can be useful to identify patients at risk for NSTEMI while undergoing elective PCI.

P638 Is the radial route relevant for 5 French percutaneous coronary interventions with abciximab in patients with acute myocardial infarction: lessons from the randomised FARMi trial

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Purpose: Aggressive anticoagulation with Gp IIb/IIIa antagonists during percutaneous coronary interventions (PCI) for acute myocardial infarction (AMI) are related to increased peripheral arterial complication rates. PCI through the radial route allows to reduce both peripheral arterial complications. The FARMi prospective randomized trial (Five French Arterial access with Reopro in Myocardial Infarction) was designed to compare bleeding complications and results of PCI in patients with AMI, treated with stent and abciximab, through a radial versus a femoral approach using 5 Fr guiding-catheters.

Methods and results: Among a total of 170 patients with AMI within 12 hours of onset, 117 were considered as eligible and prospectively randomized (rescue PCI: n=44 (37.6%) due to a fibrinolysis failure). Exclusion criteria were as follows: history of CABG, cardiogenic shock, atrio-ventricular block, contra-indication to abciximab, or negative Allen's test. Local haemostasis was achieved by manual compression. Baseline characteristics were similar between both groups. A cross-over was more frequently necessary in the radial group as compared to the femoral group (n=7[12%] vs n=1[2%]; p<0.05, respectively). The coronary angiography duration and fluoroscopy time were significantly longer in the radial group (table 1), whereas PCI duration was similar between both (28±15 vs 27±18 min; p=ns, respectively). Peripheral arterial complication rates and pa-

Table 1

	radialn=58	femoraln=59	p
Coronary angiography duration (min)	17±8	13±6	<0.005
Fluoroscopy time (min)	13±9	8±6	<0.005
Peripheral arterial complication (%)	8(14%)	20(34%)	0.014
Delay of ambulation (hours)	22±9	42±27	<0.0001

Value are expressed as mean ± SD

tient ambulation were significantly lower in the radial group (table 1), whereas in-hospital duration was similar between both groups (7.1 ± 3 vs 7.5 ± 3 ; $p=ns$, respectively). Moreover, there were no significant differences in creatine and haemoglobin changes and other parameters were similar between both groups. **Conclusion:** In the FARM trial, the radial route was associated with lower peripheral arterial complication rate and earlier ambulation without benefit on the duration of hospitalization, and was associated with a significant increase in fluoroscopy time.

P639 No difference in outcome of PTCA in hospitals with and without on-site cardiac surgery backup up to one year after the procedure



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Background: The requirement of on-site surgical back-up is a debated issue since the beginning of percutaneous transluminal coronary angioplasty (PTCA).

Patients and methods: The data of Swedish Coronary Angiography and Angioplasty Registry (SCAAR) have been used to investigate the differences in outcome between hospitals with (SB) and without (NOSB) on-site surgical standby. SCAAR consists of all patients from all centers performing coronary angiography and PTCA in Sweden. Vital status of the patients could be followed combining SCAAR and the Swedish National Population Register.

Results: The analysis included a total of 34363 procedures between January 2000 and December 2003. 8838 procedures were done in NOSB hospitals, 25525 in SB hospitals. The mean age of the patients was 64.1 (SB) and 64.5 years (NOSB; $p=0.002$). More patients in NOSB hospitals had diabetes (17.8% versus 16.8%; $p=0.03$). Other clinical characteristics (previous infarct, previous CABG) showed no significant differences between hospitals. However, there was a higher percentage of patients with STEMI (18.0% versus 9.7%; $p<0.001$) in SB hospitals. The unadjusted 30-day outcome data showed the following differences (SB versus NOSB; p -value): death 2.2% vs. 1.4%; <0.001 , emergency CABG 0.2% vs. 0.1%; $=0.02$, neurologic complication 0.2 vs. 0.3%; 0.16. After adjustment for differences in baseline characteristics was no difference found regarding major outcome data (emergency CABG after PTCA, neurologic complications, 30-day mortality, and 1-year mortality). Some results of the logistic regression analysis of 30-day mortality are shown in the table.

30-day mortality, multivariate analysis

Patient group	Odds ratio and 95% CI	p
Age	1.053	<0.001
No diabetes vs diabetes	0.56	<0.001
Stable angina vs ACS	0.53	<0.001
Previous infarct vs no infarct	1.25	<0.001
NOSB vs SB	0.84	0.18

Conclusion: On the basis of these data it does not seem warranted to recommend against PTCA in hospitals without on-site cardiac surgery backup.

P640 Femoral approach as a major risk factor for bleeding complications after percutaneous coronary procedures. Insights from a database consisting of 3265 coronary angiographies and interventions

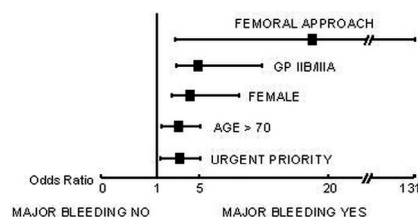


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Bleeding complications after percutaneous coronary procedures are major outcome predictors. As the majority of these bleedings are puncture related, one of the most effective bleeding prevention strategies was shown to be transradial approach (TRA) as opposed to femoral approach (FA). However no large study assessed arterial approach as a predictor of bleeding, yet.

To assess the predictors of bleedings we analysed a prospective database on 3265 consecutive procedures performed in acute and stable patients from May 2003 to September 2004 in our high volume centre by experienced TRA and FA interventionalists. Major puncture-related bleedings were defined as causing: retroperitoneal hematoma and/or death and/or surgical intervention and/or need of any blood transfusion and/or a fall in haemoglobin concentration >4 g/dl and/or local painful hematoma involving $>50\%$ of the surface of limb at visual inspection with prolonged hospital stay. Minor puncture-related bleedings were all the remaining local bleedings.

Overall, 1703 (52%) procedures were performed with TRA. Major bleedings



occurred in 2.5% patients undergoing FA and in 0.06% undergoing TRA ($p=0.00001$). Multivariate analysis results are shown in the figure. The incidence of minor bleedings was also significantly lower in patients with TRA as compared to FA [19/299 (6.3%) vs. 239/603 (40%) respectively, $p<0.0001$].

These "real world" results from the largest published outcome dataset for TRA suggest that FA is the strongest independent predictor of access-site major bleedings and therefore routine TRA, carrying significant outcome benefits, could be the preferred arterial access especially in high risk populations such as in women, in urgent procedures, when GP IIb/IIIa inhibitors are likely to be required and in older patients.

P641 Safety of percutaneous coronary intervention during anticoagulant treatment



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Many centres have a policy to interrupt anticoagulation in patients undergoing percutaneous coronary intervention (PCI), since anticoagulation is assumed to increase bleeding complications. The bridging therapy with heparin is feasible, but may prolong hospitalization and cause extra inconvenience.

Methods and Results: In this study we retrospectively analysed consecutive patients ($N=100$, 76 men, mean age 71 years) on warfarin therapy referred for PCI in two centres: one using mainly femoral and the other radial access site. Warfarin was continued throughout the hospitalization in all but 14 patients with a 1-2 days pause in therapy due to high INR values. In each centre, an age- and sex-matched control group with similar disease (unstable/or stable symptoms) was collected from the same study period. The mean INR value on the procedure day was 2.4 ranging from 1.4 to 4.0. There were 10 access site complications in the anticoagulated patients (mean INR 2.63, range 1.8-3.3) and 7 in the control group. All complications occurred when using femoral access, and a compression device (Femostop[®]; $N=12$) or a closure device (Angioseal[®]; $N=5$). Hospitalization after PCI was longer in warfarin group (4.6 vs. 2.4 days, $p<0.001$).

	Warfarin (n = 100)	Control (n = 100)	P
Radial Approach, %	33	44	ns
Acute Coronary Syndrome, %	57	72	0.027
Aspirin, %	63	95	<0.001
Clopidogrel, %	56	97	<0.001
LMWH, %	64	76	ns
GP IIb/IIIa blocker, %	12	21	ns
Manual compression, %	30	44	ns
Closure device, %	21	14	ns
Compression device, %	49	42	ns
Complication			
Pseudoaneurysm, %	1	1	ns
Bleeding, %	5	4	ns
Haematoma, %	4	2	ns

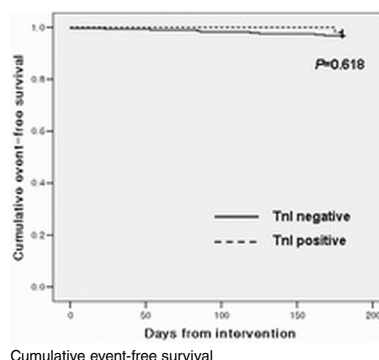
Conclusions: Our study shows that PCI is a safe procedure during uninterrupted anticoagulation with no excess bleeding complications. Radial approach seems to lead to less bleeding complications irrespective of anticoagulation status.

P642 Elevated troponin-I after implantation of drug-eluting stent: Incidence, predictors and prognostic value



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Purpose: Serum troponins are sensitive markers of cardiac myonecrosis and ischemia. Elevated troponin after percutaneous coronary intervention (PCI) is considered to reflect irreversible myocardial injury. However, its prognostic value remains unclear. Drug-eluting stents (DES) can be implanted into multiple long lesions, which was not possible in the era of bare metal stents. The purpose of this study was to investigate the incidence, risk factors, and clinical outcomes of troponin-I (TnI) elevation after the implantation of DES.



Methods: We performed a retrospective analysis of 518 patients who had undergone coronary stenting over an 18-month period at a single center. All patients who had received DES were enrolled. Patients who had acute coronary syndrome with elevated TnI levels before PCI were excluded. Finally, 335 patients were analyzed. TnI levels were measured 4-6 h after PCI and the next morning.

Results: Baseline characteristics were similar in the elevated TnI and normal TnI groups. Elevated postprocedural TnI (> 1.5 ng/mL) occurred in 52 patients (15.5%). Univariate analysis revealed that the clinically significant variables were total stent length ($P = 0.001$), stent number ($P = 0.002$), side-branch occlusion ($P < 0.001$), and bifurcation lesion ($P = 0.003$). Multivariate analysis indicated that the independent predictors of elevated TnI after DES implantation were side-branch occlusion ($P < 0.001$) and bifurcation ($P = 0.013$). There were no significant differences in adverse cardiac events between the elevated TnI and normal TnI groups ($P = 0.618$).

Conclusion: Side-branch occlusion and bifurcation were independent predictors of elevated TnI after DES implantation. Elevated TnI after successful PCI with DES was not associated with worse 6-month clinical outcomes.

P643 Relationship of C-reactive protein to adverse cardiovascular events in patients treated by PCI for stable angina pectoris (Multicentre Trial)



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Purpose: Low-grade inflammation as detected by increased C-reactive protein (CRP) levels predicts the risk of cardiovascular events. However, there is still controversy over the mid-term predictive value of CRP in patients referred for elective percutaneous coronary revascularization (PCI) for stable angina pectoris. The aim of this study is to assess the relationship between baseline CRP level and mid-term outcome of patients undergoing PCI.

Methods: Two groups of patients with stable angina pectoris were prospectively studied. Group A consisted of 150 consecutive patients with a CRP level < 3 mg/L, and group B consisted of 150 consecutive patients with a CRP level > 3 mg/L undergoing PCI at our institutions.

Results: Comparing both groups of patients, the analysis confirmed a significant difference between medians of the CRP levels (0.5 versus 8 mg/mL; $P < 0.001$). A higher level of CRP in group B was associated with a lower presence of male gender ($P < 0.05$) and history of myocardial infarction ($P < 0.05$). On the other hand, in group B there was higher occurrence of smoking ($P < 0.001$), hypertension ($P < 0.05$), hypertriglyceridemia ($P < 0.001$), and diabetes mellitus ($P < 0.01$). The incidence of myocardial infarction based on post-interventional release of TnI > 1.5 ng/mL reached 12% in group A and 14% in group B ($P = 0.73$). Analyses were repeated with adjustment for significant baseline variables, which did not change the current study findings. The incidence of adverse cardiovascular events during a six month follow-up was 13% in both groups (NS).

Conclusions: Increased CRP serum prior to PCI was not associated with the risk and extent of procedure-related myocardial injury measured by TnI release and does not portend heightened cardiovascular risk at six months after percutaneous revascularization. On the other hand, a CRP level > 3 mg/L was associated with a higher occurrence of cardiovascular risk factors (smoking, hypertension, hypertriglyceridemia, and diabetes mellitus).

P644 Prospective randomized study of sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy



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Background: Contrast-induced nephropathy remains an important complication of percutaneous coronary interventions. Recently, hydration with sodium bicarbonate was found to be significantly more protective than hydration with sodium chloride in humans. However, further studies are required to establish the consistency of sodium bicarbonate in reducing the incidence of contrast-induced nephropathy. It is also possible that pretreatment with sodium bicarbonate may offer better protection than combination of N-acetylcysteine with sodium chloride. Objective: To compare the efficacy of sodium bicarbonate in preventing radiocontrast-induced nephropathy in patients undergoing cardiovascular procedures, with two other prophylactic regimens, combination of N-acetylcysteine plus sodium chloride and sodium chloride alone. Methods: We prospectively enrolled 216 patients who were scheduled for cardiovascular procedures and had a baseline creatinine > 1.2 mg/dL. The patients were randomly assigned to receive either 154 mEq/L of sodium bicarbonate (Group 1) ($n=72$), or 154 mEq/L of sodium chloride (Group 2) ($n=72$), or 154 mEq/L of sodium chloride plus N-acetylcysteine (Group 3) ($n=72$). All patients received same dose of fluid (1 ml/kg per hour for 6 hours before and 6 hours after the procedure). Patients in combination arm, also received N-acetylcysteine orally (600 mg twice daily) starting the day before the procedure and continuing through the day of the procedure. All patients received low-osmolality ionic contrast (Ioxaglate). Contrast-induced nephropathy was defined as an increase in serum creatinine of $> 25\%$ or 0.5 mg/dL after 48 hours. Results: There were no significant group differences in age, sex, baseline

serum creatinine, creatinine clearance, hematocrit, incidence of diabetes, systolic heart failure, coronary artery disease and contrast volume. The incidence of contrast-induced nephropathy was 13.9% ($n=10$) in the sodium chloride alone group, 9.7% ($n=7$) in N-acetylcysteine plus sodium chloride group and 4.2% ($n=3$) in sodium bicarbonate group ($p = 0.13$). Hydration with sodium bicarbonate was significantly effective than hydration with sodium chloride alone for prophylaxis of contrast-induced nephropathy when compared in each other (Group 1 vs Group 2) ($p = 0.04$). Conclusion: Hydration with sodium bicarbonate provides better protection against contrast-induced nephropathy than sodium chloride infusion does alone. But it did not offer additional benefit over combination therapy of N-acetylcysteine plus hydration with sodium chloride.

P645 Renal insufficiency following contrast MEDIA administration trial (REMEDIAL): a randomized comparison of three preventive strategies



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Background: Optimal hydration by saline infusion associated to N-acetylcysteine administration represents an effective strategy to prevent contrast agent associated nephrotoxicity (CAN). Preliminary data support that sodium bicarbonate and ascorbic acid may be effective in preventing CAN.

Methods: Two-hundred and twenty-nine consecutive patients with chronic renal insufficiency (serum creatinine ≥ 2.0 mg/dL and/or creatinine clearance ≤ 40 ml/min), referred to our institution for coronary and/or peripheral procedures, were randomly assigned to receive prophylactic administration of 0.9% saline intravenously and NAC (1200 mg orally twice daily) (Control group; $n=77$), prophylactic administration of 0.9% saline intravenously associated to NAC (1200 mg orally twice daily) and ascorbic acid (Ascorbic Acid group; $n=76$); or sodium bicarbonate administration plus NAC (Bicarbonate group; $n=76$). In all cases the iodixanol (an iso-osmolality, non ionic contrast agent) was administered.

Results: Baseline creatinine levels were similar in the 3 groups (2.2 ± 0.5 mg/dL, 2.1 ± 0.5 mg/dL, and 2.3 ± 0.9 mg/dL, respectively; $p=0.10$). Amount of contrast media administration was similar in the 3 groups (181 ± 94 ml; 169 ± 101 ml and 176 ± 94 , respectively; $p=0.36$). Rate of diabetes mellitus was similar in the 3 groups (56.5%, 59.5% and 53%, respectively; $p=0.65$). Increase $\geq 25\%$ of the creatinine concentration 48 hours after the procedure occurred in 8/77 patients (10.4%) in the Control group, 8/76 patients (10.5%) in the Ascorbic acid group, and in 1/76 (1.3%) in the Bicarbonate group ($p=0.046$). There was a significant difference in serum creatinine concentration 48 h after contrast media administration between the 3 treatment strategies even when including the baseline serum creatinine level as covariate ($F=2.7$; $p<0.05$ by ANCOVA model).

Conclusions: Administration of sodium bicarbonate associated to NAC seems to be superior to alternative prophylactic strategies in preventing CAN in patients with chronic renal insufficiency.

P646 Side branch protection by jailed wires: a feasible approach to prevent the occurrence of peri-procedural myocardial infarction



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Percutaneous treatment of diffusely diseased coronary arteries with stent implantation may be associated with inadvertent closure of small (< 2 mm) side branches (SB), leading to peri-procedural myocardial infarction (MI). While the SB, due to its size, may not require direct intervention, its patency, which may be preserved by guide wire placement, is critical to the success of the procedure.

Methods: We prospectively included all consecutive patients undergoing high pressure stenting of a coronary segment from which one or more SB originate. The SB are systematically protected by guide wires, kept in place till the end of the procedure; following successful high pressure stenting of the main branch (MB) the jailed wires are removed without specific attempts to recross with another wire and perform SB balloon dilatation. The efficacy of this novel approach is being assessed by the acute angiographic success (SB patency) and the clinical outcome (peri-procedural MI).

Results: Our study cohort consisted of 30 patients with 33 lesions: 15 in the left anterior descending artery, 15 in the right coronary artery and 3 in the left circumflex artery. An average of 1.31 ± 0.53 stents per patient and 1.18 ± 0.39 stents per lesion were implanted in the MB (21 sirolimus, 16 paclitaxel-eluting and 3 bare metal stents). The mean total stent length was 31.9 ± 13.4 mm and the mean inflation pressure 17.2 ± 4.6 atm. Seven patients (23.3%) received IIb/IIIa inhibitors.

Table 1. Procedural data of the present study in comparison with the TAXUS V Multiple Stents

	SB protection	TAXUS V ² Multiple Stents
MI	3.3%	21%
Mean stent length (mm)	31.9 ± 13.3	43.6 ± 10.5
RVD pre (mm)	2.72 ± 0.58	2.65 ± 0.55

Angiographic success was achieved in all cases. There was only 1 case (3.3%) of in-hospital non-Q wave MI, following successful implantation of 7 stents. There were no instances of SB closure following jailed wires removal, nor need of SB recrossing. Relevant procedural data are summarized in Table 1.

Conclusions: The maintenance of SB patency by jailed wires during high pressure stent implantation in the MB is a feasible and safe approach. The preservation of even small SB patency may prevent the occurrence of peri-procedural MI.

P647 Stroke complicating contemporary primary percutaneous coronary interventions: patient characteristics and clinical implications



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Background: Stroke complicating percutaneous coronary interventions (PCI) is a devastating complication occurs in ~0.38% of procedures. The incidence, however, among patients who undergo primary PCI for acute ST elevation myocardial infarction (STEMI), has not been fully elucidated.

Methods: We studied the clinical characteristics and outcomes of 11 consecutive patients (1.3%) who sustained PCI related strokes out of 831 patients who underwent primary PCI for STEMI between 1.2000 and 6.2005. Patients undergoing emergent coronary bypass graft surgery following the intervention were excluded. The diagnosis of stroke was made by experienced neurologists and required evidence of sudden or rapid onset of new focal neurological signs considered to be vascular in origin.

Results: There were 7 males and 4 females with a mean age of 66 ± 9 years; all experienced thromboembolic stroke. None of the strokes were in patients who underwent rescue angioplasty or an intervention to a vein graft. Patients who experienced stroke had relatively high rate of diabetes ($n=6$, 55%), chronic renal failure (3, 27%) and history of prior stroke (2, 18%). Time from onset of chest pains to admission was extended (6.8 ± 8.4 hours) and 5 patients were admitted in Killip I, 3 in Killip 2-3 and 3 in Killip 4. Intraaortic balloon pump was used in 5 (55%) patients and IIb/IIIa was administered in 5 cases (55%). Final TIMI grade flow III was achieved only in 8 (73%) patients. Mortality rate was significantly higher in patients who experienced stroke at 30-day (27% vs 6.5%, $p=0.03$) and at 6-month follow-up (27% vs. 9.5%, $p=0.05$).

Conclusions: Stroke complicating primary PCI for STEMI is 3 times more frequent than reported rates for non-primary PCIs, occurs in patients who have high risk baseline profile and suboptimal intervention results and is associated with higher short and intermediate-term mortality rates.

P648 Incidence and treatment of left main coronary artery dissection in the modern era



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Background: Catheter-induced left main coronary artery (LM) dissection is an uncommon but life-threatening complication of selective coronary angiography and angioplasty. Emergency stenting is considered today as a gold standard but remains controversial. The use of drug-eluting stents (DES) in this setting has not been previously assessed. Objectives: To examine the incidence, clinical and angiographic features, management strategy and the outcome of LM iatrogenic dissection in a single high volume centre over a 28 months period in the era of DES.

Methods: Coronary procedures performed in our institution between May 2003 and August 2005 were reviewed, 5566 were diagnostic studies and 3179 PCI. Transradial approach (TRA) was used in 60.9% of the procedures.

Results: Catheter-induced dissection of the LM occurred in 10 patients, representing 0.11% of the total procedures. All cases occurred during PCI (0.31%), using 6 french guides in 100% and transradial approach in 60%. Patients were 69.5 ± 9.9 years old, 60% male, previous PCI in 50% and 3 vessel disease in 40% of cases. No patient had significant left main lesion at baseline. Euroscore was 4.8 ± 2.6 (predicted in-hospital mortality if they had a planned surgery: $4.3 \pm 3.1\%$). The dissection involved distal left main in 90% of cases. Hemodynamic status was immediately impaired in 8/10 patients and intra-aortic balloon pump was inserted in 5 cases while bail-out LM stenting was performed. PCI was successful in all cases using DES (2.12 ± 0.9 stents, total stent length: 58 ± 29 mm). In case of distal left main dissection, T stenting was performed with final kissing balloon inflation. Total procedure duration was 97 ± 35 minutes and amount of contrast media 346 ± 145 cc. Gp2b3a inhibitors were used in 10%. At hospital discharge there were 2 (20%) non Q-wave MI, no Q-wave-MI, no emergency CABG and no death. Follow-up was obtained in all cases at 13.2 ± 6.4 months after hospital discharge. There was no other major adverse cardiac event.

Conclusions: Iatrogenic LM dissection is a rare (0.3%), but life threatening complication of PCI that can be managed percutaneously using DES with a high rate of success and a promising mid-term outcome.

P649(W)



Predictive outcome factors in the real-world management of patients undergoing elective or primary percutaneous coronary intervention: primary results of the RIVIERA registry

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Purpose: The objective of the Registry on IntraVenous anticoagulation In the Elective and primary Real world of Angioplasty (RIVIERA) is to characterize current practice patterns in elective and primary percutaneous coronary intervention (PCI), and gain insight into early outcomes in the modern era of PCI.

Methods: RIVIERA is a multinational, prospective, observational study. Consecutive patients in hospitals with cardiac catheterization laboratories in 23 countries ($N=7962$) were enrolled between September 2003 and March 2005. In-hospital clinical and angiographic outcomes were recorded for patients undergoing elective or primary PCI. Patients were excluded if they were receiving therapeutic doses of anticoagulation when the catheterization was started, or if they were enrolled in clinical trials. Clinical outcomes included in-hospital death, myocardial infarction (MI), and major and minor bleeding. A multivariate logistic regression analysis identified variables associated with clinical outcomes.

Results: Mean age of patients was 59 ± 11 years and 77% were male. Elective PCI was performed in 92.0% of patients and primary PCI in 8.0%. Death occurred in 0.3% of patients, clinical MI in 1.0%, and major and minor bleeding in 3.4%. After multivariate analysis, PCI on the left main trunk, late presenting ST segment elevation MI (STEMI; > 12 h after symptom onset), female gender and absence of thienopyridine pretreatment were the strongest predictors of death. Primary PCI and PCI in ACS patients were among the strongest predictors of death or MI, while thienopyridine pretreatment (versus treatment after PCI) and intravenous (iv) low-molecular-weight heparin (LMWH) anticoagulation (versus iv unfractionated heparin [UFH]) were associated with a beneficial effect on death/MI. Use of glycoprotein (GP) IIb/IIIa inhibitors and female gender were independent correlates of bleeding, while small size catheters ($\leq 6F$) and iv LMWH anticoagulation (versus iv UFH) were factors independently related to less bleeding.

Conclusion: The rate of clinical complications in this unselected population of patients undergoing PCI was relatively low. Identification of the factors associated with an increased risk of major events occurring in real life supports the findings of recent randomized PCI trials. This allows for improved management of these patients in daily practice.

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Similarities between bare metal stent and drug eluting stent thrombosis in the real world

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Stent thrombosis is a major complication after percutaneous coronary interventions (PCI). The aim of our study was to compare the incidence, prognosis, delay, and risk factors for bare metal stent (BMS) and drug eluting stent (DES) thrombosis in the real world.

All 2543 consecutive patients who underwent BMS (2091 lesions treated in 1728 patients) or DES (986 lesions in 815 patients) implantation at our institution between January 2003 and July 2005 were included. Median follow-up was 16 months. Clinical, angiographic and procedural characteristics of the patients with or without thrombosis were compared.

A documented angiographic stent thrombosis occurred in 35 patients (1.4%), 12 with DES (1.4%) and 23 with BMS (1.3%). Six patients (17%) died few hours after the event, and 12 (34%) major adverse cardiac events occurred at one year, 3 with DES and 9 with BMS (25% vs 39%, NS): 8 deaths (23%), 3 re-PCI, 1 myocardial infarction (MI). The rates of acute or sub acute (< 30 days) and late (> 30 days) thrombosis were similar in patients with BMS and DES thrombosis (1% vs 0.8% and 0.5% vs 0.5% respectively). Seven cases (20%) of BMS ($n=6$, 26%) or DES ($n=1$, 8%) thrombosis arose soon after antiplatelet therapy was interrupted. Predictive factors of stent thrombosis were similar with BMS and DES, including: left ventricular failure ($p<0.0001$), initial PCI for acute MI ($p<0.0001$), multivessel PCI ($p<0.0001$), balloon dilatation prior to stenting ($p<0.05$).

Conclusions: BMS and DES thrombosis are very similar in term of incidence, delay, prognosis, and risk factors, with the same risk of late thrombosis after interruption of antiplatelet therapy.

P651 Statin pre-treatment prevents contrast-induced nephropathy and improves long-term outcome in patients undergoing percutaneous coronary intervention



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Purpose: Pleiotropic effect of statins are well known; recently, atorvastatin was demonstrated to confer protection from myocardial damage during percutaneous coronary intervention (PCI). Aim of this study is to investigate whether statins may also reduce incidence of contrast-induced nephropathy (CIN) in the setting of PCI, and to evaluate the influence of such therapy on long-term clinical outcome.

Methods: A total of 434 patients undergoing PCI were prospectively enrolled and followed at least 4 years after the procedure. Patients were stratified according to pre-procedural status of statin therapy (260 statin-treated and 174 without statins). Blood samples were drawn before and 24 hours after PCI for detection of serum creatinine and other hematological parameters. CIN was defined as a post-procedural increase in serum creatinine of ≥ 0.5 mg/dL or $>25\%$ from baseline. Follow-up assessment included the 4-year occurrence of major adverse cardiac events (MACE).

Results: Statin-treated patients had a significantly lower incidence of CIN (3% vs. 27% in patients without statins; $P < 0.0001$), corresponding to a 90% risk reduction (Odds ratio 0.10, 95% CI 0.02-0.18; $P = 0.0001$), and had higher post-procedural creatinine clearance (80 ± 25 vs. 65 ± 19 mL/min; $P < 0.0001$). Benefit of pre-treatment with statins was observed in all subgroups, except in patients with pre-existing renal failure (OR 0.42, 0.1-2.8; $P = 0.37$). Statin therapy was independently associated with lower risk of MACE during follow up and CIN was a predictor of poorer outcome; 4-year event-free survival was highest in patients statin-treated and no CIN (95%, $P \leq 0.015$) and lowest in those without statins and CIN (53%, $P \leq 0.018$).

Conclusions: This prospective cohort study indicates that patients treated with statin therapy prior to percutaneous coronary intervention have a significant reduction in the incidence of contrast-induced nephropathy, compared with patients not pretreated; this protective effect provides better long-term cardiac event-free survival. These data support a routine utilization of statins as adjuvant pharmacological therapy before percutaneous coronary revascularization.

P652 Rapid intravenous hydration for prevention of contrast induced nephropathy in patients undergoing urgent percutaneous coronary intervention



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Purpose: Contrast-induced nephropathy (CIN) frequently complicates percutaneous coronary interventions (PCI), even in patients with normal renal function, resulting in increased in-hospital and long-term morbidity and mortality. Little is known regarding effective ways of preventing CIN in patients undergoing urgent PCI. This study was designed to assess the efficacy of a rapid intravenous hydration protocol with sodium bicarbonate in patients undergoing emergency procedures to prevent CIN.

Methods: Ninety-nine consecutive patients undergoing primary and rescue PCI or urgent (<12 h) PCI for high risk non ST segment elevation acute coronary syndrome were included in a prospective, randomized controlled, single-center trial. Patients were assigned to: group A (63 ± 9 yrs, 68% men), prophylaxis with a bolus of 5 mL/kg of sodium bicarbonate plus 1200 mg N-acetylcysteine for 1 hour, starting 0-1 h before low-osmolality contrast agent, followed by infusion of 1.5 mL/kg per hour for 12 hours after procedure, or group B (64 ± 11 yrs, 69% men), receiving the current protocol of our hospital, a bolus of 1200 mg N-acetylcysteine at the beginning of the coronary angiogram, followed by an infusion of 1 mL/kg per hour for 12 hours. CIN was defined as an increase in serum creatinine (Cr) >0.5 mg/dL within the first 3 days after PCI compared to the Cr values immediately before the procedure. Patients under chronic dialysis treatment were excluded from the study.

Results: There were no significant differences in age, sex, diabetes mellitus, history of chronic kidney disease or contrast volume between groups. Treatment did not differ in both groups except for diuretics (A 60% vs. B 38%, $p = 0.028$). The incidence of CIN in the group B was 29.6% (16 patients) while in group A was 0% ($p < 0.001$). No patient in group A developed clinical heart failure during the catheterization.

	Group A	Group B	P value
Pre-procedure Cr ¹	1.0 (0.55)	1.0 (0.24)	0.96
Cr at day 3 ¹	1.02 (0.50)	1.26 (0.71)	0.056
Oligoanuria post-procedure ²	1 (1.8)	12 (22.2)	0.001
Dialysis post-procedure ²	1 (1.8)	3 (5.6)	0.36

1 N° Patients (%). 2 Means $\pm$ SD

Conclusions: Rapid intravenous hydration before contrast exposure in patients undergoing urgent procedures is effective and safe for prevention of CIN.

P653 Iloprost for prevention of contrast-mediated nephropathy in high-risk patients undergoing a coronary procedure



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Introduction: Contrast-mediated nephropathy (CMN) remains a significant problem accounting for considerable morbidity and mortality. Contrast induced renal vasoconstriction is believed to play a pivotal role. In this pilot study, we examined the safety and efficacy of two doses of the prostacyclin analogue iloprost in preventing CMN in high-risk patients undergoing a coronary procedure.

Methods: Forty-five patients undergoing coronary angiography and/or intervention who had a serum creatinine concentration ≥ 1.4 mg/dL were randomized (1:1:1) to receive iloprost at doses of 1 or 2 ng/kg/min or placebo, beginning 30-90 minutes before and terminating 4 hours after the procedure. CMN was defined by an absolute increase of serum creatinine ≥ 0.5 mg/dL or a relative increase of $\geq 25\%$ measured 2 to 5 days after the procedure.

Results: Study drug infusion was discontinued in 2 patients in the low-dose iloprost group due to flush/nausea and in 5 patients in the high-dose group due to severe hypotension. The mean creatinine concentration change in the placebo group (0.02 mg/dL) was unfavorable compared to that in the low-dose iloprost group (-0.11 mg/dL; $p = 0.08$) and high-dose iloprost group (-0.23 mg/dL; $p = 0.048$). Similarly, the mean creatinine clearance change in the placebo group (-3.1 mL/min) was unfavorable compared to that in the low-dose iloprost group (+3.0 mL/min; $p = 0.07$) and high-dose iloprost group (+8.7 mL/min; $p = 0.001$). Three cases of CMN were recorded; all in the placebo group ($p = 0.032$).

Conclusions: The results of this pilot study suggest that low doses of intravenous iloprost may safely and effectively prevent CMN in patients with pre-existing renal dysfunction. High doses are inadvisable because of frequent significant hypotension.

P654 Effects of ReoPro and vasodilators in the treatment of the noreflow phenomenon



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Background: The noreflow phenomenon occurring after thrombolysis (TIMI), or primary angioplasty (PAMI), or SVG and culprit lesions revascularization (PCI) greatly jeopardizes the microcirculation. To restore microcirculatory flow different treatments such as adenosine, nitrous donors, calcium antagonists and platelets inhibitors are used but their effects were not compared.

Methods: We retrospectively (from 1998 to present) quantified reflow by corrected TIMI frame count (CTFC) in 50 patients. Distal embolization was angiographically evident in 40 patients. Depending on the operator choice, patients were treated with ReoPro ($n = 36$), followed by verapamil (VER, $n = 18$, 0.25 mg IC). $N = 18$ patients received IC adenosine (ADE, 24 μ g bolus) combined with 10mg urapidil (URA, α_1 -adrenergic blocker), $N = 14$ received 2-3 nitroprusside boluses (NTP, 200 μ g).

Results: ReoPro did not acutely improve the noreflow condition. Adenosine improved the CTFC from 0 to 107.3 ± 18.9 , and from 64.2 ± 5.3 to 53.7 ± 5.2 frames in noflow and in remote vessels, respectively (mean $\pm$ SD). Verapamil on top of ReoPro improved CTFC from zero to 67.9 ± 52.3 frames ($P < 0.05$ vs ADE). URA given on top of ADE decreased CTFC from 107.3 ± 18.9 to 24.8 ± 1.9 (non corrected 31.4 ± 1.8 , $P < 0.05$). In remote vessels the combination of ADE and URA improved the CTFC from 53.7 ± 5.2 to 27.8 ± 2.0 frames ($P < 0.05$). NTP improved flow in the dilated vessel from zero to 33.5 ± 6.5 frames, except in 3 unsuccessful patients (two 95% SVG stenosis, and one occluded LAD with long dissections).

Conclusions: Our data suggest that the combination of adenosine and α_1 blockers or nitroprusside are preferable to verapamil to treat the noreflow phenomenon, whereas adenosine alone does not restore TIMI 3 flow. The mechanisms by which vasodilators attenuate distal embolization sequels need further investigation.

P655 A comparison of risk-adjusted gender differences in mortality and complications among patients undergoing PCI in US community hospitals



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Purpose: This research examines risk-adjusted gender differences in hospital mortality rates and two major complication rates for PCI patients treated at 95 US community hospitals.

Methods: This retrospective study is based on the HCA (Hospital Corporation of America) Casemix Database, an administrative database of consecutive patients admitted to any HCA hospital. The study population includes 43,040 patients undergoing PCI in one of 95 HCA US hospitals that performed more than 52 PCIs (at least 17 on women) between 10/1/2004 and 9/31/2005. Logistic re-

gression equations (controlling for age, gender, race, and up to 22 co-morbidities) were estimated to predict each patient's probability of experiencing in hospital death, new onset hemodialysis, and vascular complications requiring treatment. Student t-tests were used to compare risk-adjusted outcomes between men and women. All risk-adjusted outcomes by gender were calculated as follows: (the hospital's men/women observed rate - the hospital's risk-adjusted men/women rate) + the HCA average rate for men/women.

Results: The average annual number of PCI was 453 per hospital (35% of patients were women). Women were, on average, nearly 5 years older than men and the table indicates, after risk-adjustment, women were significantly more likely than men to experience each adverse outcome studied. The relative risk ratios indicates, that compared to men, women were approximately 2.2 times more likely to experience a vascular complication requiring treatment, 1.6 times more likely to experience new onset hemodialysis and 1.4 times more likely to die during their PCI hospitalization.

Risk-Adjusted Outcomes by Gender

	All Hospitals	Men	Women	p-Values
Total Patient	453±362	297±241	156±124	<0.001
Average Age	64.6±12.3	63.0±12.0	67.7±12.3	<0.001
Risk-Adjusted Mortality	1.24%	1.12%	1.53%	0.023
Risk-Adjusted A New Onset Hemodialysis	0.89%	0.73%	1.19%	0.011
Risk-Adjusted Vascular Complication	5.27%	3.72%	8.26%	<0.001

Conclusion: This study finds that the adverse gender differences based on risk-adjusted complication rates for two major complications associated with PCI is larger than the difference in-hospital mortality rates, in a large contemporary sample of US community hospital patients.

P656 Predictors of diffuse and occlusive restenosis after drug-eluting stent implantation



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Background: Our group has found that non-focal restenosis remains a common occurrence after drug-eluting stent (DES) implantation in unselected real-world lesions, with a worse prognosis than focal restenosis. We have therefore sought baseline factors associated with subsequent non-focal restenosis in DES.

Methods: Using a database of 2281 unselected de novo native coronary artery lesions treated with DES between March 2003 and March 2005, we performed uni- and multi-variate analyses to identify predictors of non-focal restenosis pattern. All episodes of angiographic restenosis after DES implantation were classified as focal or non-focal (diffuse, proliferative or occlusive).

Results: We identified 98 non-focal and 167 focal restenotic lesions respectively. Univariate positive predictors of non-focal restenosis were diabetes mellitus (DM), paclitaxel-eluting stent (PES) implantation, type C lesion, chronic occlusion, longer stent length and a greater number of stents per lesion, whilst male gender, unstable angina at presentation and increasing reference vessel diameter (RVD) were negative predictors ($p < 0.05$ for all). After multi-variate analysis, PES (OR 1.670, 95% CI 1.047-2.664, $p = 0.031$) and DM (OR 1.869, 95% CI 1.176-2.972, $p = 0.008$) remained positively associated with non-focal restenosis, whilst male gender (OR 0.392, 95% CI 0.228-0.674, $p = 0.001$), unstable angina at presentation (OR 0.334, 95% CI 0.173-0.644, $p = 0.001$), and increasing RVD (OR 0.477, 95% CI 0.321-0.707, $p < 0.001$) were found to be negatively associated.

Conclusions: Diabetes mellitus, female gender, stable angina, smaller vessels and the use of paclitaxel-eluting stents are all independent predictors of non-focal restenosis after DES implantation. It remains to be seen whether modification of these risk factors can influence the subsequent development of non-focal restenosis, thereby potentially improving long-term outcome.

P657 Risk of non-cardiac surgery after coronary drug-eluting stent implantation



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Purpose: We sought to examine the risk of adverse cardiac events when patients undergo non-cardiac surgery after coronary drug-eluting stent (DES) placement. Late stent thrombosis has been reported even >1 year after DES implantation.

Methods: We examined the records of all patients with successful drug-eluting stent implantation (60% sirolimus-eluting stents and 40% paclitaxel-eluting stents) at the Dallas VA Medical Center between April 2003 and January 2006 and identified 38 patients who subsequently underwent 41 major and 18 minor non-cardiac surgeries.

Results: Mean age was 62 ± 9 years. All patients were men, 87% had a history of smoking, 92% had a history of hyperlipidemia, 84% were hypertensive, 34% were diabetic, and 32% had a prior acute myocardial infarction.

Forty-one major non-cardiac surgeries (34% abdominal, 22% vascular, 17% genitourinary, 27% other) occurred in 28 patients after a median of 260 days post DES implantation: 4 surgeries occurred within 0-30 days, 11 surgeries between 30-180 days, 14 surgeries between 180-365 days, and 12 surgeries >365 days

after DES implantation. Aspirin and clopidogrel were continued during the perioperative period in 78% and 41%, respectively. Two patients required postoperative blood transfusions.

Eighteen minor non-cardiac surgeries (44% skin surgery, 44% injections, 12% other) occurred in 10 patients after a median of 297 days post DES implantation: 6 surgeries occurred between 30-180 days, 7 surgeries between 180-365 days, and 5 surgeries >365 days after DES implantation. Aspirin and clopidogrel were continued during the perioperative period in 94% and 39%, respectively. No patient in this group required blood transfusion.

No major adverse cardiac event or death occurred during or after the 41 major (0%, 95% confidence intervals 0-9%), and the 18 minor non-cardiac surgeries (0%, 95% confidence intervals 0-19%).

Conclusion: Although our data are limited by the small sample size, they suggest a low risk for major cardiac complications in patients undergoing non-cardiac surgery after coronary DES implantation.

P658 Cardiac outcome after noncardiac surgery in patients with recent coronary stenting



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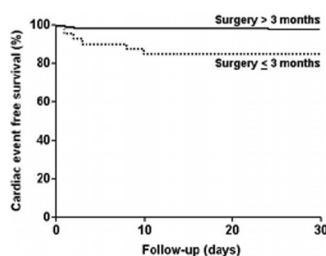
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Background: A too short interval between coronary stenting (PCI) and noncardiac surgery seems to increase the risk of perioperative adverse cardiac events. However the optimal time between stenting and noncardiac surgery is ill-defined.

Methods: Consecutive patients who underwent successful PCI followed by non-cardiac surgery within 2 years at Erasmus MC between 1999 and 2005 were identified. All patients were screened for cardiac risk factors and perioperative medication, including statins, beta-blockers and anti-platelet therapy. The type of stent was noted. Patients were divided in 2 groups: early surgery (<3 months after PCI) and late surgery (>3 months to 2 years after PCI). The main outcome was MI or cardiac death within 30 days after surgery.

Results: A total of 170 patients (124 males) were included, 37 (22%) underwent surgery within 3 months (median 41 days) after PCI. There was no significant difference in cardiac risk factors or medication use between patients with early surgery and late surgery. Patients operated within 3 months after PCI had a higher rate of postoperative cardiac events (16.2% vs. 2.3%, $p = 0.006$, figure). In the early surgery group, statin use and beta-blocker use were both associated with a lower incidence of cardiac events (44% vs 7%, $p = 0.01$ and 36% vs 4.3%, $p = 0.01$ respectively). Interruption of clopidogrel and/or aspirin 1 week before surgery and type of stent (ie drug eluting or bare metal) was not associated with a significantly worse outcome.



Conclusion: Patients requiring noncardiac surgery within 3 months after PCI are at high risk for adverse cardiac events. If possible, noncardiac surgery should be delayed until at least 3 months after PCI.

P659 Completeness of revascularization and long-term prognosis in patients with multivessel coronary artery disease treated with percutaneous transluminal coronary angioplasty



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Background: The clinical importance of the completeness of revascularization in multivessel coronary artery disease (MVD) achieved with angioplasty is still a matter of debate. There is no sufficient data regarding long-term outcome in patients (pts) with incomplete revascularization.

Aim: To evaluate the impact of completeness of revascularization on long-term prognosis in MVD pts treated with angioplasty.

Material and methods: 908 pts (83% male, aged 30-83years) with MVD treated with balloon angioplasty between 1988 and 1997 were included. Pts have been followed-up for 8-16 years (median 11years). Complete revascularization (CR) was defined as successful (residual stenosis <50%) angioplasty of all significant (stenosis ≥70%) lesions. Incomplete revascularization (IR) was recognized in case of unsuccessful or not attempted angioplasty in any significant lesion. Left ventricle (LV) dysfunction was defined as ejection fraction <40%. Information regarding cardiovascular events was obtained in 96% subjects. Analysis of vari-

ance, chi-square test, Kaplan-Meier analysis with long-rank test and proportional hazard stepwise regression were processed.

Results: The CR was achieved in 284 (31.3%) pts. The subgroups of pts with CR and IR did not differ as for age, gender, BMI and smoking. Patients with IR more frequently had previous myocardial infarction (65.9 vs 58.4%, $p<0.05$), family history of coronary artery disease (45.9 vs 8.6%, $p<0.001$), at least one chronic coronary occlusion (47.4 vs 25.0%, $p<0.0001$) and LV dysfunction (54.0 vs 9.9%, $p<0.0001$). In contrast, the prevalence of hypertension was more common in CR-subgroup (50.3 vs 42.6%, $p<0.05$).

The completeness of revascularization affected neither total (17.7% in CR and 17.0% in IR-subgroup, $p=ns$) nor cardiovascular mortality (12.9 vs 12.4% respectively, $p=ns$), as well as the prevalence of myocardial infarction (23.8 vs 24.0%, respectively, $p=ns$). Patients with IR required more re-PTCA (28.8 vs 17.2%, $p<0.001$) and re-hospitalizations during the follow-up period (49.8 vs 34.7%, $p<0.0001$). However, the independent predictors of long term mortality were LV dysfunction (HR 2.00, 95%CI 1.35-2.95; $p<0.001$) and age (HR 1.23 for every 10 years increment of age, 95%CI 1.03-1.44, $p<0.05$).

Conclusions: despite significantly different risk profile of patients with complete and incomplete revascularization, only the left ventricle ejection fraction and age were the independent predictors of long-term mortality in patients with multivessel coronary artery disease treated with angioplasty.

P660 In stent thrombosis and its risk factors



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Background: Acute or subacute in stent thrombosis (IST) is a rare, but very dangerous complication in patients after successful percutaneous coronary intervention (PCI). It is a multifactorial problem. We attempt to verify the incidence of risk factors for the IST (with the accent on the incidence of genetical abnormalities) in the patients treated by PCI in our clinic.

Methods: IST was diagnosed in our cathlab in 35 patients within the period from 1. January 2002 to 30. September 2005 (i.m. in 0.92% out of total 3784 PCI's). We assess the basic biochemical and haematological parameters, technical parameters of the interventional performance, influence of the additional medication and genetical abnormalities potentially affecting the formation of thrombus. Obtained data were compared with those from the group of all PCI's performed in this period.

Results: There was no difference in age and sex between those groups. Mortality was significant higher in patients with IST. 22 out of 35 patients treated by PCI, who suffered by IST, were examined to verify the presence of the Leiden mutation in gene for coagulation factor V (positive in 4.6%), mutation in gene for prothrombin in position 20210A (positive in 9.1%) and mutation in gene for MTHFR in position 677T (68.2% vs. 35% in common population) and 1298C (positive in 50%). The real genetic risk for the formation of thrombus we find out in 68.2% of all examined patients with IST. Otherwise it was significant higher number of thrombocytes ($p<0.01$), values of fibrinogen ($p<0.01$) and CRP in the patients with IST in the day of primary PCI. It was also significant higher number of implanted coronary stents ($p<0.01$) and the length of stented segments ($p=0.03$) in these patients.

Conclusions: The incidence of IST in the patients with the known risk factors can be expressively potentiated by the presence of the prothrombogenic genetical abnormalities.

P661 Plasma levels of soluble RAGE increase six months after percutaneous coronary interventions with stenting in coronary artery disease patients



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Background and Objective: In animal models, increased tissue advanced glycation end products (AGEs), including N ϵ -(Carboxymethyl)lysine (CML), and its specific receptor RAGE, are critically implicated in post-procedural intimal hyperplasia after balloon injury. In mice and rats, predisposed to exaggerated neointimal expansion, administration of the decoy protein soluble RAGE (sRAGE) significantly limited atherosclerosis and re-stenosis after balloon injury. We evaluated the plasma levels of CML and sRAGE in patients with coronary artery disease (CAD) before and after percutaneous coronary interventions (PCI) with stenting.

Methods: The plasma levels of CML and sRAGE were both analysed by specifically developed ELISA in 81 CAD patients: 51 with Unstable Angina (UA) [43 men; 66 $\pm$ 10.2 years] and 30 with Stable Angina (SA) [25 men; 65.4 $\pm$ 10.5 years], before, 1 and 180 days after stenting.

Results: CML levels (median [interquartile range]) of all patients (71 [44.5-103.5] μ g/mL) increased significantly one day after stenting (101 [57-141.5] μ g/mL) (anova, $p<0.0001$) and persisted slightly but not significantly elevated at 180 days (94 [51.5-125.5] μ g/mL). Baseline CML levels were not different in UA and SA patients: 63 [41.5-111] versus 72 [52-101] μ g/mL. In SA patients the log-transformed CML levels were correlated with age ($y=51.7+3.68x$, $r=0.29$, $p=0.013$).

sRAGE levels (median [interquartile range]) of all patients (406 [265.5-580.7] pg/mL), tended to decrease 1 day after the procedure (396 [227-561] pg/mL), but

increased significantly at 180 days follow up (490.5 [373-864] pg/mL, $p<0.0001$). sRAGE levels did not differ between UA and SA patients: 352 [263-449] versus 467.5 [284-656] pg/mL. In all patients, the log-transformed sRAGE levels were inversely correlated to both IL-6 levels ($y=2.586-0.277x$, $r=-0.18$, $p=0.015$) and C-reactive protein levels ($y=1.358-0.326x$, $r=-0.16$, $p=0.032$). No correlation was observed between CML and sRAGE plasma levels.

Conclusions: The significant increase of CML levels one day after PCI might reflect an oxidative response to coronary wall injury, which persisted at 180 days follow-up. Since high plasma levels of sRAGE have been associated with a lower risk to develop CAD, the increase of sRAGE levels 180 days after the procedure may indicate an improvement of inflammatory conditions of patients. The lack of correlation between CML and sRAGE levels suggests that CML levels are not involved in a negative feedback mechanism of RAGE signalling.

PERCUTANEOUS CORONARY INTERVENTION IN THE HIGH-RISK PATIENT

P662

Mechanisms of restenosis in diabetics undergoing coronary stent implantation: results of a matched-pair quantitative coronary angiography analysis with non-diabetics

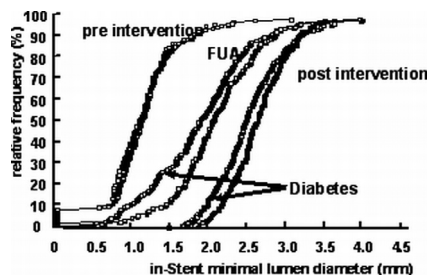


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Purpose: Diabetes mellitus is an established risk factor for stent restenosis, in part as a result of smaller vessel dimensions and longer lesions. Aim of this study was to compare the magnitude of acute lumen gain and late lumen loss after elective coronary stent implantation in diabetic and non-diabetic patients using a matched-pair analysis.

Methods: A total of 133 diabetic patients with 192 coronary lesions were included into this analysis. From a database of 993 non-diabetic patients, a group of 192 lesions in 182 non-diabetic patients were matched in a pairwise fashion stratifying for reference diameter (RD), minimal lumen diameter (MLD) and lesion length (LL). All patients underwent a follow-up angiography (FUA) 5 $\pm$ 2 month post intervention.

Results: Preinterventional baseline angiographic matching variables as well as mean stent length, stent diameter, and maximal implantation pressure were not different. The binary restenosis rate at 5 month FUA was 25% in the diabetes group and 14% in the non-diabetes group ($p<0.01$). Both, acute angiographic lumen gain (1.47 $\pm$ 0.41 vs. 1.56 $\pm$ 0.38mm, $p=0.03$), as well as late lumen loss (0.64 $\pm$ 0.42 vs. 0.55 $\pm$ 0.36mm, $p=0.02$) were significantly different between diabetic and non-diabetic patients (Figure). Suboptimal acute procedural results and the exaggerated neointimal proliferation contributed by about 50% to the lower net lumen gain in diabetic patients.



Cumulative MLD distribution

Conclusions: Patients with diabetes mellitus show a significantly higher restenosis rate even if matched for preprocedural angiographic lesion dimensions. Mechanistically, inferior procedural results as well as exaggerated neointimal proliferation are quantitatively equally important for this process.

P663

Paclitaxel-eluting stent to inhibit neointimal hyperplasia in diabetic patients: angiographic and IVUS result of the Diabetes II Trial



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Background: The DIABETES (DIABETes and drug eluting Stent) II trial is a prospective, multicenter, registry aimed to demonstrate the efficacy of paclitaxel-eluting stent (PES) on the inhibition of neointimal hyperplasia in diabetic patients.

Methods: From January to July 2004, 80 patients (130 lesions) were included in the registry. Patients were eligible for the study if they were identified as non insulin or insulin-dependent diabetics, with significant coronary stenoses in ≥ 1 vessels. The use of abiximab was recommended per protocol, and dual an-

tiplatelet therapy was prescribed for 1 year. Clinical follow-up was scheduled at 1, 9, 12 months, and angiographic and intravascular ultrasound follow-up at 9 months. The results were compared with the historical cohort of patients treated with bare metal stent (BMS) of DIABETES I trial.

Results: Mean age was 64 ± 12 years and 58 percent of patients were male. Twenty-two patients (27.5%) were insulin-dependent and multivessel disease was evidenced in 50 percent of patients. At 9-month follow-up a significant reduction in (in-segment) late lumen loss and restenosis rate were observed in the PES group as compared with the BMS group (0.47 ± 0.3 mm vs. 0.33 ± 0.3 mm; $p=0.04$; 33.7% vs. 7.6% ; $p=0.001$, respectively). Similarly, there was a reduction of NIH in the PES group (50.0 mm^3 vs. 25.4 mm^3 ; $p<0.001$). This reduction of neointimal hyperplasia was independent of the diabetes status. In addition, there was a significant increase in late stent malapposition in the PES group (5.3% vs 0% ; $p=0.01$). At 1-year follow-up, the overall incidence of major adverse cardiac events was lower in the PES group (10% vs 38.8% ; $p=0.001$) and not any stent thrombosis was adjudicated in the PES group.

Conclusions: This multicenter registry has demonstrated the safety and the efficacy of paclitaxel-eluting stent in diabetic patients. This beneficial clinical effect was independent of the diabetes status.

P664 Fasting hyperinsulinemia and increased insulin resistance are associated with worse clinical outcome after elective percutaneous coronary interventions in type 2 diabetic patients

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Objective Patients with type 2 diabetes mellitus (DM2) have worse clinical outcome after percutaneous coronary revascularization than patients without DM2. However, the reasons of this effect are still unclear. The study aimed to evaluate the influence of insulin resistance and hyperinsulinemia on the results of elective percutaneous coronary interventions in type 2 diabetic patients.

Methods We studied 137 DM2 patients aged 60 ± 6.8 years who underwent elective percutaneous coronary revascularization. Fasting insulinemia and insulin resistance were assessed on the day of coronary revascularization and 3, and 6 months after the procedure. For the purpose of analysis we used a mean value of three measurements and separately the data from the day of the intervention. Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA-IR) according to the formula: fasting insulin ($\mu\text{U/ml}$) $\times$ fasting glucose (mmol/l)/22.5. During 9 months follow-up period all patients were monitored for the incidence of cardiovascular death (CVD), nonfatal myocardial infarction (MI) and clinically driven restenosis. Patients were divided into restenosis group (27 patients), combined CVD and MI group (12 patients) and event-free group (98 patients). Fasting insulinemia and insulin-resistance were compared between the groups.

Results Fasting insulinemia in restenosis group measured on the day of intervention ($20.45 \pm 7.54 \mu\text{U/ml}$) and in follow-up ($23.82 \pm 7.7 \mu\text{U/ml}$) was significantly higher than in event-free group (15.41 ± 8.63 and $16.84 \pm 8.28 \mu\text{U/ml}$, respectively) ($p = 0.003$ and $p = 0.001$, respectively). However, there were no statistically significant differences in fasting insulinemia between combined CVD and MI group and event-free group.

Insulin-resistance was significantly higher in combined CVD and MI group both on the day of intervention (7.92 ± 5.42) and in follow-up (9.99 ± 7.37) as compared to event-free group (5.37 ± 3.52 and 5.83 ± 3.62 , respectively) ($p = 0.035$ and $p = 0.003$, respectively). There were no statistically significant differences in insulin-resistance level between combined CVD and MI group and event free group.

Conclusions: These preliminary data suggest that fasting hyperinsulinemia contributes to the development of restenosis after elective percutaneous coronary intervention in type 2 diabetic patients. Furthermore, insulin-resistance is associated with higher incidence of cardiovascular death and nonfatal myocardial infarction in these patients.

P665 Elevated AGE and not HbA1C is associated with higher restenosis rate after elective percutaneous coronary revascularization in type 2 diabetic patients

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Objective: Deleterious effect of hyperglycemia in type 2 diabetes mellitus (DM2) is at least partly attributable to intensification of glycation processes, mainly production of advanced glycation end-products (AGE). On the other hand, glycation of hemoglobin is used for diagnostic purpose that is evaluation of prolonged hyperglycemia. It has been suggested that increased glycated hemoglobin level (HbA1C) is associated with higher restenosis rate after percutaneous coronary revascularization in DM2 patients. We aimed to investigate whether there is any correlation between the levels of HbA1C and AGE. Moreover, we attempted to determine any association between these parameters and restenosis rate after elective percutaneous coronary interventions in DM2 patients.

Methods: We studied 102 diabetic patients, aged 61.3 ± 8.7 , who underwent elective percutaneous coronary revascularization. The measurements of HbA1C and AGE levels were performed on the day of intervention and 3, and 6 months after the procedure. For the purpose of analysis we used a mean value of three

measurements and separately the data from the day of the intervention. During 1 year follow-up period the patients were monitored for the incidence of clinically driven restenosis. Statistical analysis of any correlation between HbA1C and AGE was performed. Patients with and without restenosis were compared in respect to HbA1C and AGE levels. Furthermore, we searched for any differences in restenosis rate between patients with HbA1C $> 7\%$ and HbA1C $\leq 7\%$.

Results: Patient with restenosis (21.6%) had significantly higher level of AGE on the day of intervention (109.6 ± 37.7) than patients without restenosis (92.9 ± 30.6) ($p < 0.05$). However, there were no statistically significant differences in HbA1C levels and mean of AGE levels between patients with and without restenosis. Moreover, the rate of restenosis in patients with HbA1C $> 7\%$ was no statistically different as compared to patients with HbA1C $\leq 7\%$. Finally, there were no statistically significant correlations between HbA1C and AGE measured both on the day of intervention and in follow-up.

Conclusions: Our preliminary data indicate that elevated AGE level on the day of elective percutaneous coronary revascularization in type 2 diabetic patients is associated with higher restenosis rate after the procedure. This association was not observed with respect to HbA1C level. Furthermore, glycation of hemoglobin due to hyperglycemia has no correlation with the level of advanced glycation end-products.

P666 Impact of percutaneous intervention on the clinical course and outcomes in diabetics with coronary heart disease and left ventricular dysfunction

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Approximately 35% of patients hospitalized with heart failure (HF) are diabetic. The prevalence increases further among patients with more severe HF, ranging from 47% to 86%. The most common etiology of HF in diabetics is Coronary Heart Disease (CHD). There is limited and conflicting data regarding the effectiveness of PCI on survival and morbidity in diabetics with CHD and LV dysfunction (LVD).

Objective: We evaluated our Registry data to determine the impact of PCI on immediate and long-term clinical outcomes in diabetics with advanced HF (LVEF $< 35\%$). From 1/00 to 12/05, we performed PCI in 374 patients in this subset (mean age 64; 32% female). Of them, 35% had prior MI and 35% had prior CABG. Co-morbidities included hypertension (77%), dyslipidemia (55%) and prior CVA (10.4%). Mean NYHA class was 3.2; diastolic dysfunction (DD) was seen in 69%. Mean global LVEF at presentation was 28.3%. Indications for PCI: acute MI (17.1%), unstable angina (34%), cardiogenic shock (4.5%), and objective evidence of ischemia on stress testing (31%). The culprit lesion was ostial/proximal in 52%, implying large volume of potentially salvageable myocardium. Adjunctive IABP support was used in 22%; 11% received drug-eluting stents.

Results: Procedural success was 96%; TIMI 3 flow was achieved in 85%. Incidence of in-hospital adverse events (acute reocclusion 0.8%; CABG 1.1%; death 0.8%) was low. At 1-year follow up, there was demonstrable improvement in symptoms and signs of HF. Mean functional class improved to 1.7 ($p=0.002$), DD persisted in 13% ($p<0.0001$). Mean global LVEF rose to 40.2% ($p=0.000$). The need for diuretics and inotropic support fell significantly ($p<0.0001$). The incidence of ER visits (2.2%) and hospitalization (2.9%) for worsening HF was low. Mortality (8.6%), target vessel revascularization (5.6%) and stroke (1.3%) rates were favorable.

Conclusions: (1) In selected diabetic patients with ischemic CMP and advanced HF, PCI is a safe and effective means of myocardial salvage, resulting in significant improvement in multiple functional and clinical parameters. (2) Procedural success was impressive, despite a high prevalence of co-morbidities at baseline. (3) At 1 year follow-up, there was significant improvement in LV systolic and diastolic performance; this translated into improved functional class, low incidence of hospitalization and acceptable 1-year mortality. (4) Our experience demonstrates that PCI strategies may be especially rewarding in diabetic patients with advanced HF. Effective myocardial salvage may be the key to improved event-free and absolute survival in these patients.

P667 Myocardial function improves equally in diabetes following both multivessel PCI and CABG. Results from a CARDia trial substudy

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Background: Optimal revascularisation in patients with diabetes and multivessel coronary disease has been controversial since the subset analysis of BARI (Bypass Angioplasty Revascularisation Investigation) in 1995. The 600 patient CARDia (Coronary Artery Revascularisation in Diabetes) Trial is the first dedicated study in patients with diabetes that compares up to date Coronary Artery Bypass Grafting (CABG) with Percutaneous Coronary Intervention (PCI) using abciximab and drug eluting stents.

Aim: This substudy was undertaken in 2 centres recruiting to the CARDia Trial. Its aim was to assess comparative improvement in reversible ischaemia following the 2 modes of revascularisation.

Methods: A subset of patients underwent stress echo at baseline and at 6 months. They were classified as having either a normal left ventricle, reversible ischaemia or an impaired ventricle without reversible ischaemia. A wall motion score index [WMSI] was assigned to each stress echo at baseline [WMSI(pre)] and at 6 months post revascularisation [WMSI(post)]. These scores were calculated as the sums of the individual segment scores (1 to 4, where 1 is normal and 4 is akinetic) divided by the number of segments. Individual patients were then defined as having either an improvement in reversible ischaemia, no change from normal, no change from positive ischaemia or a worsening of reversible ischaemia. They were then assigned an overall wall motion score which defined this difference where $WMSI(d) = WMSI(pre) - WMSI(post)$.

Results: Fifty patients have been recruited into this study to date. Of these, 29 underwent PCI and 21 CABG. Nineteen of the PCI patients had a significant improvement in reversibility (66%) with 7 showing no change from normal and 2 showing no improvement in ischaemia and 1 having a worsening of ischaemia. In the CABG group 13 patients had a significant improvement in reversibility (62%), with 6 showing no change from normal, 1 showing no improvement in ischaemia and 1 having a worsening of ischaemia. The mean WMSI(pre) in the PCI group was 1.65 and the mean WMSI(post) was 1.34. In the CABG group mean WMSI(pre) was 1.65 and the mean WMSI(post) was 1.29. The PCI WMSI(d) was 0.31 and CABG WMSI(d) was 0.36, which were not significantly different ($p=0.64$).

Conclusion: Optimal revascularisation in multivessel diabetes has been controversial for many years. Initial data from the CARDia Trial in this subset analysis of patients undergoing stress echo at baseline and at 6 months post revascularisation shows that both PCI and CABG achieve a similar improvement in myocardial function.

P668 Microvascular Complications And Outcome After Drug-Eluting Stent Implantation In Diabetic Patients



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Background: We tested whether microvascular complications predict 1-year outcome after successful elective drug-eluting stent (DES) implantation in type 2 diabetic patients

Methods: All consecutive type 2 diabetic patients who had elective DES implantation on de novo lesion in native vessels at our Institution from April 2002 to December 2004 were analyzed. According to presence of microvascular complications (retinopathy and/or nephropathy), 2 groups of patients were identified: 1) group without microvascular complications, and 2) group with microvascular complications.

Results: Four-hundred-nineteen-six consecutive diabetic patients were analyzed: in both groups sirolimus-eluting stent was implanted in the 63% of cases, and paclitaxel-eluting stent in the remaining 37% of cases. As compared to patients without microvascular complications ($n=198$), patients with microvascular complications ($n=298$) were older, more often insulin-treated and with lower left ventricular ejection fraction. At 12 months, major adverse cardiac events (MACE) occurred in 42 of the 198 patients (21%) in the group without microvascular complications and in 125 of the 298 patients (42%) in the group with microvascular complications ($p<0.001$). By Cox regression analysis independent predictors of MACE were: multivessel stenting (hazard ratio = 7.48; [95% confidence interval 4.19-13.38]; $p<0.001$), diabetic retinopathy (hazard ratio = 2.50 [95% confidence interval 1.44-4.34]; $p=0.001$), diabetic nephropathy (hazard ratio = 1.78 [95% confidence interval 1.04-3.02]; $p=0.033$), glycosylated hemoglobin $>7\%$ (hazard ratio = 0.48 [95% confidence interval 0.26-0.87]; $p=0.016$) and complete revascularization (hazard ratio = 0.59 [95% confidence interval 0.35-0.99]; $p=0.049$).

Conclusions: Presence of microvascular complications identifies a subgroup of diabetic patients with higher risk of MACE following DES implantation.

P669 Comparison of sirolimus-eluting and paclitaxel-eluting stents in patients with diabetes mellitus



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Background: Percutaneous coronary intervention in diabetic patients is associated with an increased risk of restenosis and repeat revascularization procedures even in the era of drug-eluting stents. We analyzed clinical and angiographic outcome differences between sirolimus-eluting (SES) and paclitaxel-eluting stents (PES) in the diabetic subpopulation of the randomized, prospective SIRTAX trial.

Methods: In the SIRTAX trial, 1012 patients with 1401 lesions were prospectively assigned treatment with the sirolimus-eluting (SES: $n=503$) or paclitaxel-eluting stent (PES: $n=509$). The primary endpoint was the incidence of major adverse cardiac events (MACE) defined as a composite of cardiac death, myocardial in-

fraction, or target lesion revascularization. We performed a pre-specified stratified analysis of the primary endpoint (MACE) at 12 months according to the presence or absence of diabetes.

Results: 201 patients had a diagnosis of diabetes (20%). Diabetic compared with non-diabetic patients were more likely to have a diagnosis of arterial hypertension ($p<0.001$), a previous MI ($p=0.06$), and multivessel disease ($P=0.04$) at baseline. Among patients with diabetes, 108 patients were treated with SES (21%) and 93 patients with PES (18%). In diabetics, SES reduced the rate of MACE by 58% (9% versus 20%, hazard ratio [HR]=0.42, 95% CI 0.20-0.90, $P=0.03$) compared with paclitaxel-eluting stents. This difference was largely driven by a 67% reduction in the rate of target lesion revascularization (5% versus 13%, HR=0.33, 95% CI 0.12-0.93, $P=0.04$) in the SES group. The treatment effect in favor of SES tended to be more pronounced in diabetic as compared with non-diabetic patients for both, MACE and target lesion revascularization (P for interaction=0.30). There were no significant differences with respect to cardiac death ($P=0.34$), myocardial infarction ($P=0.19$), and stent thrombosis ($P=1.0$). In-segment late loss (SES: 0.19 mm, SD 0.46; PES 0.35 mm, SD 0.60; $P=0.12$) and in-segment binary restenosis (SES: 7.6%; PES 17%; $P=0.11$) tended to be lower in SES compared with PES.

Conclusion: In diabetic patients with coronary artery disease, SES reduce clinical and angiographic measures of restenosis more effectively than PES. The treatment effect in favor of SES tends to be more pronounced in diabetic than non-diabetic patients, supporting the notion of a more potent suppression of neointimal hyperplasia afforded by SES in high-risk patients.

P670 Low revascularisation rates and relatively high stent thrombosis rate after implantation of DES in high-risk patients: one year final results of the EVASTENT registry



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Background: randomized studies demonstrated a low rate of sub-acute or late stent thrombosis (ST) after implantation of a DES, and a three fold reduction of further revascularizations of the treated lesion (TLR) and treated vessel (TVR). However real-life non-selected patients and lesions are often more severe, and concerns have been raised about the safety and efficacy of DES in such setting. EVASTENT is a nation wide matched-cohort registry allowing a direct comparison of diabetic (db+) and non-diabetic patients. An optimal follow-up was obtained, with on site monitoring for every patients. The on-label using of DES (Cypher) were recommended but not always followed. Aspirin + clopidogrel was recommended for at least 3 months. A critical Event Committee has assessed all the major events (death, acute MI, ST (proven or suspected), TLR, TVR and non TVR). One year F-up is complete for 98% of the 1741 included pts. Three-years results are on-going.

Results: one-year results are summarized in table 1. After this first year 6 further deaths occurred, as well as 4 very LAST, 16 TLR, 20 TVR and 22 non-TVR. Independent predictors of death were age, a low EF, presence of diabetes or multiple vessel disease, previous MI, and stroke. Independent predictors of ST were female status, low EF, previous stroke, renal failure, calcified lesions, length of implanted stents and a complete (for 7 patients) or partial withdrawal of the bi therapy Aspirin + Clopidogrel. Independent predictors of TLR were female status, low EF, diabetes, and length of implanted stents.

Safety and Efficacy results

	Death	ST	TLR*	TVR	Non-TVR
Total	55 (3.2%)	41 (2.3%)	61 (3.5%)	103 (5.9%)	67 (3.9%)
db+ SVD	20	13	15	28	14
db+ MVD	21	12	25	39	21
db- SVD	3	2	8	13	15
db- MVD	11	14	13	23	17

(*)21/61 TLR consisted in ST desobstruction

Conclusion: in high-risk real-life pts TLR and TVR rates remain low whereas ST rate is higher than reported in other series.

P671 Gp IIb/IIIa inhibitors administration in chronic renal insufficiency patients undergoing percutaneous coronary intervention: results of the SHAKESPEARE international registry



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We assessed the impact of Gp IIb/IIIa inhibitors administration on the outcomes of chronic renal insufficiency (CRI) pts undergoing percutaneous coronary intervention (PCI) in a large, prospective, multicenter, international registry. Between 11/2001 and 12/2002, data on a total of 13,456 consecutive pts undergoing PCI

were obtained at 30 centers in 7 countries (France, Germany, Israel, Italy, Poland, Portugal, UK) of the ESC as part of the international SHAKESPEARE Registry. A total 393 pts had CRI (serum creatinine >2.0 mg/dL); 120 (30.5%) were treated with Gp IIb/IIIa inhibitors and 273 were not (69.5%). Baseline characteristics were similar between the two groups (Table). There was a higher incidence of myocardial infarction (ST and non-ST elevation) in pts treated with Gp IIb/IIIa inhibitors. Abciximab was used in 48% of pts and eptifibatide in 28%. Stents were deployed in 73% of all patients. In-hospital outcomes were similar between the two groups. However, there were no deaths in NSTEMI pts treated with Gp IIb/IIIa inhibitors. Bleeding complications were more frequent in the Gp IIb/IIIa inhibitors, mainly due to minor bleeding.

Table 1

	Gp IIb/IIIa=120	No Gp IIb/IIIa=273	p
Age (years)	70 (64-76)	70 (62-76)	0.9
Female gender (%)	21	23	0.6
Hypertension (%)	78	73	0.37
Diabetes mellitus (%)	46	37	0.11
STEMI/NSTEMI (%)	23/18	13/9	0.01/0.009
In-hospital death (%)	5.8	7.3	0.59
Death in STEMI pts (%)	18.5	29.4	0.32
Death in NSTEMI pts (%)	0	17.4	<0.0001
Major/Minor bleeding (%)	4.2/10	1.8/2.6	0.18/0.0015
MACCE (%)	9.2	8.1	0.72

Therefore, the use of Gp IIb/IIIa inhibitors in CRI pts undergoing PCI, seems to be safe and beneficial, especially in NSTEMI patients, with only a significant increase in minor bleeding complications. Whether the administration of these agents has a beneficial effect, needs to be assessed in properly randomized, controlled studies.

P672 In the era of drug-eluting stent, clinical outcomes following sirolimus-eluting stent implantation in patients with end stage renal disease



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Background: Sirolimus-eluting stents (SES) have been shown to markedly reduce the restenosis, compared with bare metal stents (BMS). However, a lot of clinical trials have excluded subset of patients (pts) with end stage renal disease (ESRD). In the era of drug-eluting stent, it is unclear whether there is a clinical improvement in pts with ESRD after SES implantation.

Methods: We analyzed clinical and angiographic characteristics and 1-year major adverse cardiac events (MACE) following SES implantation in 50 pts (72 lesions) with ESRD in COMATE registry (SES-ESRD group). We compared clinical outcomes of SES-ESRD group with those of 42 pts (45 lesions) with ESRD who had received BMS (BMS-ESRD group) previously in our registry.

Results: SES-ESRD group was; diabetes 78%, hypertension 94%, and age 62±10.3 years. SES-ESRD group was more likely to have diabetes (diabetes of BMS-ESRD, 57%; p=0.04). Other clinical characteristics were similar on both groups. Compared with BMS-ESRD group, reference vessel diameters and lesion length of SES-ESRD group were smaller (2.76±0.50 vs. 3.05±0.46 mm, p<0.001) and longer (25.6±7.0 vs. 19.1±8.8 mm, p<0.001). Although SES-ESRD group had more clinical and angiographic risk factors, SES-ESRD group had a lower 1-year major adverse cardiac events (MACE) rate than BMS-ESRD group (6.0% vs. 33.3%; p<0.001). There were no differences in mortality and incidence of myocardial infarction between groups. The incidence of target vessel revascularization decreased significantly in SES-ESRD group (2.0% vs. 19.0%, p=0.01). By multivariate regression, the use of SES was the only significant independent predictor of MACE (OR=0.054, 95% confidence interval 0.01 to 0.26, p<0.001).

Conclusion: Compared with BMS, SES has caused improvement of clinical outcomes in pts with ESRD. The use of SES was the most important factor that decreased MACE in ESRD.

P673 Influence of age on the outcomes of percutaneous and surgical treatment in patients with multivessel disease



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The aim of this study is to evaluate the age-outcomes relationship in patients undergoing surgical or percutaneous revascularization, based on the data of

ARTS 1 and ARTS 2 trials. The ARTS 1 trial was a randomized trial comparing surgery (CABG) and coronary stenting with bare metal stent (BMS) for the treatment of patients with multivessel disease. The ARTS 2 trial assessed the results of sirolimus eluting stenting (SES) in a matched population with similar clinical and angiographic characteristics. Data of 1782 patients actually treated by CABG (n=585), BMS (n=597) or SES (n=600) were reviewed according to four age quartiles: Q1, n=446, mean age: 48.8yrs ±4.8; Q2, n=445, 58.6yrs±2.1; Q3, n=446, 65.7yrs±2.0; Q4, n=445, 73.4yrs±3.1.

Results: Older patients had more often hypertension, diabetes, peripheral vascular disease and COPD. The proportion of male, current smokers, hypercholesterolemia, family history and previous MI decreased with age. In general, the clinical presentation was similar among groups as well as the treatment at discharge, but ACE inhibitors, more frequently prescribed in elderly.

The use of LIMA in patients treated by CABG was not influenced by age, neither the number of stents implanted in BMS and SES groups. The hospital stay was longer in older patients.

Death and MACCE rates amongst groups

	Q1	Q2	Q3	Q4	p-value
Death CABG	0.7%	1.9%	3.5%	5.8%	0.07
Death BMS	1.8%	2.7%	2.1%	3.0%	0.90
Death SES	0.8%	0.7%	0.6%	1.7%	0.78
MACCE CABG	4.9%	10.1%	13.2%	15.1%	0.02
MACCE BMS	23.7%	22.8%	32.4%	23.9%	0.21
MACCE SES	5.3%	10.9%	8.9%	12.2%	0.19

MACCE (death, stroke, MI, revascularization)

Conclusion: Technological advancements in PCI techniques and the use of SES have completely offset the one year outcome difference seen between CABG and BMS, notably by abolishing the excess need for reintervention seen with BMS. PCI with SES may even be safer and life saving in the elderly population as compared to CABG.

P674 Clinical outcome remains poor in patients with recurrent ischemia requiring PCI post CABG



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Purpose: Patients requiring PCI of SVG lesions are known to have poor outcomes. It is unclear the degree to which this outcome is attributable to limitations of SVG intervention versus the patient substrate. All patients undergoing PCI for recurrent ischemia following CABG at two tertiary care hospitals in Vancouver were examined. We specified a comparison of those undergoing PCI of an SVG vs those undergoing PCI of a native vessel only.

Methods: The BC Cardiac Registry is a prospectively collected cohort of patients presenting for diagnostic cardiac catheterization in BC, Canada. Patients were identified from April 1999 to Dec 2004 who underwent PCI and had an SVG with >50% stenosis. Only patients with an indication for catheterization of stable angina or ACS were included. The patients were then grouped based on whether they had an SVG PCI or native vessel PCI. Eligibility for either native vessel or SVG PCI was not available. Clinical outcomes were obtained by linkage to BC Cardiac Registries and Vital Statistics.

Results: Median f/u was 828 days in 745 patients. Nineteen percent of patients were female. SVG PCI was performed in 401; native vessel PCI in 344. Patients with SVG PCI were older with 69.8% vs 61.9% over 65 years old. In addition, they were more likely to have ACS (68.1% vs 54.1%) and be done as an urgent or emergency procedure (70.8% vs 57%). Clinical outcomes at 1 year are displayed in the table. There were no significant differences in clinical outcome whether the PCI was performed on native vessel or SVG in univariate analyses.

Clinical outcomes at 1 year

	Native PCI	SVG PCI	Overall
N	344	401	745
Death at 1 year	24 (7%)	30 (7.5%)	54 (7.3%)
Repeat PCI at 1 year	59 (17.2%)	70 (17.5%)	129 (17.3%)
Repeat CABG at 1 year	9 (2.6%)	1 (0.3%)	10 (1.3%)
Death or repeat revasc at 1 year	83 (24.1%)	97 (24.2%)	180 (24.2%)

Conclusions: In patients presenting with recurrent ischemia post CABG, PCI to SVG appears to be a reasonable option. Recurrent procedures and death are relatively frequent, regardless of PCI strategy.

P675 Target lesion and vessel characteristics in percutaneous coronary intervention: Predictors of outcomes in the modern era



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Background: The original American College of Cardiology (ACC)/American Heart Association (AHA) and Society for Cardiovascular Angiography and Inter-

ventions (SCAI) classification of lesion and vessel characteristics according to percutaneous coronary intervention (PCI) outcomes arose from the pre stent and early stent era respectively, and do not reflect current practice.

Methods: Characteristics for 10,800 PCI lesions in 6,719 consecutive cases were classified according to ACC/AHA type and entered prospectively into a database (January 2000 to December 2004). Multivariate forward stepwise logistic regression was used to identify predictors of angiographic failure and in-hospital major adverse cardiac events (MACE).

Results: Stents were used in 93.8% of lesions, radial procedures comprised 29.2% of cases, and left main stem interventions (LMS) comprised 1.2% of cases. Successful angiographic outcomes (<50% residual stenosis) occurred in 97.3% of lesions. Success rates did not differ between ACC/AHA type A (98.9%), B1 (99.0%), and B2 lesions (99.1%), but each was higher than the success rate for type C lesions (94.2%, $p<0.001$, $p<0.001$, and $p<0.001$ respectively). Predictors of 295 angiographic failures were total occlusion, severe calcification, excessive target vessel tortuosity, graft intervention, and lesion angulation >90 degrees (see table). Lesion length, ostial location, bifurcation or LMS lesions, and thrombus presence were not significantly associated with angiographic failure, but LMS PCI was a predictor of MACE (Odds ratio 3.7, 95% confidence interval 1.6 to 8.8, $p=0.003$).

Adverse angiographic outcome predictors

Predictor	Odds ratio (95% confidence interval)	P value
Total occlusion > 3 months	38.1 (28.7 to 50.6)	<0.001
Total occlusion < 3 months	8.4 (5.7 to 12.4)	<0.001
Severe Calcification	4.9 (3.0 to 8.1)	<0.001
Excessive vessel tortuosity	3.0 (1.8 to 4.9)	<0.001
Vein graft intervention	2.5 (1.1 to 5.7)	0.026
Severely angulated lesion	2.3 (1.1 to 4.9)	0.041

Conclusions: Lesion and vessel characteristics once predictive of adverse angiographic outcomes are now associated with successful outcomes. LMS PCI is associated with MACE as a whole but not angiographic failure itself.

P676 In hospital and long term follow-up after percutaneous coronary revascularization in high risk patients



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Aims: Percutaneous coronary intervention (PCI) is increasingly been performed in patients (pts) with a high risk profile and therefore poor candidates for coronary artery bypass graft (CABG). The aim of our study was to evaluate in hospital and long term evolution of pts with multivessel coronary disease and a high surgical risk, who underwent PCI.

Methods: We included in the study all consecutive pts who underwent PCI and who had a high surgical risk as assessed by the Parsonet risk score (higher than 10). Baseline clinical, angiographic and procedural characteristics were collected. Clinical follow-up was performed and death, acute myocardial infarction (AMI) and repeat revascularization (RR) were considered as major adverse cardiac events (MACE).

Results: We included 142 pts, with a mean age of 69 ± 8 years old, 56.4% were diabetics, 97% had multivessel coronary disease and mean ejection fraction was $47\pm 14\%$. Mean Parsonet score was 17 ± 7 . PCI was performed in 223 lesions (1.5 lesions/pts), with 89.9% of stent implantation and a final angiographic success of 90.6%. In hospital mortality occurred in a significantly lower proportion of pts compared with what would have been predicted by the Parsonet score (6% vs 17%, $p<0.001$). Factors associated with in hospital mortality were female sex (RR 5; 2.4-6.6), pulmonary disease (RR 25; 4-154) and three vessel disease (RR 1.7; 1.49-2.0). During a follow-up period of 41 ± 20 months, global MACE were detected in 48 pts (32.2%): death in 25 pts (16.8%), AMI in 29 pts (19.5%) and RR in 31 pts (20.8%). Long term mortality was associated with heart failure during admission (RR 3.1; 1.1-8.5), pulmonary disease (RR 5.3; 2.0-14.2) and previous myocardial infarction (RR 2.7, 1.1-7.0).

Conclusion: In a group of high risk pts, PCI procedure offers a lower mortality than predicted by the surgical Parsonet risk score. Pulmonary disease, heart failure and prior AMI were associated with a worse prognosis.

P677 Is there a gender difference in outcome of percutaneous coronary intervention (PCI) in the era of drug eluting stents?



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Women undergoing percutaneous coronary intervention (PCI) are characterized by worse adverse clinical (older age, diabetes, hypertension) and angiographic (smaller and more calcified vessels) characteristics than men. Several studies, however, paradoxically demonstrate higher periprocedural complications but similar long-term clinical outcomes after bare-metal stents.

Aim: to assess results of PCI with taxol-eluting stents (TES) according to sex in a high risk group of patients.

Results: 660 pts (135 women), with 1114 lesions (213 in women) were consecu-

tively treated with a TES. Women were older (mean age 67.5 ± 10.4 vs 62.7 ± 9.9 in men, $p<0.001$), with higher prevalence of diabetes (41.5 vs 29.7%, $p=0.009$) and hypertension (78.5 vs 68.8%, $p=0.026$). Procedural success rates (99%) and in-hospital MACE - death, MI, TLR, CABG (<2%) were similar. At follow-up (mean 9.69 ± 5.37 months, range 6 to 27), MACE included death (1.48 vs 2.09, women vs men, respectively, $p=1$), MI (0.74 vs 1.71, $p=0.69$), angina (43.80 vs 32.34, $p=0.01$), and TLR (7.14 vs 9.78, $p=0.27$).

Multivariate analysis identified the presence of total coronary occlusions, diabetes and small vessel (<2.5 mm) diameter as predictors of restenosis and TLR. When the data was analyzed according to sex, reference vessel diameter remained as the only independent adverse predictor in women, while diabetes and CTO were strongly associated with restenosis in men.

Conclusion: adverse pre-procedural clinical and angiographic characteristics in women treated with TES did not translate in worse long-term outcomes when compared to men. The most important predictor of TLR in women is small vessel size, while diabetes plays a dominant role in men.

P678(W) Angiographic complications in patients undergoing percutaneous coronary intervention: findings from the multinational RIVIERA registry



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Purpose: The objective was to prospectively evaluate angiographic complication rates and identify predictors of these complications in the Registry on Intravenous anticoagulation in the Elective and primary Real world of Angioplasty (RIVIERA).

Methods: RIVIERA is a multinational, prospective, observational study. Consecutive patients in hospitals with cardiac catheterization laboratories in 23 countries (N=7962) were enrolled. Angiographic complications are listed in the table. Variables associated with any of these angiographic complications in the univariate analysis ($P<0.05$) were identified and used in a stepwise multivariate logistic regression analysis.

Results: Of the total population, 7949 patients underwent procedures classified as primary or elective. Elective PCI was performed in 7310 (92.0%) patients and primary PCI in 639 (8.0%) patients. The angiographic complications are listed in the table. Following multivariate logistic regression analysis, the strongest and most significant predictors of angiographic complications were the presence of STEMI on admission ($P<0.001$), PCI of a coronary graft ($P<0.05$), and GP IIb/IIIa inhibitor use ($P<0.001$). Left anterior descending artery PCI ($P=0.012$) and intravenous enoxaparin use (vs. UFH) during PCI ($P<0.001$) were independently associated with less angiographic complications.

Angiographic complications, n (%)	N=7962
Coronary dissection	297 (3.7)
No reflow	162 (2.0)
Thrombus at the treated lesion site	152 (1.9)
Distal embolism	55 (0.7)
Occlusion of collateral branches	51 (0.6)
Acute vessel closure	24 (0.3)
Coronary rupture	6 (0.1)
Other angiographic complications	109 (1.4)
At least one complication	689 (8.7)

Conclusion: Angiographic complications still occur in 8.7% of patients in an unselected population of patients undergoing elective or primary PCI. Angioplasty of STEMI or graft patients is strongly associated with angiographic complications.

P679 Comparison of long-term clinical results of sirolimus-eluting stent and paclitaxel-eluting stent in consecutive unselective multivessel coronary artery disease: multicenter registry in asia



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Background and Purpose: Both Sirolimus-eluting stent (Cypher™) and Paclitaxel-eluting stent (TAXUS™) have been reported to be effective in preventing restenosis. The aim of study is to compare the long-term clinical efficacy of these 2 stents on the outcome of patients with multivessel coronary artery disease (MVD).

Methods: A prospective analysis of 804 consecutive patients with MVD (416 Cypher™ and 388 TAXUS™) after successful multivessel stenting in these patients was performed (Cypher™: male 75%, age 69.6, TAXUS™: male 77.3%, age 70.4). Lesion location of MVD were Cypher™: LMT 48, LAD 356, LCX 216, RCA 272, TAXUS™: LMT 58, LAD 340, LCX 198, RCA 278.

Results: See table.

	Cypher™	TAXUS™	p
Number of patients	416	388	-
Procedural success (%)	99.5	99.5	NS
MACE at 30 days (%)	1.4	1.8	NS
Angiographic restenosis rate at 12 months (%)	6.7	7.7	NS
Angiographic restenosis rate at 24 months (%)	6.7	7.7	NS
MACE at 12 months (%)	4.8	4.6	NS
MACE at 24 months (%)	4.8	4.6	NS

Conclusion: The use of both stents in multivessel coronary artery disease was equally safe and feasible in terms of long-term clinical results.

P680 Comparison of efficacy and safety between sirolimus-eluting stent (Cypher) and paclitaxel-eluting stent (TAXUS) in patients with diabetes mellitus: multicenter registry in Asia

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Background and Purpose: Both Sirolimus-eluting BX velocity stent (Cypher™, Cordis) and Paclitaxel-eluting Express stent (TAXUS™, Boston Scientific) have been reported to be effective in preventing neointimal formation and in-stent restenosis. However, little is known about long-term efficacy of these 2 stents in patients with diabetes mellitus (DM). The aim of this study is to compare the safety and efficacy of these 2 stents on the outcome of patients with DM.

Methods: A prospective analysis of 928 patients with DM (Cypher™: 508 patients, 952 lesions. TAXUS™: 420 patients, 728 lesions) in five high volume Asian centers after successful stenting was performed. The study endpoints were major adverse cardiac events (MACE) at 30 days, 12 months and restenosis rate at 12 months.

Results: The baseline clinical characteristics between 2 groups were similar. See table for clinical results.

	Cypher™ (n=508)	TAXUS™ (n=420)	p
Age (mean/yr)	63.8	65.8	NS
Multivessel disease (%)	78.5	78.6	NS
MACE at 30 days (%)	0.8	1.2	NS
Lesion length (mm)	30.8 ± 10.9	31.4 ± 10.4	NS
Reference diameter (mm)	2.80 ± 0.70	2.76 ± 0.59	NS
MLD post (mm)	2.54 ± 0.77	2.53 ± 0.70	NS
MLD at 12 months (mm)	2.20 ± 0.70	2.08 ± 0.88	NS
Restenosis rate at 12 months (%)	7.9	9.5	NS
MACE at 12 months (%)	7.9	9.5	NS

Conclusion: The use of both stents in patients with DM was equally safe with low acute complication and low incidence of restenosis.

P681 Comparison of efficacy and safety between Sirolimus-eluting stent (Cypher) and Paclitaxel-eluting stent (TAXUS) on the outcome of patients with small coronary arteries: multicenter registry in Asia

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Background and Purpose: Both Sirolimus-eluting BX velocity stent (Cypher™, Cordis) and Paclitaxel-eluting Express stent (TAXUS™, Boston Scientific) have been reported to be effective in preventing neointimal formation and in-stent restenosis. However, little is known about long-term efficacy of these 2 stents in patients with small vessel disease (reference diameter ≤25 mm). The aim of this study is to compare the safety and efficacy of these 2 stents on the outcome of patients with small coronary arteries (SC).

Methods: A prospective analysis of 1,410 patients with SC (808 Cypher™ and 602 TAXUS™) in five high volume Asian centers after successful stenting for SC (Cypher™: LAD 46.8%, LCX 26.0%, RCA 19.9%, HL 7.3%. TAXUS™: LAD

	Cypher™	TAXUS™	p
Number of patients	808	602	-
Procedural success (%)	99.8	99.7	NS
MACE at 30 days (%)	0.4	0.7	NS
Reference diameter (mm)	2.40 ± 0.55	2.40 ± 0.80	NS
Lesion length (mm)	12.6 ± 5.8	11.3 ± 5.9	NS
MLD post (mm)	2.32 ± 0.62	2.30 ± 0.70	NS
MLD at 12 months (mm)	2.10 ± 0.60	2.08 ± 0.71	NS
Restenosis rate (%)	7.4	13.0	NS
MACE at 12 months (%)	7.4	11.6	NS

48.5%, LCX 22.6%, RCA 19.9%, HL 9.0%) was performed. The study endpoints were major adverse cardiac events (MACE) at 30 days, 12 months and restenosis rate at 12 months.

Results: The baseline clinical characteristics between 2 groups were similar. See table for clinical results.

Conclusion: The use of both stents in patients with small coronary arteries was equally safe with low acute complication and low incidence of restenosis.

P682 Outcome and quality of life one year after PCI in octogenarians

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Background: Percutaneous Coronary Interventions (PCI) is increasingly performed in octogenarians. However, little is known about the quality of life (QOL) of these patients one year after PTCA. We assessed the one-year outcome and QOL after PCI.

Methods: Assessment of QOL in all patients of 80 years and older who underwent PCI between October 2003 and January 2005 at our institution. We used the RAND-36 health survey to assess health related QOL at follow-up (mean 22 ± 7 months). The EuroSCORE (surgical mortality risk) was used for reference risk assessment.

Results: 98 patients (5.4% of total PCI, mean age 82.7 ± 2.9 years; range 80-95 years; 60% female) underwent PCI. Canadian Cardiovascular Society (CCS) angina class before the procedure: 36% III, 64% IV. Acute PCI was performed in 36% of the patients (high risk subset with large myocardial infarction, cardiogenic shock and rescue PCI). The mean additive and logistic EuroSCORE were respectively 10 (±3) and 23% (±15), 98% was in the highest risk group (additive EuroSCORE 6+). The overall PCI success rate was 94%. Mortality in the first week was 12%, at 30-day 15% (31% acute vs. 9% non-acute PCI), and at one year 19%. Re-intervention was performed in 6% of the patients. Event free survival at one year was 75%. At follow-up the general health was rated as fairly good and better than before PCI (CCS I and II: 77%). On a scale from 0-100, the patients gave their current health 57 (±19) points. The scores of the mental component were better than the scores of the physical component. Physical functioning (41 ± 28) and the ability to fulfil physical role expectations (32 ± 37) had the worst scores. The mental component, vitality had the lowest (55 ± 20) and mental health the highest (70 ± 21) score. Social functioning was in general good (67 ± 26).

Conclusions: Octogenarians have a high mortality risk following PCI, especially in acute PCI. If surviving, QOL is acceptable with a better mental than physical score. In general, PCI has a positive effect on health perception, with less symptoms of angina pectoris. The limited effect of PCI on physical disability is probably due to existing co-morbidity and the ageing process.

P683 Revascularization in CAD - an important factor suppressing serum cytokine and adhesion molecule activation

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Our studies revealed a considerable increase of selected inflammatory markers in the serum of patients with coronary artery disease (CAD) as compared to levels observed in healthy controls. A complex therapy might positively modify inflammatory activation in CAD.

Aim: to determine the dynamics of changes in serum TNF alpha, soluble forms of its receptors (sTNFR 1, sTNFR 2), and adhesion molecules (sE-selectin, sP-selectin, sVCAM-1, sICAM-1) over a two-year follow-up of patients with CAD.

Methods: The study involved 70 patients with stable CAD (stable angina class II/III acc. to CCS; mean age±SD: 58.8±3.8 years; M/F: 40/30), and 20 healthy subjects (mean age±SD: 55.4±3.6 years; M/F: 12/8).

Results: Over the follow-up period a marked attenuation of angina (p<0.001) was observed. Interventional treatment (PCI, CABG) was used in 53 CAD patients. Laboratory analysis revealed a significant decrease of serum TNF alpha and sTNFR1 at 2 years (TNF alpha: 12.1±0.7 pg/ml; sTNFR 1 1306±46 pg/ml) as compared to baseline levels (16.5±0.7 pg/ml, p=0.030; 1551±82 pg/ml, p=0.048, respectively). The levels of sP-selectin (159±7 vs 201±14 ng/ml, p<0.01) and sICAM-1 (133±4 vs 153±6 ng/ml, p<0.05) were found significantly increased as compared to the baseline. Interventional procedures resulted in suppression of both cytokine (TNF alpha, sTNFR 2) and adhesion molecule (sE-selectin, sP-selectin) activation in CAD group. The baseline and post-follow-up TNF alpha and sTNFR 1 levels showed persistent elevation in CAD patients as compared to the controls (9.0; 956.3 pg/ml; respectively; p<0.01). There were no differences between baseline and final cytokines and adhesion molecules in healthy subjects.

Conclusion: The course of CAD as modified by a clinically effective therapy is characterized by changes of immune markers activation - revascularization seems to be an important factor suppressing both cytokine and adhesion molecule activation in CAD patients.

P684 Correlation of gender and body mass index with drug eluting stent diameter and major adverse cardiac events



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Background: It is postulated that poor outcomes following percutaneous coronary intervention (PCI) occur more frequently in women than men due to small coronary artery diameters. Lumen diameter plays a crucial role in target vessel revascularization and re-stenosis. We examined this hypothesis by exploring the association between vessel diameter, as determined by stent diameter, with gender, body mass index (BMI) and major adverse cardiac events (MACE).

Methods: We studied 402 consecutive patients who underwent PCI requiring stent placement utilizing a retrospective, cross-sectional study design. We examined cardiac arterial diameter, as determined by stent diameter in male and female adults and assessed correlations with BMI, and the association with MACE. Hypotheses regarding arterial size were examined utilizing the student's T-test for continuous variables and Chi square test for categorical variables, and assuming that $\alpha=0.05$. A Pearson's correlation coefficient was used to examine the association between stent diameter and BMI.

Results: Among the 402 subjects, 239 (59%) were males and 163 (41%) females. The mean age for males was 62 years and for females, 67 years. Stent diameters for two arterial territories in males and females were as follows: Male LAD=3.6 mm (± 0.36 , n=216); Male RCA=3.3 mm (± 0.44 , n=124); Female LAD=3.1 mm (± 0.35 , n=75); Female RCA=3.2 mm (± 0.36 , n=88). The differences in stent diameters across arterial distribution and gender were not statistically significant. The correlation between stent diameters and BMI for males were LAD 0.102 and RCA -0.089, and for females LAD 0.216 and RCA 0.102. There was no evidence of a significant correlation between stent diameter and BMI for males or females. The risk of MACE did not differ across males and females [OR=1.2 (95% CI 0.68, 2.11)]. When we compared the gender and territory-specific arterial diameters across patients with and without MACE, there was no statistical difference in vessel size.

Conclusions: Based on stent diameters as an estimate of arterial size, our results suggest that the variation in arterial diameter for this sample of patients undergoing coronary intervention was similar for males and females. We found no significant correlation between stent diameter and BMI, and no association between stent diameter and MACE. While further prospective analyses with larger samples will be necessary to confirm these findings, the observations raise the possibility that factors other than arterial size contribute to observations of increased risk of adverse outcomes among women treated for coronary artery disease.

P685 Role of echocardiography in northern Uganda



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Introduction: although infective conditions remain the dominant causes of death and disability in Africa, it is expected that by 2020, 35% of all deaths in these nations will be due to cardiovascular disease (CVD). The spectrum of CVD in developing countries, however, varies among different contexts. The population of Gulu District, in northern Uganda, has been severely incapacitated by war, epidemics and social displacement. Majority of diseases are those of poverty: malnutrition, diarrhoea and infectious diseases, particularly malaria, HIV-AIDS and tuberculosis. Aim of our work was to describe CVD profile in this rural ugandan population and to evaluate the contribution of Echocardiography in this context.

Methods: 553 known or suspected cardiologic patients admitted in Medicine Ward, in Paediatric Ward or referred by physicians working in Out Patients Department were evaluated by Echocardiography. Two cardiologists from Italy provided their service to this Hospital and executed the echocardiograms.

Results: we confirmed a heart disease in 348 patients (63%), the most common diagnosis was hypertensive cardiomyopathy (39.6% among cardiologic patients), followed by dilated cardiomyopathy (24.4%) and rheumatic heart disease (13.5%), see table 1. Considering subgroups for age the most common heart disease among children were rheumatic (28.6%), congenital cardiopathies (21%) and pericardial diseases (21%), instead among patients older than 60 years-old hypertensive cardiomyopathy represented more the 50% of diagnosis.

Conclusions: this is the first attempt to tackle the problem of cardiovascular diseases in this rural region of northern Uganda, in a context of war and social displacement. The most common diseases we found are hypertensive and dilated cardiomyopathies, rheumatic valvulopathies e pericarditis, thus confirming WHO reports about the prevalence of heart disease in rural african countries. So the awareness that overall mortality due to heart disease is more in developing countries in comparison to developed world, makes necessary a more adequate knowledge about the real prevalence of these diseases in different ethnic groups, in different social and geographic contexts, distinguishing various patterns of risk and disease, thus implementing effective health programmes. Echocardiography, an easily applied, noninvasive technique, could be a simple and cheap aid in-

strument, suitable to confirm cardiac diagnosis, guide pericardiocentesis, stratify patients on the grounds of their ventricular dysfunction and thus with different therapeutic needs.

P686 Myocardial bridging is related to endothelial dysfunction but not atherosclerotic plaque as assessed by intracoronary ultrasound



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Purpose: Longstanding compressive-relaxing effect of the myocardial bridge (MB) may produce endothelial dysfunction through direct stress to endothelium. Therefore, we assessed the hypothesis that MB would alter the endothelial function and subsequently, influence the extent of atherosclerotic plaque.

Methods: In 128 patients with typical angiographic systolic milking effects with $> 30\%$ reduction in diameter of the coronary artery in systole after intracoronary NTG (200 μ g) infusion (54.7 $\pm$ 10.9 yr, 42 men) and 231 control patients without MB and overt coronary artery disease (54.1 $\pm$ 13.2 yr, 111 men), endothelial function was estimated by incremental acetylcholine infusion (ACh: 20 μ g, 50 μ g and 100 μ g/min) into the left coronary ostium. In 74/128 patients with MB and 64/231 control patients, intracoronary ultrasound (ICUS) assessments were obtained.

Results: The mean percent change of MB segments was 44.01 $\pm$ 16.55%. Coronary vasoconstriction ($> 50\%$) to ACh was seen in 114/128, 89% of MB group and 81/231, 35.1% of controls ($p < 0.001$). In MB group, vasoconstriction in response to ACh was dominantly at MB segments (101/114, 88.6%). The mean vasoconstriction response to ACh was more pronounced at MB segments than matched segments in controls (-71.91 $\pm$ 24.49 vs -37.83 $\pm$ 35.44, $p < 0.001$). There was a significant correlation between severity of MB and vasoconstriction in response to ACh ($r=0.338$, $p < 0.001$). By ICUS, there was a typical half-moon phenomenon in 71/74 (95.9%) cases of MB group, but not in controls ($p < 0.001$). The atherosclerotic plaques at MB segments were absent in 67/74 (90.5%) and only mild in 7/74 (9.5%) cases as compared with those of matched segments of LAD in controls (plaque burden 3.91 $\pm$ 1.37 vs 24.71 $\pm$ 24.21%, $p < 0.001$).

Conclusions: Despite the prominent relationship between MB and endothelial dysfunction, the MB segments were spared from the atherosclerotic plaques. These results suggest that high flow velocity and high wall shear stress at MB segments may be a protective mechanism to development of atherosclerosis.

EXERCISE TESTING IN CORONARY ARTERY DISEASE

P687 End-tidal PCO2 during exercise predicts future cardiovascular events in patients with coronary artery disease



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Background: End-tidal PCO2 (PETCO2) during exercise, an index of arterial PCO2, is known to decrease with progressing severity of heart failure. No studies, however, have established whether the measurement of PETCO2 is useful to predict future cardiovascular events. We compared the prognostic power of PETCO2 at peak exercise with those of established respiratory gas indexes during exercise testing in cardiac patients.

Methods: A total of 347 consecutive patients with coronary artery disease (65 $\pm$ 9 years) performed a symptom-limited incremental exercise test with respiratory gas measurements. PETCO2 at peak exercise, peak O2 uptake (VO2), the slope of the increase in ventilation to the increase in CO2 output (VE/VO2 slope), and the slope of the increase in VO2 to the increase in the work rate (Δ VO2/ Δ WR) were measured.

Results: A total of 56 cardiovascular-related events such as worsening of heart failure, worsening of angina pectoris, and cardiovascular death occurred over 757 $\pm$ 421 days of prospective follow-up. Peak VO2 ($p < 0.0001$), VE/VO2 slope ($p < 0.0001$), Δ VO2/ Δ WR ($p < 0.0001$), and PETCO2 at peak exercise ($p < 0.0001$) were significant prognostic indexes for total cardiovascular events. Among the cases who died of cardiovascular related causes, however, a lower PETCO2 at peak exercise was a stronger index ($p=0.003$) than a lower peak VO2 ($p=0.02$) in multivariate Cox proportional hazards analysis. Both the VE/VO2 slope and Δ VO2/ Δ WR were insignificant prognostic indices in this analysis.

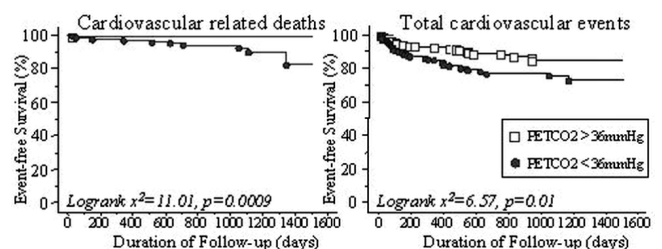


Fig. 1

Conclusion: A lower PETCO₂ at peak exercise is useful to predict future cardiovascular events, especially cardiovascular-related deaths, in patients with coronary artery disease.

P688 The predictive value of cardiorespiratory fitness combined with European systematic coronary risk evaluation and the risk of cardiovascular and all-cause death



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Purpose: There are no data on directly measured cardiorespiratory fitness combined with European Systematic Coronary Risk Evaluation (SCORE) with respect to death from cardiovascular diseases (CVDs) and all-causes. However, it is proposed that exercise test with the global risk scores may provide additional information for risk stratification in an asymptomatic subjects.

Methods: Cardiorespiratory fitness (maximal oxygen uptake, VO_{2max}) was measured by exercise test with an electrically braked cycle ergometer and respiratory gas analyser. This study included a random population sample of 1639 men (42-60 years) without history of type II diabetes, coronary heart disease, stroke or claudication. During an average follow-up of 16 years, a total of 304 deaths occurred.

Results: In a multivariable model, independent predictors for all-cause death were European SCORE (for 1% increment, RR 1.15, 95% CI 1.10-1.20, p<0.001), VO_{2max} (for 1 MET increment, RR 0.83, 95% CI 0.78-0.89, p<0.001), C-reactive protein (CRP) (for 1 mmol/L increment, RR 1.05, 95% CI 1.03-1.07, p<0.001) and alcohol consumption (for 100 g/week increment, RR 1.17, 95% CI 1.09-1.27, p<0.001), adjusting for serum HDL cholesterol, waist-to-hip ratio, physical activity, exercise-induced ST changes and the use of medication for hypertension or dyslipidemia and the use of aspirin. European SCORE and VO_{2max} in addition to exercise-induced ST changes, CRP and alcohol consumption were independently associated with the risk of CVD death, respectively. RR for all-cause death was 4.06 (95% CI 2.82-5.83, p<0.001) among those with poor VO_{2max} (<31.8 mL/kg/min, median) and high risk SCORE (at least 5%), 1.88 (95% CI 1.43-2.47, p<0.001) among those with poor VO_{2max} and low risk SCORE (<5%), and 2.50 (95% CI 1.21-5.17, p=0.013) among those with good VO_{2max} (>31.8 mL/kg/min) and high risk SCORE as compared to those with good VO_{2max} and low risk SCORE, after adjustment for CRP, alcohol, serum HDL cholesterol, waist-to-hip ratio, physical activity, exercise-induced ST changes and medications. In the group with poor VO_{2max} and high SCORE, the RR for CVD death was 5.96 (3.35-10.57, p<0.001), after adjustment for risk factors.

Conclusions: This study provides additional information beyond the widely used European risk SCORE based on conventional risk factors. An important finding is that the European SCORE can be used to identify men for whom low cardiorespiratory fitness predicts especially high risk for death from all-causes and CVDs.

P689 A1166C polymorphism of the angiotensin II type 1 receptor gene affects aerobic power response to training in coronary artery disease

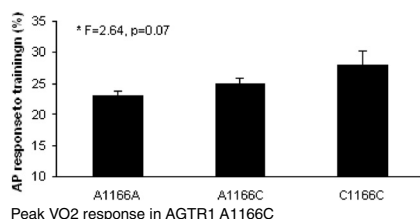


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Introduction: Aerobic phenotypes show wide variability to similar aerobic training stimuli, which is partly attributed to heritability. The Angiotensin II type 1 receptor (AGTR1) gene is the major mediator of the effects of Angiotensin II, which has been shown to be involved in the determination of aerobic power. The aim was to evaluate whether the AGTR1 gene A1166C single nucleotide polymorphism (SNP) is associated with aerobic power or with its response to training in patients with coronary artery disease (CAD).

Methods: All biologically unrelated Caucasian patients with CAD who had achieved maximal exhaustion during incremental bicycle testing at baseline and after completion of three months of cardiac rehabilitation from 1990 through 2001 (n=1095) were eligible for inclusion in the CAREGENE Study. 935 blood samples were obtained for DNA-analysis. In 927 patients the AGTR1 gene A1166C SNP was identified by sequenom MassARRAY RT technology (Lark technologies, Essex, UK).

Results: Frequencies of the AGTR1 gene A and C alleles were 0.71 and 0.29, respectively. Covariate-adjusted aerobic power (mL/min/kg) at baseline was comparable (F=2.43, p=0.08) for patients homozygous for the wild-type A allele (22.5



± 0.2), heterozygous (22.1 ± 0.1), and homozygous for the mutative (rare) C allele (21.3 ± 0.6) (mean ± SE). Aerobic power increased significantly (p<0.001) for each genotype with physical training. The adjusted response of aerobic power to training tended to be larger (F=2.64, p=0.07) in patients homozygous for the mutation (28.0 ± 2.2%) as compared with the AA (23.1 ± 0.8%) and AC (25.0 ± 0.9%) genotype of A1166C.

Conclusions: In CAD the AGTR1 gene A1166C SNP may be associated with the aerobic power response to physical training.

P690 Extracellular superoxide dismutase gene Arg213Gly polymorphism and aerobic power in coronary artery disease

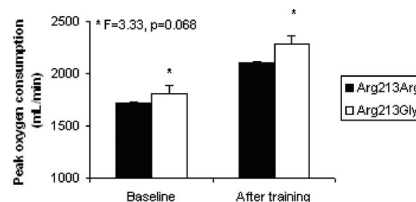


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Introduction: Endothelial nitric oxide (NO) release increases arterial vasodilation. The extracellular superoxide dismutase (EC-SOD) gene Arg213Gly single nucleotide polymorphism (SNP) is associated with EC-SOD plasma levels. EC-SOD quickly dismutates superoxide production, preventing loss of NO-bioactivity. The association of the EC-SOD Arg213Gly SNP with aerobic power (AP) and its response to physical training was evaluated in coronary artery disease (CAD).

Methods: All biologically unrelated Caucasian patients with CAD who had exercised until exhaustion during graded bicycle testing at baseline and after 3 months of cardiac rehabilitation from 1990 through 2001 (n=1095) were eligible for inclusion in the CAREGENE Study. 935 DNA samples were obtained and in 902 patients the EC-SOD gene Arg213Gly SNP was identified by sequenom MassARRAY RT technology.

Results: 97.1% of the patients were homozygous for Arg213, 2.9% were heterozygous, none were homozygous for Gly213. Overall, the Arg213Gly SNP was modestly associated (F=3.33, p=0.068) with covariate-adjusted AP at baseline and after training in favour of the mutation. At baseline AP (mL/min) was higher, although not significantly (F=1.75, p=0.19), in heterozygous patients as compared with Arg213Arg homozygotes (1815±72 v 1718±13, respectively) (mean±SE). AP increased significantly (p<0.001) for both genotypes with physical training and remained higher (F=4.72, p=0.03) in Gly213-carriers after training (2281±81 v 2101±14, respectively). In the latter patients the response to training (mL/min) tended (F=2.57, p=0.11) to be higher (460±49 v 380±8, respectively).



Peak VO₂ in ecSOD Arg213Gly

Conclusions: In CAD the EC-SOD Arg213Gly SNP was associated with aerobic power, particularly after physical training. An impact on training response should not be dismissed.

P691 Prevalence and procedural related implication of Cardiac Troponin I release following bicycle exercise testing in patients with chronic stable angina



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Cardiac troponin I (cTnI), the highly sensitive and specific marker of myocardial damages, is associated with adverse short and long term outcome. The purpose of this study was to investigate the prevalence of moderate cTnI release following a diagnostic exercise testing (ExT) and its impact on the subsequent angiographical outcome in coronary artery disease (CAD) patients.

Methods: Consecutive CAD patients (pts, n=580, mean age 64±11, 77% males) underwent a standard bicycle-ExT. Venous blood samples for measurements of cTnI were collected before, 6-8h and 24h after the ExT. The detection limit for cTnI was 0.01 ng/mL, the 99. percentile in a healthy population was 0.07ng/mL.

	cTnI+	cTnI-	P
Age (y)	63±15	65±10	n.s.
Female (%)	22	23	n.s.
Total WL (Watt)	108±35	118±39	n.s.
HRxBP product	20368±4592	19545±6580	n.s.
Previous MI (%)	82	38	<0.01
Previous PCI (%)	87	53	<0.05
Multivessel Disease (%)	93	57	<0.05
cTnI baseline (ng/mL)	0.02±0.02	0.01±0.02	n.s.
cTnI 6h (ng/mL)	0.12±0.05	0.01±0.02	<0.01
cTnI 24h (ng/mL)	0.15±0.08	0.01±0.01	<0.01

Baseline characteristics, work load (WL) and cardiac troponin I (cTnI) values at baseline, at 6h and 24 h after ExT among cTnI+ and cTnI- patients.

Based on prospective ROC curves the value of 0.08 ng/mL was selected as the threshold for detection of myonecrosis.

Results: cTnI was negative at baseline in all pts, but reached the cut-off value of 0.08 ng/mL after ExT in 51 (9%) patients. Baseline characteristics, cTnI-values and factors significantly associated with cTnI release are presented in the table. cTnI value $\geq 0.08 \mu\text{g/L}$ had a positive predictive value of 88% for a subsequent percutaneous coronary intervention (PCI).

Conclusion: cTnI after ExT was observed in CAD patients with previous MI and multiple PCI demonstrating short term prognostic implication, i.e. necessity of subsequent PCI. If follow up of this subset of patients proves to be at a higher risk for future events, cTnI-measurements following ExT will be a helpful additional diagnostic and prognostic tool.

P692 Safety of exercise training below rating of perceived exertion on the next day after elective coronary stent implantation



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Background: Strong anti-platelet therapy reduce the frequency of subacute stent thrombosis (SAT) after coronary stent implantation apparently. However it has been believed that exercise training immediately after coronary stent implantation induce SAT. **PURPOSE:** To investigate safety of exercise training below rating of perceived exertion of anaerobic threshold (AT) level immediately after elective coronary stent implantation.

Methods: We enrolled 293 patients who underwent elective coronary stent implantation from September 2004 to June 2005. All patients were treated with ticlopidine (200mg) and aspirin (100mg) at least from the day before coronary intervention. We performed exercise training by bicycle ergometer on the next day after coronary stent implantation. Patients continued to exercise training below rating of perceived exertion of Borg index 13. We studied the incidence of major adverse event (MAE: death, acute myocardial infarction, coronary artery bypass surgery and SAT) within 30 days after stent implantation. SAT was defined as the following criteria: 1) a angiographically documented stent occlusion or presence of filling defect in the stent within 1 month after SES implantation or 2) Myocardial infarction or sudden cardiac death without proven patency of the stent within 1 month after stent implantation.

Results: This study population comprised of 293 pts with a mean age of 68 ± 8 years, 74% of male gender, 29% with DM, 64% with hypertension, 44% with hyperlipidemia, 45% with obesity and 22% with smoking. Total of 383 stents implanted. Stent composed of bare-metal stent 298 (78%) and drug-eluting stent 85 (22%). Two patients suspended exercise test for getting out of shape on that day. The incidence of MAE in exercise training was none. Within thirty days, death, acute myocardial infarction, coronary artery bypass surgery and SAT were none, either.

Conclusions: We considered that exercise training below rating of perceived exertion of AT level after elective coronary stent implantation is safety under the continuation of antiplatelet therapy.

P693 Do resting and exercise electrocardiograms contribute incrementally to the prognostic assessment of patients with ambulatory undifferentiated chest pain?



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Purpose: The rapid assessment of undifferentiated chest pain has been given high priority by policy makers but clinical factors and electrocardiogram (ECG) findings predictive of adverse outcomes in this ambulatory patient population have not been defined. Our objective was to measure the incremental value of the resting (rECG) and exercise (ETT) ECG in predicting adverse outcomes (CHD death, non-fatal acute coronary syndromes) in patients presenting to rapid access chest pain clinics (RACPCs).

Methods: We studied 1672 patients with undifferentiated, recent onset chest pain and no previous cardiac history who had resting and exercise ECGs as part of their clinical assessment, with a median follow up of 2.26 (1.51-5.11) years. We developed 3 iterative prognostic indices from clinical factors, clinical + rECG factors, and clinical + rECG + ETT factors. All significant covariates from each iterative model were used to calculate a prognostic index and C-statistic (ROC). Finally we refitted the model and applied it to 329 patients with follow up for from another chest pain clinic for external validation

Results: The table shows covariates retained in the final prognostic models and the relevant c-statistic for the main cohort and for the external validation sample.

Prognostic model and C-statistic

Model	Covariates	Main Cohort	Validation Cohort
C-statistic	C-statistic		
Clinical factors	Age, sex, typicality of symptoms	0.71	0.81
Clinical factors + rECG	+ Q waves, ST change	0.74	0.83
Clinical factors, rECG + ETT	+ exercise time, diagnostic ST change	0.77	0.85

Conclusion: In patients with undifferentiated chest pain presenting to RACPCs, simple assessment of age, gender and typicality of symptoms embraces most of the prognostic information provided by the rECG and ETT. However these widely applied tests remain useful in this setting by providing incremental prognostic data that contribute to identification of patients at greatest risk of CHD death and non-fatal acute coronary syndromes.

P694 Can stress echocardiography with tissue characterization evaluate non-critical coronary stenosis? A validation study against simultaneous measurement of fractional flow reserve



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Aim of this study was to evaluate comparatively the ability of different echocardiographic modalities to detect myocardial ischemia due to non-critical coronary stenosis.

Methods: We investigated 22 consecutive patients presenting with stable chest angina, negative exercise tests and coronary 1-vessel disease with 50-75% diameter stenosis. Tissue Doppler echocardiography with strain rate imaging (TDE/SRI) was performed at baseline and at peak hyperemia during 0.14 mg/kg/min adenosine infusion simultaneously with intracoronary measurements of fractional flow reserve (FFR). Angioplasty was carried out if FFR < 0.75. In this case, TDE/SRI was repeated during first balloon inflation. Visual wall motion score (WMS), peak systolic myocardial velocity (V_s), strain rate (SR_s), strain (S_s) and peak overall strain (S_{max}) were determined at each step in the region of interest. Postsystolic shortening (PSS) was defined as a ratio ($S_{max} - S_s$)/ S_{max} > 0.3 with reduced S_{max} < 15%.

Results: Pathologic FFR < 0.75 was found in 11 patients. Myocardial contractility, reflected by SR_s , increased during hyperemia only in the patient group with FFR > 0.75. Visual (WMS) and quantitative (V_s) analysis of wall motion were inferior compared to deformation parameters (SR_s , S_{max} , PSS) for detection of myocardial ischemia. PSS as typical marker of ischemia was identified in 10 of 11 patients during vessel occlusion, but had a low sensitivity (2 of 11 patients with FFR < 0.75) for the more subtle changes during hyperemia.

FFR-related subgroups	TDE/SRI timing	SR_s (s^{-1})	S_{max} (%)	PSS	WMS	V_s (mm/s)
FFR > 0.75 (0.81 $\pm$ 0.08)	Baseline	0.91 $\pm$ 0.27	18 $\pm$ 6	0	1.1 $\pm$ 0.3	27 $\pm$ 10
(9 LAD, 1 CX, 1 RCA)	Hyperemia	1.33 $\pm$ 0.24 *	19 $\pm$ 7	0	1.1 $\pm$ 0.3	34 $\pm$ 15
FFR < 0.75 (0.63 $\pm$ 0.09)	Baseline	1.02 $\pm$ 0.44*	19 $\pm$ 7°	0°	1.1 $\pm$ 0.3°	32 $\pm$ 17
(8 LAD, 3 RCA)	Hyperemia	1.12 $\pm$ 0.37°	18 $\pm$ 8°	2°	1.1 $\pm$ 0.3°	37 $\pm$ 16
	Inflation	0.50 $\pm$ 0.29	9 $\pm$ 4	10	2.6 $\pm$ 1.1	22 $\pm$ 13

p < 0.05: * vs. baseline, ° vs. inflation

Conclusion: Although TDE/SRI enhances the diagnostic accuracy of adenosine stress echocardiography, it still cannot serve as a reliable noninvasive alternative to FFR for the functional assessment of moderate-to-severe coronary stenosis.

P695 Predictive factors of aerobic capacities improvement after exercise training program in patients with preserved left ventricular function



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Aim: An exercise training program (ETP) is usually performed after valve surgery and myocardial infarction. However, the predictive factors for aerobic capacities improvement after ETP are poorly documented.

Methods: Prospective multicentric study. Patients with preserved left ventricular function (LVEF>45%) underwent an ETP including 30 min on cycloergometer, 3 to 5 times/week during 3 weeks after myocardial infarction or cardiomyopathy. An exercise test with gas analysis was performed before and after the ETP. The aerobic capacities improvement were assessed mainly by the anaerobic threshold (AT) values, a parameter independent of maximum level of exertion (and of patient's motivation), and by the maximal workload (MWL) and peakVO₂ values, obtained after and before the ETP completion.

Results: 202 patients were included; 119 after cardiac surgery (100 Mitral valve repair, 19 aortic replacement) and 83 after myocardial infarction. Mean age was 57 $\pm$ 12 years, mean LVEF was 55 $\pm$ 9%. The study population included elderly patients (patients>70 years, n=43), patients with permanent atrial fibrillation (n=19), women (n=45) and patients receiving a betablocker therapy (n=132). AT, PeakVO₂ and MWL significantly increased after ETP completion (+19 $\pm$ 2%, +22 $\pm$ 1.6%, +25 $\pm$ 1.7%, respectively, p<0.0001). Age, gender, existence of a sinus rhythm, etiology of the cardiopathy, and betablocker therapy were not predictive of AT improvement. AT improvement was inversely correlated to the AT value before ETP (r=0.32, p=0.002).

Conclusion Aerobic capacities improvement was similar regarding age, gender, rhythm, etiology of the cardiopathy, presence or absence of a beta-blocker therapy. Aerobic capacities improvement was inversely correlated with peripheral de-adaptation state before ETP.

P696 Determinants of platelet reactivity in response to exercise in patients with chronic stable angina

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Background: On average, exercise increases platelet reactivity in patients with coronary artery disease (CAD). However there are significant individual differences in the response of platelet reactivity to exercise. No previous study investigated whether clinical and laboratory variables influence the exercise induced increase of platelet reactivity in these patients.

Methods: Venous blood samples were collected from consecutive, unselected patients with chronic stable CAD before and immediately after a symptom-limited exercise stress test (Bruce protocol). Platelet reactivity was measured by the platelet function analyzer (PFA)-100 system as the time for flowing whole blood to occlude a collagen-adenosine diphosphate coated ring (closure time, CT), with shorter CT indicating higher platelet reactivity. Patients taking anticoagulant drugs were excluded. Platelet reactivity was considered to be increased by exercise when a $\geq 10\%$ decrease in CT was observed after exercise, compared to the basal value.

Results: Overall, 214 patients with stable, angiographically documented CAD were enrolled in the study (147 men, mean age 61.9 ± 9 years). Coronary angiography revealed 1-, 2- and 3-vessel CAD in 43%, 36% and 21% of patients, respectively. ST-segment depression ≥ 1 mm and angina were induced by exercise test in 150 (70%) and 58 (27%) patients, respectively. CT decreased significantly after exercise in the whole population of patients (from 95.9 ± 22 to 81.2 ± 18 sec, $p < 0.001$). However a significant exercise-induced increase in platelet reactivity was observed in 125 patients (58.4%). The only univariate predictors of increased platelet reactivity after exercise included exercise duration ($p = 0.027$) and absence of long-acting nitrate therapy ($p = 0.027$). On multivariate regression analysis only nitrate use was associated with the response of platelet reactivity to exercise (odds ratio, 0.55, 95% CI, 0.31-0.97, $p = 0.037$).

Conclusions: Our data confirm that exercise increases platelet reactivity in CAD patients and that the effect is independent of several clinical characteristics, including coronary atherosclerotic burden, platelet count, hematocrit, stress induced ischemia and most medications. Long-term nitrate therapy, however, emerged as an independent protective factor against exercise induced increase in platelet reactivity in this study. This unexpected finding due to its potential relevant clinical implications merits further investigation.

P697 QRS score improves the diagnostic ability of exercise testing in females

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Background: It is known that exercise testing (ET) in female patients has a low diagnostic ability to detect coronary artery disease (CAD) using ST-segment deviations. The aim of the study was to investigate the diagnostic ability of ET using a QRS score compared to the ST-segment deviations.

Methods: We studied 114 female patients with angina-like symptoms, aged 59 ± 6 years. All patients underwent an ET and coronary arteriography. QRS score was calculated as: $(dR - dQ - dS) aVF + (dR - dQ - dS) V5$.

Results: Normal coronary arteries had 53, while CAD was detected in 61 patients (30 had one-vessel-disease, 19 had two-vessel-disease and 12 had three-vessel-disease). The ET showed 68 positive and 46 negative results using ST-segment depression criteria. Sensitivity, specificity and diagnostic accuracy for ST-segment depression and QRS score were found: 59% (36/61) versus 80% (49/61), 40% (21/53) versus 94% (50/53) and 50% (57/114) versus 87% (99/114), respectively ($p < 0.001$). ROC curves for CAD detection showed that the values of the area under the curve for ST-segment depression and QRS score were 0.536 and 0.934, respectively, while the values for the detection of multivessel CAD for ST-segment depression and QRS score were 0.470 and 0.936, respectively. QRS score reduced significantly the false-positive results from 32 (28%) to 3 (3%) ($p < 0.0001$) compared to the ST-segment depression.

Conclusions: QRS score increased significantly the diagnostic ability of the ET and reduced significantly the false-positive results ST-segment depression for CAD detection in female patients.

P698 Post-exercise combination analysis of oxygen consumption and oxygen pulse can enhance diagnostic accuracy of exercise ECG for myocardial ischemia

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Background: Exercise ECG is widely used for diagnosing coronary artery disease (CAD). However false-positive ST responses frequently occur and limit the value of exercise ECG for this purpose. It has also been acknowledged that left ventricular ischemia decreases stroke volume. After stopping exercise, afterload reduction to the left ventricle may result in increases of stroke volume, oxygen consumption, and oxygen pulse in patients with CAD. Accordingly, we investi-

gated whether cardiopulmonary exercise testing could enhance the diagnostic accuracy of exercise ECG for myocardial ischemia.

Methods: Study subjects consisted of 28 patients with a significant ST-segment depression for suspicious myocardial ischemia who were chosen from consecutive 174 patients suffering from chest pain underwent ergometer test. Then, they were divided into 2 groups: 18 patients with CAD on angiography (True Positive: TP group) and 10 patients with normal angiography or normal perfusion on exercise single photon emission computed tomography (False Positive: FP group). In cardiopulmonary exercise test, oxygen consumption and oxygen pulse were measured at peak exercise and 30 seconds after stopping exercise.

Results: Oxygen consumption did not change in TP (1169 ± 372 to 1142 ± 321 ml/min, $p = 0.079$) after exercise but it significantly decreased in FP (1281 ± 434 to 1187 ± 368 ml/min, $p = 0.008$). Oxygen pulse also did not change in TP (8.92 ± 2.64 to 9.08 ± 2.65 ml/beat, $p = 0.253$) after exercise but it significantly reduced in FP (8.75 ± 3.04 to 8.13 ± 2.69 ml/beat, $p = 0.023$). FP patients were discriminated from TP by the reduction of oxygen consumption with a sensitivity of 100% and a specificity of 44% and by the decrease of oxygen pulse with a sensitivity of 90% and a specificity of 78%. The negative predictive value for this analysis was superior with the use of oxygen pulse than oxygen consumption (69% vs 50%).

Conclusion: False-positive ST responses for myocardial ischemia could be detected by the reduction of oxygen consumption from peak to 30 seconds after stopping exercise with a high sensitivity and a relatively low specificity. If a decrease of oxygen pulse is also observed, the accuracy for detecting false-positive ST responses should be increased, however, if not, it should be decreased. These findings indicate that post-exercise combination analysis of oxygen consumption and oxygen pulse could enhance the diagnostic value of exercise ECG for myocardial ischemia.

P699 Obesity influences the stress-ECG in the detection of SPECT reversible defects

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Background: The surface ECG is widely used for screening patients suspected for CAD. The influence of body mass index (BMI) on the accuracy of ECG-stress tests has not been previously assessed in a large population. We assess the diagnostic utility of stress-ECG stratified according to BMI in detecting ischemia using reversible defects (RD) on single-photon emission computed tomography as a gold standard.

Methods: Retrospective database analysis of 29,687 patients (65.7% males, aged 59 ± 12 years) with suspected or known CAD, who had stress-rest SPECT between 1986 - 2002. Bruce-protocol exercise was performed in 20,016 patients (Ex) and Dipyrindamole-stress in 9,671 (Dip). In a subgroup of 1,325 patients (966 Ex, 359 Dip) the coronary angiography was abnormal (CA). Stress ECG's were compared to SPECT acquired the same day, using BMI as a variable.

Results: According to BMI, 1% of the patients were underweight, 35% normal weight (NW), 43% overweight (OW) 21% were obese (OB). In the Ex group, the likelihood of a non-diagnostic or equivocal exercise-ECG (non-diag ECG) increased with BMI (Chi-square=51.12, OR=1.02, 95%CI=1.02-1.03, $p < 0.001$). In NW patients 36% ECG's were non-diagnostic, 37% in OW and 42% in OB. In the Dip group, the positive predictive value of Dip to identify RD was 68% in NW, 73% in OW and 87% in OB. In the Ex group, subgroup CA, the sensitivity of RD was 82% in NW, 88% in OW and 91% in OP, while the sensitivity of exercise-ECG was 33% in NW, 41% in OW and 23% in OB. In the Dip group, subgroup CA, the sensitivity of RD was 92% in NW, 91% in OW and 94% in OB, while only 8/359 patients developed diagnostic ST changes - 3 NW, 5 OW and none OB.

Conclusions: In obese patients, an exercise-ECG is more likely to be non-diagnostic or equivocal and its sensitivity is lower than in patients with normal weight or overweight. The Dipyrindamole-stress test seems to be less influenced by weight, than the exercise-ECG.

P700 Are repolarization abnormalities really the expression of coronary flow reserve impairment?

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Background: The appearance of a down-slope of the ecg ST wave during an exercise-ecg test (ExT) is commonly considered as a marker of myocardial ischemia and therefore of coronary stenosis. On the contrary, in patients with normal coronary angiography it is not clear if repolarization abnormalities are given by an impairment of microvascular function. Coronary flow reserve (CFR) can be measured by transthoracic echocardiography (TTE) during vasodilator stress on the mid-distal left anterior descending (LAD) and posterior descending coronary arteries (PDCA).

Methods: Starting from January 2003, we studied 248 consecutive patients suspected of having coronary artery disease: each of them underwent a treadmill exercise test, adopting the Bruce protocol, and coronary flow evaluation by TTE. Twelve patients with poor acoustic windows were excluded as they did not allow correct evaluation of coronary flow in both coronary arteries. Within 3 months all pts with positive exercise test underwent coronary angiography. We subdivided the patients by applying the conventional positive criteria of ExT. We considered

the pts with positive ExT and negative coronary angiography (< 50%) (166 pts) as group 1 and the pts with negative ExT as group 2 (70 pts). Coronary flow and reserve were evaluated by stress echocardiography TTE (S3-S8 probe, second harmonic 3.6-7 MHz, HP 5500-7500, Philips technology). The mid-distal LAD coronary artery was imaged from a modified apical two-chamber view and mid-distal right coronary was mapped by highlighting the diaphragmatic wall of LV. The peak diastolic coronary flow velocity of each coronary artery was recorded by pulsed Doppler under the guidance of Color Doppler flow mapping. CFR was calculated as the ratio of dipyridamole/rest peak diastolic flow velocity (0.84 mg over 6 m').

Results: The CFR value of LAD was correctly detected in 230/236 (92.4%) and in 176/236 (75%) for PDCA. We matched the mean CFR value between LAD and RCA in the two different groups: Group 1 showed a mean down-slope of 1.9 ± 0.6 and Group 2 showed 0.4 ± 0.3 ($p < 0.001$). The mean value of CFR resulted lower in Group A (2.32 ± 0.41) in comparison with Group B (3.18 ± 0.40) ($p = 0.0037$).

Conclusion: By analysing the two major coronary arteries, LAD and RCA, we conclude that an impairment of coronary flow reserve, in patients without coronary stenosis, may play an important role in inducing a down-slope of the ST wave during ExT. CFR reduction induces a subendocardial flow redistribution and therefore can induce an inversion of the repolarization wave at Ecg-test.

P701 VE/VC02 slope and oxygen uptake efficiency slope in patients with coronary artery disease and intermediate VO2max



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Background: Peak exercise oxygen uptake (VO₂max) is a widely used prognosticator. Novel spirometric parameters, less affected by submaximal performance, such as the rate of increase of minute ventilation per unit decrease of carbon dioxide production (VE/VC02 slope) and the oxygen uptake efficiency slope (OUES) have recently been introduced.

Aim: To evaluate the discriminative value of OUES, as compared to VE/VC02 slope in patients with coronary artery disease (CAD) and intermediate VO₂max values.

Methods and results: Bicycle spirometry was applied in 214 patients with CAD (age 67 ± 8 years, 85% men). OUES was strongly related to VO₂max ($r = 0.79$). Severity of heart failure was evaluated with New York Heart Association (NYHA) class, 6 minutes walking distance, N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), inflammatory markers, left ventricular (LV) volumes and ejection fraction. NT-proBNP levels predicted independently VE/VC02 slope and OUES. Patients with intermediate VO₂max (12-18 ml/kg/min) and increased VE/VC02 slope (≥ 35) had higher NYHA class, lower walking distance, higher NT-proBNP levels and higher LV volumes as compared to patients with a similar VO₂max but lower VE/VC02 slope. Similar findings were found for patients with intermediate VO₂max and high OUES/kg (median value > 15.3).

Conclusion: In CAD patients, OUES was strongly correlated to VO₂max. Both VE/VC02 slope and OUES were independently predicted by NT-proBNP levels and were related to heart failure severity parameters. Both VE/VC02 slope and OUES/kg were able to identify a subgroup of patients with an intermediate VO₂max that was characterized by advanced remodelling and a higher degree of neurohumoral activation.

P702 Value of post-exercise B-type natriuretic peptide level in the prediction of coronary artery disease in patients with positive exercise electrocardiogram



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Background: Exercise electrocardiography (ECG) is a well-established and the most widely used noninvasive tool to detect the presence of coronary artery disease (CAD), however, its usefulness is limited by relatively modest sensitivity and specificity. False positivity of exercise ECG is an important problem resulting in many unnecessary further investigations. In this study, we aimed to test the hypothesis that, if postexercise B-type natriuretic peptides (BNP) secreted in response to transient myocardial ischemia induced by exercise, add any further information on positive test results.

Methods: Patients who underwent exercise ECG with the suspicion of CAD were prospectively screened and those with positive test results based on standard ECG criteria were selected. Patients with history of CAD (stable, unstable or previous myocardial infarction), heart failure, significant valvular disease (including replacement), echocardiographic left ventricular ejection fraction $< 45\%$ or those with abnormal resting ECGs that would preclude interpretation of exercise-induced changes were excluded. Blood samples for BNP were obtained within 5 minutes after exercise test. At least 60% stenosis of one epicardial coronary artery on coronary angiogram was diagnosed as significant CAD.

Results: Of the 55 patients (age 59.8 ± 7.6 yrs; 48 male, 7 female) included in the study, 30 had (54.5%) CAD requiring revascularization (CAD+) and 25 (45.6%) did not have significant CAD (CAD-). Groups were similar with respect to

age, sex, cardiac risk factor profile and commonly used medications (all $p > 0.05$). Means of achieved metabolic equivalents, rate-pressure product, max. ST depression in mm, and number of anginal episodes were also similar (all $p > 0.05$). However, max. heart rate (HR), percent of target HR achieved and the frequency of patients achieving $> 85\%$ of predicted max. HR were significantly higher in CAD+ group ($p = 0.013$, $p = 0.001$ and $p = 0.013$, respectively). The mean postexercise BNP level was significantly higher in CAD+ (55.4 ± 46.6 pg/ml) than CAD- patients (24.8 ± 18.5 pg/ml) ($p = 0.004$). The sensitivity and specificity of a postexercise BNP level > 30 pg/ml for the diagnosis of CAD in exercise ECG positive patients were 70% and 68% respectively. The diagnostic accuracy of this BNP level was 69%. The prevalence of significant CAD was 72% in patients with a postexercise BNP over 30pg/mL, whereas it was decreased to 34% when the BNP was below 30pg/mL (Odds ratio: 2.4, 95% CI: 1.2-4.4). Conclusion: The measurement of postexercise BNP levels may increase the diagnostic value of positive exercise ECG results.

P703 Prompt human coronary collateral vasomotor function induced by dynamic physical exercise



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Introduction: The existence of coronary collateral vessels and their benefit against cardiac events have been recognized for many years, but their functional capacity in response to physical exercise has partially remained elusive. Via endothelial shear stress, the fundamental stimulus for collateral development, exercise theoretically leads to collateral vasodilation and recruitment by an increase in heart rate and blood pressure during exercise. Moreover, the phenomenon of "walking through angina" indicates that collateral function and physical activity are related and their interaction is of clinical relevance. The purpose of the present study in humans with stable coronary artery disease was to assess the instantaneous response of coronary collateral function to dynamic physical exercise.

Methods: Ten patients (age 62.5 ± 9 years) undergoing PCI because of stable angina pectoris were included in the study. Collateral function was determined before and during the last minute of a 6-minute protocol of supine bicycle exercise during radial access coronary angiography. Collateral flow index CFI (no unit) was assessed by means of a pressure guide wire distal to the balloon-occluded artery. To avoid confounding due to recruitment of coronary collaterals by repetitive balloon occlusions, patients were randomly assigned to a group 'rest first' with CFI measurement during rest followed by a measurement during exercise, and to a group 'exercise first' with antecedent CFI measurement during exercise before measurement during rest.

Results: Collateral flow index was 0.163 (0.117) and 0.257 (0.224) during rest and during exercise, respectively ($p = 0.013$). CFI of the group 'rest-first' was 0.123 (0.061) during rest and 0.197 (0.109) during exercise ($p = 0.08$). In the group 'exercise first', CFI at rest was 0.203 (0.152), and 0.317 during exercise (0.303) ($p = 0.08$).

Conclusion: Exercise instantaneously improves collateral function during dynamic exercise. The phenomenon of "walking through angina" seems to be explainable, at least partly, by recruitment of coronary collaterals during physical effort.

P704 Safety and utility of exercise test in the evaluation of low risk patients with acute chest pain in the emergency department



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Background Safe and efficient management of low risk patients presenting to the emergency department (ED) with acute chest pain is a continuing challenge. Optimal management and risk stratification of this group could prevent unnecessary hospital admission, affording more patient care, and improve cost effectiveness. We evaluated the safety and utility of early exercise treadmill testing (ETT) in the assessment of short-term risk for such patients.

Methods Patients presented to the ED with acute chest pain compatible with a possible cardiac origin and clinical evidence of low risk on initial assessment underwent early ETT after 6-12 hours of observation in the chest pain unit (CPU). Indicators of low clinical risk included absence of hemodynamic instability, arrhythmias or electrocardiographic signs of ischemia, and serial negative cardiac marker (Troponin-I & Ck-MB).

Results One hundred and seventy patients were enrolled; 135 (79.4%) patients with no prior history of coronary artery disease (CAD) group-I, and 35 (20.6%) patients with prior history of CAD (group-II). ETT using standard Bruce protocol was performed to all patients after 6-12 hours of observation. The ETT result was negative in (74.8% of group-I patients vs. 60% of group-II patients, $p = NS$), positive in (15.6% of group-I patients vs. 31.4% of group-II patients, $p = 0.03$) and was non-diagnostic in (9.6% of group-I patients vs. 8.6% of group-II patients, $p = NS$). There were no adverse events related to ETT and all patients with a negative ETT were discharged directly. Patients with positive or non-diagnostic ETTs underwent coronary angiography. CAD was documented in (92.9% of group-II patients vs. 44.1% of group-I patients, p value = 0.002). At six months follow-up there were no major adverse cardiac events, defined as fatal, non-fatal myocardial infarction and sudden death in both groups. Patients in group-I had fewer additional

revisits to the ED and hospital admissions than those in group-II (2.2% vs. 2.8%, $p=NS$) respectively.

Conclusion Early exercise treadmill testing after a period of observation in the CPU of low-risk patients presenting to the ED with chest pain is safe and effective in further stratifying this group into patients who can be safely discharged and those who require further evaluation after admission.

P705 Comparison of real-time three-dimensional bicycle stress echocardiography with conventional two-dimensional bicycle stress echo



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Purpose: Two-dimensional bicycle stress echo (2-D-BSE) is a safe and accurate method for diagnosing coronary artery disease (CAD), but adequate image acquisition is difficult at peak stress due to motion artefacts and hyperventilation. Newly introduced three-dimensional echo allows rapid image acquisition of the entire left ventricle using an apical imaging plane. The aim of the study was 1) to evaluate the diagnostic accuracy of three-dimensional bicycle stress echo (3-D BSE) and 2) to answer the question if image acquisition is facilitated by this new approach. **Methods:** 35 consecutive patients (pts) with clinically suspected CAD scheduled for coronary angiography were investigated. In all pts 2-D BSE and 3-D BSE were performed in a randomized order by one experienced investigator; there was a time delay of at least 2 hours between the first and the second BSE. 2-D BSE images were acquired from parasternal and apical image planes, 3-D BSE images from the apical window. Analysis of 3-D BSE was performed from anatomical images by cropping the full volume data sets.

Results: Mean time for adequate image acquisition at peak stress was shorter for 3-D BSE than for 2-D BSE (26 ± 6 s compared to 78 ± 9 s, $p < 0.001$). Image quality at rest and peak stress was sufficient to evaluate all three coronary territories in 92% in 3-D BSE and in 96% in 2-D BSE. There was no significant difference regarding sensitivity and specificity of 3-D BSE (89 and 92%) compared with 2-D BSE (92 and 94%), to detect CAD.

Conclusions: In bicycle stress echo 3-D image acquisition is rapid and accurate and allows reproducible assessment of myocardial ischemia. The shortening of the acquisition time in stress echocardiography makes this technique a promising and useful tool for daily clinical practice.

EXERCISE AS A DIAGNOSTIC AND THERAPEUTIC MODALITY

P706 The improvement in cardiopulmonary physiology following cardiac resynchronisation therapy



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Background: Cardiac Resynchronisation Therapy (CRT) has been shown to improve morbidity and mortality in patients with symptomatic heart failure and evidence of electromechanical dyssynchrony. The physiological changes underpinning this improvement have not been fully described. We investigated the longitudinal effect of CRT on exercise haemodynamic measures.

Methods: 53 patients referred to our centre for CRT were assessed pre CRT and 2 weeks, 6 weeks, 3 months and 6 months post CRT. At each test the patients NYHA class was recorded and then a modified Bruce Protocol treadmill test was performed. VCO₂ and VO₂ were measured on a breath-by-breath basis. Total exercise duration, peak VO₂ and VE/VCO₂ slopes were measured. The Anaerobic Threshold (AT) was calculated using the V-slope method. A repeated measures ANOVA was used to look for statistically significant differences between the baseline and post CRT tests.

Results: Post CRT there was significant improvement in NYHA class, Exercise Duration, Peak VO₂ and VE/VCO₂ slopes within 2 weeks of implantation. This improvement was maintained till 6 months. The VO₂ at the Anaerobic Threshold did not change throughout the study ($p=1.0$). See table for full results (given as mean (SE)).

	Pre CRT	2 weeks post	6 weeks post	3 months post	6 months post
NYHA class	3.0 (0.0)	2.1 (0.1)*	2.0 (0.1)*	1.8 (0.1)*	1.5 (0.1)*†
Exercise Duration (secs)	355 (38)	502 (37)*	584 (41)*	603 (47)*	694 (46)*†
Peak VO ₂ (mls/kg/min)	16.10 (0.69)	18.14 (0.55)*	18.34 (0.62)*	19.15 (0.71)*	19.52 (0.73)*
VO ₂ at AT	12.64 (0.54)	12.41 (0.42)	12.67 (0.53)	13.02 (0.52)	12.85 (0.57)
VE/VCO ₂ slope	42.14 (2.10)	37.88 (1.38)*	38.09 (1.39)*	37.92 (1.37)*	37.41 (1.51)*

* $p < 0.05$ compared to Pre CRT, † $p < 0.05$ compared to 6 weeks post

Conclusions: CRT leads to significant improvements as early as 2 weeks post CRT. The improvement in Exercise Duration and NYHA class is brought about by an improvement in peak VO₂ and respiratory efficiency, as shown by the significant reduction in the ventilatory equivalent for CO₂. During the study the VO₂ at

the Anaerobic Threshold was unchanged. This coupled with the improvements in peak VO₂ shows that there is an improved ability to perform anaerobic exercise following CRT.

P707 Response of the oxygen uptake efficiency slope to exercise training in patients with chronic heart failure



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Background: The oxygen uptake efficiency slope (OUES) is a new objective and effort-independent exercise parameter that highly correlates to peakVO₂ and provides prognostic power in patients with CHF. Little is known about effects of exercise training (ET) on OUES. Aim: To describe the response of OUES to 6 months of ET in patients with CHF and to compare its evolution to that of other exercise variables.

Methods: 35 patients with stable CHF (NYHA II-III, age 54 ± 9 years, LVEF of $31 \pm 10\%$) participated in an ET program. Patients performed 3 maximal exercise tests i.e. at the start, in the middle and at the end of the ET program. OUES was determined from the linear relation between oxygen uptake and the logarithm of ventilation during exercise. PeakVO₂, anaerobic threshold (VAT) and slopeVE/VCO₂ were determined.

Results: OUES/kg correlated to peakVO₂ ($r=0.78$; $p < 0.001$). OUES/kg, peakVO₂, VAT, slopeVE/VCO₂, peakWatt, 6MWT and NYHA-class improved during the first half of the ET period ($p < 0.05$), whereas only VAT, peakWatt and 6MWT continued to improve during the second part of the ET period ($p < 0.05$). The improvements in OUES/kg after the first and the second part of the training period correlated better with the improvements in peakVO₂ ($r=0.64$ and $r=0.77$, $p < 0.001$) (see fig. 1), than with changes in other exercise variables.

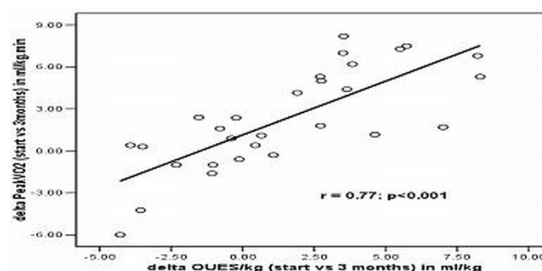


Fig. 1

Discussion: OUES/kg improves significantly after 6 months of ET. The changes in peakVO₂ correlate better with the changes in OUES/kg than with changes in other prognostic exercise parameters. In conclusion, OUES is sensitive to ET and can be used to objectively evaluate the progression of exercise capacity in patients with stable CHF.

P708 Critical level of cerebral oxygenation during exercise in patients with dilated cardiomyopathy

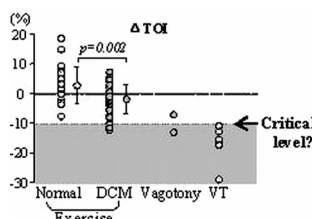


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Background: Our group recently reported that the indexes of cerebral oxygenation decreased during maximal exercise in nearly half of all patients with left ventricular dysfunction, indicating a condition of cerebral hypoxia. In this study we evaluated whether these levels decrease severely enough to influence brain function.

Methods: Thirty-five patients with dilated cardiomyopathy (DCM) and 22 healthy subjects underwent a symptom-limited maximal exercise test. The cerebral tissue oxygenation index (TOI) was continuously monitored using near infrared spectroscopy. The magnitude of the change (decrease) in TOI was obtained in 2 subjects who experienced episodes of reduced consciousness due to sudden decreases in blood pressure during exercise recovery induced by a parasympathetic reflex, and 5 subjects who exhibited sustained ventricular tachycardia during an electrophysiological study.

Results: The cerebral TOI during exercise in DCM patients changed by -



2.0±5.0% (ranging from -11.7 to 7.3%), or to a level significantly lower than that recorded in normal subjects (2.9±6.2%, $p=0.002$). The cerebral TOI decreased in 23 out of 35 patients. The mean decrease in cerebral TOI was -9.7% in the patients with parasympathetic reflex and -16.5% in those with ventricular tachycardia.

Conclusions: The present findings suggest that the TOI may drop severely enough to influence brain function in some patients with DCM during maximal exercise.

P709 Exercise-induced desaturation at high altitude: the role of thoraco-abdominal coordination



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Purpose - While hyperventilation is a key factor for successful physical performance and acclimatisation at high altitude, the importance of maintaining breathing efficiency is less clear. We tested whether a loss in breathing efficiency can reduce oxygen saturation (SpO₂%) during exercise, hence contributing to limit physical performance.

Methods - We studied 8 elite male climbers (age 36-52) during the 2004 Italian expedition to Everest and K2, at sea level (SL) and at the North Face Everest base camp, 5200m, reached after 7 days of staying above 3500m. Measurements were made at rest (30' monitoring) and during exercise. At SL: a cardiopulmonary exercise test (cycloergometer) until exhaustion was performed. At 5200m the climbers covered a set route around base camp. The distance, the slope and the speed were continuously acquired in each subject by a portable data logger equipped with a global positioning system (GPS, Ashtech) used in differential mode (80cm precision). Breathing patterns (thoraco-abdominal coordination index, RC%, as an index of breathing efficiency), minute ventilation (VE) and SpO₂% were continuously recorded by computerised devices (LifeShirt®, VivoMetrics), synchronised with the GPS system.

Results: At SL, VE increased from rest to exercise causing no significant changes in RC% and SpO₂%. At 5200m, resting VE and RC were higher ($p<0.05$) than at SL, but during exercise (average distance: 905±4m, mean±SD, exercise time: 17.5±8.0min, slope: 9.2±2.3%, speed: 0.95±0.012m/s, VE: from 21.3±1.7 to 46.5±5.5L/min, $p<0.05$) we found a marked drop in SpO₂% (from 73.4±6.9 to 63.6±3.4%, $p<0.05$) and a negative correlation between RC% and: mean speed ($r=-0.72$, $p=0.02$), mean slope ($r=-0.58$, $p=0.028$), difference in altitude ($r=-0.88$, $p=0.01$) and the exercise-induced SpO₂% decrease ($r=-0.58$, $p=0.028$).

Conclusions: During acclimatisation to high altitude, exercise at faster speed impairs thoraco-abdominal coordination and worsens SpO₂%, suggesting that breathing inefficiency may occur during hyperventilation. This, in turn, may increase the cost of breathing, and thus contribute to limit exercise performance in hypoxia. These results support the use of training aimed at improving thoraco-abdominal coordination, and may be relevant when planning physical tasks to be performed at high altitude, or when planning exercise programs in cardiac or pulmonary patients prone to exercise desaturation.

P710 Effects of chronic physical exercise on dominant frequency of ventricular fibrillation heterogeneity produced by acute coronary artery occlusion. A study in isolated rabbit heart



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Several reports indicate that chronic exercise can protect against cardiac sudden death. Nevertheless, the reasons why physical training exerts beneficial effects are not completely understood. As it is known, myocardial electrophysiological heterogeneities are major determinants of conduction block and spatial dispersion of repolarization and thus for reentrant arrhythmias. Cardiac tissue contains structural discontinuities and heterogeneities that become more important in pathophysiological circumstances (i.e., myocardial ischemia). The objective of this research was to investigate the effect of physical training on the electrophysiological heterogeneity of ischemic myocardium, by means of the dominant frequency (DF) of ventricular fibrillation (VF) analysis. Eight NZW rabbits were submitted to a six-week endurance exercisetaining program, and eight controls were not trained. When the exercise program was finished, rabbits were anaesthetized (ketamine, 10 mg/kg i.v.), killed and the hearts excised, isolated and perfused in a Langendorff system. A pacing electrode and a plaque with 256 recording electrodes were positioned on the left ventricle. VF was induced by pacing at increasing frequencies before to the coronary artery occlusion (CAO) and later defibrillated. To produce VF after CAO two successive series of coupled extrastimuli were applied five minutes after the CAO, and if VF did not appear, the arrhythmia was induced by ventricular pacing at increasing frequency 25 min. after CAO (5 min before finishing the experiment). DF of VF was determined by a spectral analysis (Welch's method). Mean DF of VF and its standard deviation in each experiment was determined in order to calculate the variation coefficient (VC), as an index of myocardial heterogeneity. Maximum and minimum DF were also

determined. Paired Student's *t* test was used to compare basal versus 30 min. post-occlusion data.

VC increased 30 min after CAO versus basal value in the control group (19.6% ± 12.3 vs 11.9% ± 3.7; $n=8$; $p<0.05$), but did not change in the trained group (16 ± 7.1% vs 11.9 ± 5%; $n=8$; ns). Minimum DF decreased 30 min after CAO versus basal value in the control group (5.3 ± 1.6 vs 9.2 ± 3 Hz; $n=8$; $p<0.05$), but did not change in the trained group (7.9 ± 4 vs 11.2 ± 1 Hz; $n=8$; ns). Mean and Maximum DF of VF did not change after CAO either in the control and the trained groups.

These results indicate that physical training could exert beneficial effects against ischemic reentrant arrhythmias by means of decreasing myocardial heterogeneity.

P711 The initial slope of the VO₂/VCO₂ curve (s1) in cardiopulmonary exercise testing is the strongest predictor of outcome in patients with ischemic cardiomyopathy



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Prognosis of heart failure remains poor despite novel therapeutic strategies. Therefore, identification of parameters to detect heart failure patients at risk remains one major goal. We assessed 103 patients with chronic heart failure due to ischemic heart disease (IHD) by sequential cardiopulmonary exercise testing (CPET), measurement of ANP and NT-BNP-serum concentrations as well as ejection fraction determined by volumetric analysis of LV angiograms. Anaerobic threshold (AT) was calculated by the v-slope method. All patients received optimized medical therapy (i.e. beta blocker, ACE inhibitor and combined diuretics).

Results: Left ventricular ejection fraction (EF) and CPET-parameters were reduced (EF: 42 ± 11%, VO₂max: 16 ± 4 ml/min/kg, maximal oxygen pulse (O₂Pmax): 12 ± 4 ml), NT-BNP-serum-levels were elevated (1177 ± 1500 pmol/ml), and the average NYHA-class was II. After 1 year of follow-up, the combined endpoint of death, stroke and myocardial infarction occurred in 9 patients; 5 patients died from cardiac-related causes. Surprisingly, none of the parameters EF, NYHA-class, ANP or NT-BNP-level was associated with an elevated risk for adverse outcome after 1 year. Regarding CPET-parameters related to maximal exercise, only VO₂max correlated with cardiac-related death (VO₂max: -0.285, $p=0.005$). Among "submaximal" CPET parameters, s1, which is the slope of the VO₂/VCO₂ curve until reaching the AT, was significantly elevated in patients with adverse outcome (0.92 ± 0.05 vs. 0.83 ± 0.08 $p=0.004$). In contrast to VO₂max and O₂Pmax, s1 did not correlate with NT-BNP levels. Multivariate analysis revealed s1 as the predominant independent predictor of adverse outcome ($p<0.001$).

Conclusion: In patients with moderate to severe chronic ischemic cardiomyopathy under maximal pharmacological treatment, ejection fraction and NT-BNP-levels did not provide sufficient predictive value for adverse events after 1 year. In contrast, s1, the steepness of the VO₂/VCO₂ slope, proved to be the strongest independent predictor of 1-year-outcome. As some patients are not capable or willing to attain maximal exertion, VO₂max and O₂Pmax might be underestimated. S1, in contrast, is easily obtained at submaximal exercise levels and might prove a more reliable prognostic parameter for patients with ischemic cardiomyopathy already under optimized treatment.

P712 Relationship between exercise tolerance and prolonged QRS duration, diastolic function and etiology of the syndrome in patients with heart failure



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The factors limiting exercise tolerance in chronic heart failure (CHF) remain a matter of debate. It have been suggested in different studies, that among others, BNP level, QRS duration and diastolic dysfunction are independent predictors of peak VO₂. It is not clear if the etiology of the syndrome has an impact on peak VO₂. Our aim was to assess the relationship between peak VO₂ and BNP levels, QRS duration, diastolic function and etiology in patients with clinically stable CHF.

Methods: In 70 patients (age 51.9 ± 10.1 yrs) with LVEF 26.8 ± 7.9%, in sinus rhythm, a complete echocardiography (with assessment of severe diastolic dysfunction - restrictive filling pattern - RFP) and cardiopulmonary exercise test with assessment of peak VO₂ were performed. BNP was measured using RIA method.

Results: In 35 pts ischaemic cardiomyopathy (CAD) was diagnosed, 13 with narrow QRS (100.6 ± 7.6 ms) and 22 with wide QRS (143 ± 23.9 ms); in 25 pts - dilated non-CAD cardiomyopathy, in 22 with normal QRS (100.7 ± 10.7 ms) and 13 with prolonged QRS duration (162 ± 23 ms; $p=0.015$ compared with CAD). In the whole investigated group peak VO₂ was significantly lower (15 ± 4.5 vs 18 ± 4.4 ml/kg/min; $p=0.003$) and BNP level significantly higher (89 ± 76 vs 44 ± 39 pg/ml; $p=0.008$) in patients with QRS ≥ 120 ms vs pts with QRS < 120 ms. In patients with CAD there weren't any significant differences between groups with QRS ≥ 120 ms and < 120 ms in peak VO₂, BNP levels and severe diastolic dysfunction frequency. Contrary in patients with non-CAD cardiomyopathy there were significant differences between groups with QRS ≥ 120 ms and < 120 ms in

peak VO₂ (16 ± 3.6 vs 19.6 ± 3.4 ml/kg/min; $p = 0.009$), BNP levels (87 ± 80 vs 32 ± 27 pg/ml; $p = 0.02$) and severe diastolic dysfunction frequency (62 vs 27% ; $p = 0.045$). In the whole group there were significant reverse correlations between peak VO₂ and BNP levels ($r = -0.31$; $p = 0.02$); peak VO₂ and QRS duration ($r = -0.27$; $p = 0.02$). There was a significant correlation between peak VO₂ and parameter of diastolic function: DTE ($r = 0.28$; $p = 0.02$). Furthermore peak VO₂ was significantly lower in CAD in comparison to non-CAD cardiomyopathy (14.7 ± 4.8 vs 18.4 ± 3.8 ml/kg/min; $p = 0.0009$). In multivariate regression analysis etiology, DTE and QRS duration were independently associated with peak VO₂.

Conclusion: In patients with CHF peak VO₂ may be predicted based on etiology of the syndrome, left ventricular diastolic function and QRS duration. Prolonged QRS may be better predictor of more advanced CHF in patients with non-CAD than in CAD cardiomyopathy.

P713 Combined use of peak VO₂ and exercise-induced ST elevation accurately predicts future cardiac deaths in patients with non-ischemic DCM

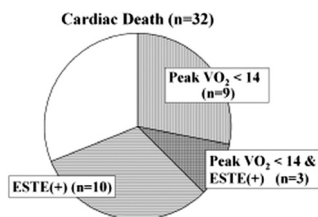


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Background: Although peak VO₂ is an established marker for predicting prognosis, its predictive power is not necessarily sufficient. We have recently reported that, even in the absence of coronary artery disease, exercise-induced ST elevation (ESTE) can be seen in patients with non-ischemic dilated cardiomyopathy (DCM) and that ESTE seen in these patients indicates a markedly depressed LV dysfunction and predicts poor prognosis. We hypothesized that the combined use of peak VO₂ and ESTE would greatly enhance the predictive power for mortality.

Methods: In patients with DCM ($n=238$, LVEF= $30 \pm 11\%$), we examined 12-lead ECGs during symptom-limited exercise testing. Patients ($n=18$) with wide QRS (>120 ms) were excluded. ESTE was defined as ST-segment elevation (J-point >1.0 mm) compared with baseline level. We conducted long-term follow-up (51 ± 23 months) for cardiac death (including hospitalizations for transplantation and LVAD support).

Results: Low peak VO₂ (<14 ml/min/kg) was observed in 28, while ESTE was seen in 27. During the follow-up period, cardiac deaths occurred in 32; only 12 of these 32 patients (38%) showed low peak VO₂ <14 , while half of the remaining 20 patients (10/20=50%) had ESTE. Both of peak VO₂ <14 and ESTE were found in only 3 patients (Figure). Combined criteria (either peak VO₂ <14 or ESTE) greatly increased the sensitivity from 38 to 69% without significantly compromising the specificity (91% vs 85%), compared with low peak VO₂ alone.



Predictors for cardiac death.

Conclusion: Combined use of peak VO₂ and ESTE greatly enhances the predictive power for mortality. The measures of low peak VO₂ and ESTE may reflect different aspects of the pathophysiological processes leading to cardiac death.

P714 Comparison of the prognostic value of peak VO₂, peak circulatory power and VE/CO₂ slope in chronic heart failure patients treated with beta-blockers



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Background: Beta-blockers (BB) improve survival in chronic heart failure (CHF) without influencing peak oxygen uptake (PVO₂), a strong predictor of mortality. This raises the concern that the prognostic value of PVO₂ may be impaired in the setting of beta-blockade.

Purpose: To ascertain the value of PVO₂ in predicting outcome in CHF patients treated with BB and to compare it with two other exercise parameters: the slope of increase in ventilation relative to carbon dioxide production (VE/CO₂) and the peak circulatory power (CP) defined as PVO₂ x maximal systolic blood pressure.

Methods: We analyzed prospectively collected data on 127 consecutive patients with CHF treated with BB who underwent symptom-limited treadmill cardiopulmonary testing. Using the Cox proportional hazards model, univariate and multivariate hazard ratios (HR) were determined for all variables predicting the combined end point of death or heart transplantation. The discrimination power of independent predictor variables was tested by calculating the area under a ROC curve (C-index).

Results: During a median follow-up of 14.2 months among survivors (interquartile range 11.2-18.2), 5 (3.9%) patients died and 11 (8.7%) underwent cardiac transplantation. Univariate analysis yielded 4 predictors of death or transplantation: PVO₂ (HR 0.81 for each increase of 1ml/kg/min; 95%CI 0.71-0.93; $p=0.003$);

VE/CO₂ slope (HR 1.18; 95%CI 1.11-1.26; $p<0.001$); CP (HR 0.98 for each increment of 10mmHg.ml/kg/min; 95%CI 0.97-0.99; $p<0.001$); and the increase in systolic blood pressure (HR 0.65 for each 10mmHg; 95%CI: 0.52-0.81; $p<0.001$). However, only VE/CO₂ slope (HR 1.18; 95%CI 1.10-1.26; $p<0.001$) and the increase in systolic blood pressure (HR 0.77; 95%CI 0.60-0.98; $p=0.033$) remained statistically significant in the multivariate Cox model. Both these variables showed good discrimination power: area under ROC curve 0.87 (95%CI 0.77-0.98; $p<0.001$) and 0.80 (95%CI 0.68-0.93; $p<0.001$), respectively.

Conclusions: - PVO₂ is not an independent predictor of death or cardiac transplantation in CHF patients treated with BB. VE/CO₂ slope has greater prognostic value than PVO₂ and CP in this setting.

P715 Relationship of cardiopulmonary exercise performance to myocardial tissue velocity in heart failure and atrial fibrillation



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Background: Myocardial function determines tissue oxygen delivery and thus exercise capacity. The relationship of myocardial wall motion and oxygen uptake during exercise requires further investigation.

Methods: Thirty one subjects (25 male, 6 female) were studied: healthy subjects ($n=11$, age 29 ± 8 yrs); heart failure ($n=8$, age 77 ± 6 yrs, NYHA III/IV) and atrial fibrillation ($n=12$, age 73 ± 9 yrs). Incremental exercise testing was performed using a semirecumbent cycle ergometer. Apical pulsedwave tissue velocity traces for the anterior, inferior, septal and lateral walls were taken at the level of the mitral valve annulus using a System V GE scanner. Data was analysed offline using Echopac. Longitudinal systolic myocardial velocities for the left ventricle were averaged for rest (rVel) and peak exercise (pVel). Peak oxygen uptake (VO₂ peak) was measured using a Jaeger Oxycon system. Changes in myocardial velocities (Δ Vel) and oxygen uptake (Δ VO₂) from rest to peak exercise were calculated.

Results: Significant differences between groups were found for rVel, pVel, Δ Vel, VO₂ peak and Δ VO₂ ($p<0.001$). Significant relationships using linear regression were found between rVel and VO₂ peak ($r^2=0.672$, $p<0.001$); pVel and VO₂ peak ($r^2=0.878$, $p<0.001$), Δ Vel and VO₂ peak ($r^2=0.843$, $p<0.001$); Δ Vel and Δ VO₂ ($r^2=0.854$, $p<0.001$). Multiple regression analysis showed pVel to be the best predictor of VO₂ peak (see figure). pVel and rVel but not LVEF, age or Δ Vel showed a significant ($p<0.05$) relationship with pVO₂ in the heart failure and AF groups.

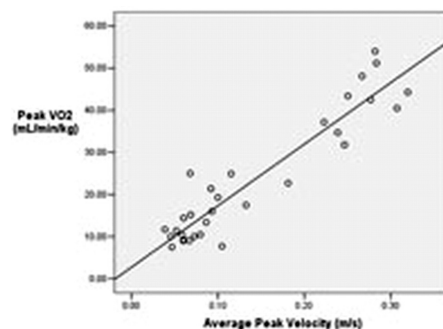


Fig. 1. Linear regression of peak VO₂ and peak myocardial systolic velocity.

Conclusion: Resting and exercise left ventricular peak systolic tissue velocities can be used as a surrogate marker for VO₂ peak and exercise capacity in heart failure and atrial fibrillation patients.

P716 Oxygen Uptake Efficiency Slope is a useful objective parameter of cardiopulmonary function in subjects with insufficient metabolic stress



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Background: Peak oxygen consumption (peak VO₂) has been frequently used as one of the most reliable parameters of cardiopulmonary function and acknowledged that peak VO₂ is greater than 20 ml/min/kg in normal subjects. However, this index is effort-dependent and may be underestimated because of inadequate patient's motivation and of problems in lower extremities. The Oxygen Uptake Efficiency Slope (OUES) derived from the logarithmic relation between oxygen uptake (VO₂) and minute ventilation (VE) during incremental exercise has been introduced as a new submaximal parameter which may objectively predict the maximal exercise capacity. Thus we investigated whether OUES could be useful in the evaluation of cardiopulmonary reserve in subjects with insufficient metabolic stress.

Methods: We performed symptom-limited exercise testing with respiratory gas analysis in 114 elderly subjects over 60 years. We selected 68 patients in whom peak VO₂ was lower than 20 ml/min/kg. According to the peak respiratory quotient

(RQ), they were divided into Group 1 ($RQ \leq 1.2$, $n=36$) and Group 2 ($RQ > 1.2$, $n=32$). During incremental exercise, $\dot{V}O_2$ was plotted against the logarithm of VE, and then the OUES was determined. OUES and $\dot{V}O_2$ were calculated from the data of the first 75%, 90% and 100% of exercise duration to evaluate the stability at different stages.

Results: Peak $\dot{V}O_2$ /kg in Group 1 was significantly lower than that in Group 2 (15.0 ± 3.1 vs 16.4 ± 2.6 ml/min/kg, $p=0.046$). On the contrary, OUES/kg in Group 1 was significantly greater than that in Group 2 (23.4 ± 3.8 vs 21.4 ± 3.7 , $p=0.036$). $\dot{V}O_2$ /kg at 75% and 90% of exercise duration were significantly lower compared with the peak $\dot{V}O_2$ /kg ($p < 0.0001$). In contrast, OUES/kg did not change between 75%, 90% and 100% of exercise duration ($p=0.825$).

Conclusion: These findings suggest that peak $\dot{V}O_2$ is effort-dependent and is underestimated in subjects with insufficient metabolic stress. OUES remains stable over the entire exercise duration and could be a useful objective parameter of cardiopulmonary function in such subjects.

P717 Aortic stiffness is an independent determinant of exercise capacity in patients with coronary artery disease

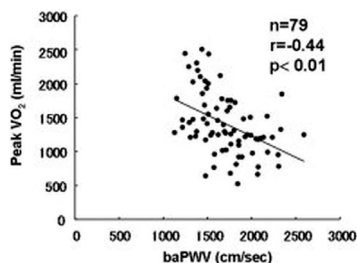


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Objective: Pulse wave velocity (PWV), which is a useful index of arterial stiffness, is elevated in patients with coronary artery disease (CAD). Previous studies demonstrated that PWV modulates left ventricular systolic and diastolic function; however, an influence of PWV on exercise capacity in patients with CAD has not been fully clarified. In this study, we evaluated the relationship between PWV and exercise capacity in patients with CAD.

Methods: We studied 79 clinically stable patients with angiographically proven CAD (69±7yo, 64men). Subjects underwent symptom limited cardiopulmonary exercise testing (CPX) as a measurement of exercise capacity. We also measured brachial-ankle PWV (baPWV) using an automated device (form ABI/PWV, Colin, Japan) prior to CPX.

Results: In univariate analysis, baPWV significantly correlated with $\dot{V}O_{2\text{peak}}$ ($r=-0.44$, $p<0.05$, figure). In multivariate analysis, baPWV was an independent predictor of $\dot{V}O_{2\text{peak}}$ independently of left ventricular function. In patients with increased baPWV (over 2000cm/sec, $n=16$), time to ST depression was shorter (317 ± 83 vs 410 ± 84 sec, $p<0.05$) and increase in systolic blood pressure (SBP) rise during CPX was smaller (45 ± 33 vs 61 ± 30 mmHg, $p<0.05$) than in patients without increased baPWV (under 2000cm/sec, $n=73$), whereas severity of CAD was comparable between the two groups. In addition, postexercise SBP recovery (defined as SBP 3min/SBP peak exercise) was delayed in patients with increased PWV (0.89 ± 0.18 vs 0.80 ± 0.14 , $p<0.05$).



Conclusions: Aortic stiffness is an independent predictor of exercise capacity. Impairment of left ventricular functional reserve and lowering of threshold myocardial ischemia caused by increased aortic stiffness may be involved in the impairment in exercise capacity.

P718 Effects of combined endurance-resistance training in patients with chronic heart failure and preserved left ventricular ejection fraction



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Background: Exercise training has shown to be an effective therapy to increase exercise capacity and quality of life in pts with chronic heart failure (CHF) and reduced ejection fraction (EF). In this study we evaluated the effects of combined endurance-resistance training (ERT) in pts with CHF and preserved EF and compared the results to those in CHF pts with moderately and severely reduced EF.

Methods: We studied 82 pts with stable CHF (NYHA class II-III, 85% men, age 58 ± 10 years, 21% nonischemic CMP): 20 with EF $> 40\%$ (group 1, EF $49 \pm 11\%$), 27 with EF $30-40\%$ (group 2, EF $34 \pm 2\%$) and 35 with EF $< 30\%$ (group 3, EF $24 \pm 5\%$) who participated in a 3 months ERT program after hospitalisation for CHF. Maximal spirometry results ($\dot{V}O_{2\text{max}}$), submaximal 6 minutes walking distance (6MWD), NYHA class, quality of life using the Minnesota and Global Mood Score (GMS) questionnaires as well as blood pressure, total and LDL cholesterol, glycemia and creatinine levels were assessed before and after training.

Results: The 3 groups were comparable regarding age, baseline $\dot{V}O_{2\text{max}}$ (13.4 ± 0.7 vs 15.6 ± 0.7 vs 14.7 ± 0.7 ml/kg/min, $p=ns$) and 6MWD (364 ± 19 vs 398 ± 19 vs 395 ± 13 meters, $p=ns$). Similar absolute improvements (*: $p < 0.01$) in $\dot{V}O_{2\text{max}}$ ($+2.6$ vs $+2.6$ vs $+2.4$ ml/kg/min, $p=ns$ between groups) and 6MWD ($+50$, $+57$, $+43$ meters, $p=ns$ between groups) were obtained in the 3 groups. Also a significant ($p < 0.05$) but comparable absolute decrease in Minnesota score (-9 vs -15 vs -11 , $p=ns$ between groups) and negative GMS score (-4 vs -4 vs -6 , $p=ns$ between groups) was documented. Blood pressure, total and LDL cholesterol, as well as glycemia and creatinine levels remained unchanged in the 3 groups.

Conclusions: Combined endurance resistance training in pts with CHF and preserved EF results in improvements in exercise capacity and quality of life that are at least comparable to those obtained in pts with CHF and reduced EF.

P719 Oxygen uptake efficiency slope in patients with chronic heart failure and coexisting respiratory disease



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Oxygen uptake efficiency slope (OUES) is a new objective index of cardio-respiratory functional reserve. The aim of the study is to evaluate the effect of coexisting respiratory diseases on OUES in patients with CHF (II - III NYHA functional class) during incremental exercise testing.

Population and methods: Fifty five males originally split up into three groups took part in the study: 1) 19 patients with CHF and no additional pathology (CHF); 2) 17 patients with CHF and history of respiratory disease (CHF-RD); 3) 19 age matched controls (C). All subjects underwent a symptom-limited ramp cardiopulmonary exercise test on a cycle ergometer.

Results: We found very good correlations between OUES and $\dot{V}O_{2\text{peak}}$ ($r = 0.838$ for all the participants in the study and $r=0.687$ for patients only), VAT ($r=0.767$; $r=0.589$; respectively) and negative with VE/ $\dot{V}CO_2$ slope ($r=-0.757$ and $r=-0.678$). Patients with CHF showed reduced physical capacity and significantly lower values of parameters describing ventilatory and gas exchange efficiency - VE/ $\dot{V}CO_2$ slope (26.4 ± 2.4 vs 33.0 ± 4.7 ; $p < 0.001$) and OUES (2112 ± 263 vs 1727 ± 230 ; $p < 0.001$). Patients (in the combined CHF group) had much lower values for $\dot{V}O_{2\text{peak}}$ and OUES, but neither of these parameter was able to discriminate between CHF and CHF-RD group ($p = NS$, for both). CHF-RD patients showed slight, but statistically significant decrease of the spirometric and diffusion parameters (TL, CO % = 82.9 ± 15.9 vs 71.0 ± 14.3 ; $p < 0.05$).

Conclusions: OUES is stable and reliable parameter for the evaluation of exercise capacity of CHF patients unable to perform maximal exertion. However, we couldn't prove that it may be useful in differentiating cardiac patients with and without additional pathology. There were slight, but statistically significant reduction in spirometric and diffusion parameters in the patients groups. The extent of these changes depends on the history of a previous respiratory disease.

P720 Correlates of oxygen kinetics during early recovery after maximal cardiopulmonary exercise testing in patients with chronic heart failure



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Background: Oxygen kinetics during early recovery reflects the oxidative capacity of the muscles and is prolonged in patients with chronic heart failure (CHF). However, the relationship between hemodynamic and cardiopulmonary exercise testing (CPET) parameters and metabolic performance of the muscles has not been yet elucidated in these patients.

Methods: We assessed 98 stable CHF patients (90 male, age 51 ± 12 yrs, EF $31 \pm 12\%$) who underwent a ramp maximal CPET on a treadmill and right-heart catheterization (RHC) within 72 h of CPET. We evaluated oxygen consumption both at peak ($\dot{V}O_{2\text{peak}}$) and at anaerobic threshold ($\dot{V}O_{2\text{AT}}$) of CPET, VE/ $\dot{V}CO_2$ slope, maximum ventilation ($\dot{V}E_{\text{max}}$), and maximum heart rate (HR_{max}). We also calculated the 1st degree slope of $\dot{V}O_2$ at early recovery ($\dot{V}O_{2\text{t}}$ slope) and the heart rate recovery (HRR) defined as $\text{HR}_{\text{max}} - \text{HR}$ in 1st min of recovery.

Results: The main parameters are presented in Table. $\dot{V}O_{2\text{t}}$ slope correlated with $\dot{V}O_{2\text{peak}}$ ($p < 0.001$, $r=0.76$), $\dot{V}O_{2\text{AT}}$ ($p < 0.001$, $r=0.66$), $\dot{V}E_{\text{max}}$ ($p=0.001$, $r=0.65$), VE/ $\dot{V}CO_2$ ($p < 0.001$, $r=-0.56$), PCWP ($p < 0.001$, $r=-0.53$), HR_{max} ($p < 0.001$, $r=-0.48$), HRR ($p < 0.001$, $r=0.48$), PAP ($p < 0.001$, $r=-0.41$). In multivariate linear models, $\dot{V}O_{2\text{peak}}$ ($p < 0.001$, $\beta = -0.46$), PCWP ($p=0.001$, $\beta = -0.231$) and $\dot{V}E_{\text{max}}$

Table 1

Parameters	N=98
$\dot{V}O_{2\text{peak}}$ (ml/kg/min)	19.1 ± 5.6
$\dot{V}O_{2\text{AT}}$ (ml/kg/min)	13.7 ± 4.0
VE/ $\dot{V}CO_2$	30.4 ± 5.8
HR_{max} (beats/min)	140 ± 22
HRR (beats/min)	18 ± 9
$\dot{V}O_{2\text{t}}$ slope	-0.61 ± 0.33
PCWP (mmHg)	14 ± 8
PAP (mmHg)	24 ± 11

($p=0.002, \beta=0.27$) emerged as the most important independent correlates of VO_2/t slope.

Conclusions: Interstitial pulmonary edema and ventilatory response to exercise appear to be important modulators of the prolonged metabolic recovery in patients with CHF.

P721 Exercise training in patients with left ventricular systolic dysfunction



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Objective: 1) to determine the effect of exercise training on exercise capacity in patients with heart failure (HF) due to left ventricular systolic dysfunction 2) to assess the effect of exercise in prespecified subgroups.

Method and results: observational study, 110 consecutive patients with stable HF sent to a 24 weeks supervised aerobic and resistance exercise training programme, 85% male, aged 59.5 ± 11.4 , left ventricular ejection fraction (EF) $34.7 \pm 11\%$. Statistics: T test. There was a significant increase in maximal treadmill exercise capacity (METS): before 7.06 ± 3.2 vs 10.35 ± 3.5 after training ($p=0.0001$), and in 6 minute walking test distance (m): 448.6 ± 85.5 before vs 565.4 ± 120.6 after ($p=0.005$). The sample was divided in subgroups according to 1) exercise capacity (EC): low $<5\text{METS}$ 37(33.6%), intermediate 5-9 METS 40 (36.4%) and high $>9\text{METS}$ 33 (30%); 2) New York Heart Association (NYHA) functional class: I-II 79 (87%), III-IV 15 (13%); 3) etiology: ischaemic 90 (82%), non ischaemic 20 (18%); 4) EF(%): <30 : 22 (20%), 30-39: 39 (35.5%) and 40-50: 49 (44.5%).

	Before training (METS)	After training (METS)	change %	p
1)Low EC	3.8 ± 0.8	8.6 ± 2.8	127	<0.001
Intermediate EC	7.3 ± 4.1	8.9 ± 3.1	35.5	<0.001
High EC	11.3 ± 2.1	13.2 ± 3	16.3	0.0092
2)NYHA I-II	7.4 ± 3.2	10.7 ± 3.4	45.3	<0.001
NYHA III-IV	5.1 ± 2.7	8.3 ± 3.6	60.7	<0.001
3)Ischaemic	7.1 ± 3.1	10.5 ± 3.4	46.9	<0.001
Non ischaemic	6.9 ± 3.7	10.1 ± 4.2	46.1	0.009
4)EF % 40-50	8.3 ± 3.3	11.2 ± 3.5	35.1	0.04
30-39	6.9 ± 3.3	10.6 ± 3.8	53.6	0.001
<30	6.4 ± 2.9	9.6 ± 3.1	50.5	0.001

1)Low vs intermediate vs high EC $p<0.001$; 2)NYHA I-II vs III-IV $p=0.007$; 3)Ischaemic vs non ischaemic $p=NS$; 4)EF(%) 40-50 vs 30-40 vs <30 $p=NS$

Conclusions: The exercise training programme showed a significant increase in exercise capacity in patients with HF due to systolic dysfunction. The change was greater in subgroups with poor aerobic capacity and worse functional class at baseline. The benefit obtained was independent of the etiology and the grade of the systolic dysfunction.

P722 A Controlled Exercise Training Trial in Patients with Diastolic Dysfunction



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Background: Exercise training (ExT) improves functional capacity in systolic heart failure, but the role of ExT in diastolic dysfunction patients (DD) is unclear.

Methods: Twenty four DD patients were randomized to ExT or normal treatment. ExT was completed in 15 patients (8 men, 63 ± 4 years, LVEF $55 \pm 9\%$) 9 DD patients undertook usual treatment (7 men, 58 ± 8 years, LVEF $57 \pm 7\%$). Peak VO_2 , quality of life QOL; Minnesota Living with Heart Failure [MLWHF] and Hare-Davis [HD] questionnaires and echo measures (EF, systolic [Sm] and diastolic tissue velocity [Em] and filling pressure [E/E']) were performed at baseline and 16 weeks ExT.

Results: Both groups showed similar baseline VO_2 (13.2 ± 5.8 vs 16.4 ± 4.2 mls/kg/min, $p=0.16$), Sm (5.2 ± 1.2 vs 6.0 ± 0.9 cm/s, $p=0.10$) and E/E' (21.6 ± 12 vs 11.2 ± 10 , $p=0.12$) but different Em (3.7 ± 3.8 cm/s vs 6.6 ± 1.6 , $p=0.04$). Baseline MLWHF and HD scores were similar in both groups, change in the total ($p=0.01$) and emotional ($p=0.006$) dimensions of MLWHF and HD ($p=0.05$) scores were significantly improved at 12 weeks in ExT patients. After ExT, the increment in peak VO_2 was significantly greater in ExT (27%) versus control group (3%), ($p=0.02$).

Conclusions: In patients with exercise limitation attributed to DD, the improvement in peak VO_2 and QOL with ExT is similar to those with SD, but unrelated to changes in diastolic function.

P723 Dance-hall dancing can improve the maximal exercise tolerance in patients with cardiovascular disease



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Background: Maximal exercise tolerance during stress testing is an important predictive variable for survival and quality of life in patients with heart disease. Efficacy of exercise training on these patients is well established, but patient's compliance is often inadequate. Dancing could be an attractive way to make patients more active.

DESIGN: This is a randomized, prospective, protective, and comparative clinical trial to evaluate maximal exercise tolerance improvement in patients with heart disease after a 4 weeks dancing training period.

Methods: Thirty nine consecutive patients with heart disease, referred to a cardiac rehabilitation program were randomized. Dancing group (G1, $n=19$) and conventional cycling training group (G2, $n=20$). Patients from G1 danced (salsa, rock & roll, Cuban danzon or Big Band music) during 30 minutes daily, five days a week, in a 4 weeks period. Training intensity was set on a rate of perceived exertion of 12 to 14 (on a 6-20 Borg Scale). G2 patients trained during the same time and frequency and period as in G1, but they cycled on electromagnetic cycloergometers. Workload was controlled using a heart-rate bio-feedback mechanism at 70% of their reserve heart rate. Patients performed two stress testing; one at baseline and other one 4 weeks after training. Both groups complemented their training therapy with risk factors control sessions, psychological relaxation therapy sessions, gymnastics routines (balance, coordination, flexibility and strength), and nutritional advice. Maximal exercise tolerance during stress testing was measured in METs and differences were analyzed with paired student t test.

Results: Thirty two patients had previous diagnosis of coronary artery disease (prior myocardial infarction ($n=27$), stable angina (4), prior unstable angina (1), percutaneous angioplasty (8), bypass surgery (3)) or idiopathic dilated cardiomyopathy (6), two patients underwent to aortic valve replacement. Maximal exercise tolerance improved significantly for both groups, G1 (6 ± 2 to 7.7 ± 2 METs*) and G2 (5.4 ± 1.4 to 7.1 ± 2.1 METs*) $p<0.01$, and no statistical difference was found between groups. There were no complications during training sessions.

Conclusions: Dancing therapy improves maximal exercise tolerance on stress testing after 4 weeks of training. This improvement is similar to the change observed after a conventional cycling therapy.

P724 Effects of functional electrical stimulation on endothelial function and peripheral inflammatory process in patients with chronic heart failure



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Background: Previous studies have shown beneficial effects of functional electrical stimulation (FES) on muscle performance and exercise capacity of patients with chronic heart failure (CHF). This study evaluates the impact of FES on endothelial function and peripheral markers of immune activation in patients with moderate to severe CHF.

Methods: Twenty-four patients with a left ventricular ejection fraction $<40\%$ and NYHA II-III symptoms, undergoing optimized drug therapy, were randomized (2:1) in a 6-week training program of FES ($n=16$) or served as a control group ($n=8$). Endothelial function were assessed by Doppler Flow Mediated Dilatation (FMD) of the brachial artery, as well as peripheral pro-inflammatory/anti-inflammatory markers such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, soluble intercellular adhesion molecule (sICAM)-1, soluble vascular cell adhesion molecule (sVCAM)-1 and interleukin (IL)-10 were measured before and after the training program.

Results: A significant improvement of 6-min walk test ($p<0.05$), Minnesota Living score ($p<0.01$) and FMD (5.77 ± 2.58 vs $7.56 \pm 2.63\%$, $p<0.05$) was observed only in the FES treated group. FES also causes a significant reduction of TNF- α (7.2 ± 2.1 vs 6.2 ± 1.5 pg/ml, $p<0.01$), sICAM-1 (319 ± 63 vs 264 ± 67 ng/ml, $p<0.05$), and sVCAM-1 (751 ± 96 vs 663 ± 71 ng/ml, $p<0.05$), as well as a respective increase in ratio IL-10/TNF- α . In FES group, percentage improvement of Minnesota Living score was significantly correlated with respective changes in circulating TNF- α ($r=0.624$, $p<0.01$), sVCAM-1 ($r=0.665$, $p<0.001$) and ratio IL-10/TNF- α ($r=-0.641$, $p<0.01$).

Conclusion: FES is an alternative exercise training program that improves endothelial function in patients with CHF, having also beneficial immunomodulatory effects.

P725 Inspiratory muscle strength as a determinant of oxygen uptake efficiency slope in heart failure



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Background: We have previously shown that, in patients with chronic heart failure (CHF) and inspiratory muscle weakness, inspiratory muscle training results in marked improvement in inspiratory muscle strength, as well as improvement in functional capacity, ventilatory responses to exercise, recovery oxygen uptake kinetics, and quality of life (Dall'Ago et al. J Am Coll Cardiol 2006;47:757-63). The oxygen uptake efficiency slope (OUES) has been proposed as a measure of the cardiorespiratory functional reserve, a new submaximal parameter in evaluating exercise capacity in CHF patients.

Aims: We tested the hypothesis that increased inspiratory muscle strength was similarly associated with improvement in the OUES in patients with CHF and inspiratory muscle weakness.

Methods: Twenty-seven patients with CHF and weakness of inspiratory muscles (maximal inspiratory pressure [P_{Imax}] < 70% of predicted) were randomly assigned to a 12-week program of inspiratory muscle training (IMT - 14 patients), or to a placebo-inspiratory muscle training (P-IMT - 13 patients). Before and after intervention, resting P_{Imax} was measured and a maximal graded cardiopulmonary exercise test was performed to measure OUES. This later parameter was calculated as the relationship between oxygen uptake (VO₂) and ventilation (VE), via a logarithmic transformation of VE, and defined as the regression slope "a" in VO₂ = a log VE + b.

Results: IMT resulted in 115% increment P_{Imax} and OUES also increased significantly (1.0 ± 0.32 vs 2.1 ± 0.7; p = 0.001). There were no significant changes in P_{Imax} or OUES with P-IMT. There was also a strong and significant correlation between OUES and P_{Imax} (r = 0.99; p < 0.05).

Conclusion: In patients with CHF and inspiratory muscle weakness, inspiratory muscle training results in improvement in OUES. The strong correlation between OUES and P_{Imax} suggests that inspiratory muscle strength is a major determinant of OUES in CHF.

P726 Combined endurance-resistance training versus endurance training in patients with Chronic Heart Failure



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Introduction: Despite theoretical advantages and observed clinical benefits, official recommendations still caution against resistance exercise training in patients with Chronic Heart Failure (CHF). The aim of this study was to compare the effects of combined endurance-resistance training (CT) with endurance training (ET) only on exercise capacity, ventilatory parameters and skeletal muscle strength in patients with CHF.

Methods: 86 patients with stable CHF (EF < 40%) were randomized into a CT-group (n=42, 58.4 ± 10.9, 26% Female (F), coronary heart disease (CAD) in 64%, left ventricular ejection fraction (LVEF) 27.1% ± 7.4, VO_{2peak} 18.1 ml/kg/min ± 4.3) or an ET-group (n=44, 58.8 ± 10.7, 25%F, CAD 62%, LVEF 24% ± 9.1, VO_{2peak} 21.1 ml/kg/min ± 6.2). All patients trained for 1 hour in hospital, 3 times a week during 6 months. The ET-group trained on five different devices (bike, stepper, treadmill, reclined-bike and arm-cycle) that automatically adjusted load to heart rate (HR) (90% of HR achieved at pulmonary compensation for lactate accumulation during exercise testing). The CT-group started each session with 40-min resistance training of 9 muscle groups (pectorals, deltoids, quadriceps, biceps, triceps, chest-, lower- and upper-back muscles). The first 4 months only 8 minutes were spent on endurance training with a gradual increase until 45 minutes at the end of the programme. Evaluation at baseline, after 4 and 6 months consisted of Cardiopulmonary Exercise Testing, Lung Function Tests and assessment of skeletal muscle strength.

Results: Both groups benefited equally in terms of Maximal Workload (Wattmax) and Peak Oxygen Consumption (VO_{2peak}). However the increase of Maximal Steady State Workload (SSW) (p=0.004) and the decrease in Heart Rate/SSW (p=0.001) was significantly greater in the CT-group. The decrease in VO₂ t_{1/2}, an important prognostic parameter, was significantly more pronounced in the CT-group (p=0.003). Upper Limb Strength increased with 38.2% in the CT-group versus 21.4% in the ET-group (p=0.0001). Percentage of predicted value for Maximal Expiratory Pressure (PE_{max}) was significantly higher (p=0.037) in the CT-group.

Conclusions: Despite the fact that maximal exercise capacity (i.e.: VO_{2peak} and Wattmax) did not differ, patients with CHF allocated to the combined endurance-resistance training group benefited more in terms of sub-maximal exercise parameters (SSW) and exercise efficiency (Heart Rate/SSW). Moreover, following this particular training programme, changes observed in Recuperation Time after maximal exercise (VO₂ t_{1/2}) and Maximal Expiratory Pressure (PE_{max}), both important independent prognostic determinants, were more pronounced.

P727 Effect of creatine supplementation in conjunction with exercise training on physical fitness in coronary artery disease



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Introduction: Creatine monohydrate is an established ergogenic aid in sports and is claimed to have therapeutic applications in a variety of diseases. The effect of oral creatine supplementation (CR; 5g/day) in conjunction with exercise training on physical fitness was investigated in patients with coronary artery disease (CAD) with varying left ventricular function.

Methods: 80 cardiac patients (m/f: 74/6), were included in a double-blind randomized placebo-controlled (PL) trial over 3 months. Cardiorespiratory endurance training as well as moderate resistance training was followed (3 sessions/wk). At baseline and after training left ventricular ejection fraction (LVEF) was measured by ECG-gated SPECT, aerobic power was determined during graded bicycle testing, peak isometric and isokinetic knee extensor strength, endurance and recovery were assessed by an isokinetic dynamometer, and health-related quality of life (HRQL) was evaluated with the SF-36 and MacNew Heart Disease questionnaires. Furthermore, in a subgroup (PL: n=8; CR: n=8) biopsies were taken from m. vastus lateralis to determine total creatine (TCr) content.

Results: At baseline LVEF, physical fitness, HRQL and TCr were similar in both groups (p>0.05). With training aerobic power, muscular strength, endurance and recovery, and HRQL improved significantly (p<0.001). Similar training effects, however, were found in CR and PL (p>0.05), irrespective of LVEF at baseline. TCr after training was similar to baseline values in both groups. After 3 months of training only exercise duration (min) differed significantly (p<0.05) between CR (10.3±3.7) (mean ± SD) and PL (8.6±2.0). No detrimental effect on renal or liver function was observed, nor were there any reports of adverse effects in CR.

Performance changes (%) with training

	Placebo (n=37)	Creatine (n=33)	P-value
Peak VO ₂ (%)	20.7 ± 11.4 #	20.3 ± 16.3 #	0.91
Exercise Duration (%)	19.1 16.1 #	26.0 22.7 #	0.16
Peak Isokinetic Torque at 180°/s (%)	16.5 12.1 #	11.4 16.6 #	0.15
Strength Endurance (%)	13.5 21.9 #	16.4 39.6 *	0.71

p<0.001, * p<0.05 as compared between the exercise test at baseline and after training. P-value of the comparison between PL and CR is presented.

Conclusions: The training programme was effective in improving physical fitness and HRQL. An additional benefit of oral creatine in CAD was observed for post-training exercise duration.

P728 Physical exercise training in patients with end-stage chronic heart failure: impact on regenerative capacity of circulating progenitor cells and peripheral endothelial function



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The attenuated peripheral perfusion in patients with end-stage chronic heart failure (CHF) is at least partially the result of a generalized endothelial dysfunction. This impaired endothelium-dependent vasodilatation has been causally linked to an augmented regenerative capacity of circulating progenitor cells (CPC) due to an attenuated stem cell liberation from the bone marrow or an impaired CPC function. Aim of the present trial was to elucidate, whether regular physical exercise training affects number and function of CPCs in patients with end-stage CHF and whether this is associated with a correction of peripheral vasomotion.

Methods: Twenty-four patients with CHF (LVEF 23±2%, NYHA class IIIb) were randomized to 12 weeks of exercise training (30 min bicycle ergometer training daily at 50-60% of peak oxygen uptake) or sedentary lifestyle (control). At beginning and after 12 weeks, the number of CD34+ stem cells was quantified by FACS. AcLDL/lectin+ CPCs were harvested from blood-derived mononuclear cells by cell culture and counted using FACS analysis. Functional capacity of CPCs was determined by migration and matrigel assay. Endothelium-dependent, flow-mediated dilatation (FMD) of the radial artery was assessed by high resolution ultrasound.

Results: Exercise training increased the number of CD34+ stem cells by 51±16% and the amount of CPCs by 98±29% (p<0.05 vs. begin and control). Migratory capacity of CPCs augmented by 204±27% and their ability to integrate into endothelial networks increased by 63±35% after exercise training (p<0.05 vs. begin and control). FMD improved from 7.2±1.6% to 17.1±4.0% in the training group (p<0.05 vs. begin and control). The increase in the CD34+ cell count was linked to the improvement in FMD (r=0.72, p<0.05). All of the above-mentioned parameters remained virtually unchanged in the control group.

Conclusion: Exercise training augments the regenerative capacity of circulating endothelial progenitor cells, which might rejuvenate damaged endothelium thereby potentially contributing to the correction of endothelial dysfunction in CHF.

P729 Italian preparticipation screening program and decreasing trend of sudden cardiovascular death in young competitive athletes



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Background: A nationwide systematic preparticipation screening was introduced in Italy in 1982. To evaluate the impact on mortality of such prevention program, we analyzed the changing pattern of incidence rates and cardiovascular causes of sudden death in young competitive athletes and relation to screening implementation over a 24-year time period.

Methods: Using data from the Registry of the Veneto Region of Italy, we compared time-trends of sudden cardiovascular death in the athletic and nonathletic populations 12-35 of years of age during 1979-2002. Time periods were divided into three screening eras (pre/early-screening, 1979-1986; mid-screening 1987-1994; and late-screening, 1988-2002). We also examined the changing pattern of cardiovascular causes of disqualification in 38,273 athletes undergoing preparticipation screening at the Center for Sports Medicine in Padua during the study period.

Results: The average annual incidence of sudden cardiovascular death in athletes declined from 4.0 per 100,000 athlete-years in 1981-1982 to 0.43 per 100,000 athlete-years in 2001-2002, or 89% (P for trend <0.001), but showed no significant changes among the unscreened nonathletic population. The declining incidence of sudden cardiovascular death in athletes paralleled the implementation of the screening program over time. As compared with pre/early-screening-era, the relative risk of sudden cardiovascular death was 0.43 in the mid-screening-era (CI=0.21-0.83; P=0.007) and 0.24 in the late-screening-era (CI=0.10-0.54; P<0.001). Most of the reduced mortality was due to fewer cases of sudden death from cardiomyopathies and was accompanied by an increasing proportion of athletes with cardiomyopathies who were identified and disqualified from competitive sports at the Center for Sports Medicine in Padua (4.3% during 1982-1991 and 9.5% during 1992-2001, p=0.005).

Conclusions: The incidence of sudden cardiovascular death in young competitive athletes has substantially declined in the Veneto Region of Italy since the introduction of a nationwide systematic screening. These data support the success of the current Italian screening program to reduce mortality during competitive sports activity.

P730 UK national target for cardiac rehabilitation not met



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Introduction: The Cochrane review of cardiac rehabilitation combined 48 RCTS to show a 26% relative reduction in cardiac mortality at 2-5 years. In recognition of this, in 2000 the UK Department of Health set a target that by 2002 85% percent of MI, CABG and PCI patients should be attending rehabilitation. We ascertained the percentage taking part in 2003-2004.

Design: Postal survey of the co-ordinator from every CR programme

Main outcome measure: The number and diagnosis of patients attending rehabilitation as a percentage of those discharged from hospital in each of the nine Government Regions of England.

Results: No district came close to meeting the NSF target of 85% of patients. The range was from 15% to 40% differences were significant (p<0.001). Across England 38% (154,866) took part. Attendance also differed by condition 27% of the 133,080 MI survivors received rehabilitation, 66% of the 23,249 coronary artery bypass patients and 47% of the 20,538 percutaneous coronary intervention patients (p<0.001).

Number of patients eligible for rehabilitation, number and percent receiving rehabilitation following hospitalisation for AMI, CABG and PCI, by region

Rehabilitation	AMI*			CABG*			PCI*			Total*		
	Rec'd	Eligible	%	Rec'd	Eligible	%	Rec'd	Eligible	%	Rec'd	Eligible	%
North East	2850	9109	31	1150	1514	76	702	1120	63	4702	11743	40
North West	6922	22560	31	2935	3707	79	1552	2245	69	11409	28512	40
W Midlands	4221	14238	30	1659	2444	68	1112	2345	47	6992	19027	37
South E	3901	17931	22	2602	3287	79	2308	3355	69	8811	24573	36
East of England	4003	14563	27	1518	2417	63	613	2174	28	6134	19154	32
Yorks & Humber	3974	13764	29	1331	2412	55	476	2111	23	5781	18287	32
South W	3725	16616	22	1768	2716	65	949	2180	44	6442	21512	30
London	2013	12370	16	1698	2982	57	1835	3566	51	5546	18918	29
E Midlands	1518	11929	13	624	1770	35	138	1441	10	2280	15140	15
Total	33127	133080	25	15285	23249	66	9685	20538	47	58097	154866	38

Conclusion: The majority of patients for whom cardiac rehabilitation had been ordained did not take part and there was evidence of a 'postcode lottery' with patients in some districts and some conditions at significantly greater risk.

HYPERTENSION – NEW DEVELOPMENTS

P731 Sympathetic neuronal rarefaction in essential hypertension: neuroplasticity regulated by nerve growth factor?



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Purpose: Essential hypertension is commonly "neurogenic", the blood pressure elevation being initiated and sustained by the sympathetic nervous system. In hypertensive patients, increased spillover of norepinephrine (NE) from sympathetic nerves of the heart and kidneys is commonly present, apparently due to activation of the sympathetic outflow from the brain. An alternative possible explanation of the increased NE-outflow, not tested in human hypertension but documented in a genetic animal model of hypertension, is the presence of abnormally dense sympathetic innervation.

Methods: We tested for this in 39 patients with essential hypertension (EH), making comparisons with 73 normotensive healthy volunteers (NT). We applied NE-plasma kinetic methodology to determine cardiac NE stores and 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. Sympathetic nerve density was also assessed directly in hand vein biopsies. In parallel, we measured cardiac release of nerve growth factor (NGF), which is pivotal in the differentiation, maturation and neuroplasticity of sympathetic neurons in adulthood.

Results: Sympathetic activation was documented in hypertensive patients by increased cardiac NE-spillover (p<0.01) and sympathetic nerve firing rates (p<0.01). Cardiac NE-stores were reduced in hypertensive patients (NT:713±67 vs EH:328±180nmol; p<0.02) as was the heart-to-mediastinum MIBG uptake ratio (p<0.01). Tyrosine hydroxylase staining of hand veins demonstrated decreased sympathetic innervation density in hypertensive patients (p<0.05). The NGF plasma concentration gradient across the heart was reduced in hypertension (NT:21.1±6.6 vs EH:-5.8±6.2pg/ml; p<0.05).

Conclusion: We propose that in response to the prevailing high sympathetic tone in essential hypertension a neuroplastic reduction in sympathetic nerve density occurs, with suppression of NGF being the mediating mechanism.

P732 Polymorphisms of the Renin Angiotensin Aldosterone System related with hypertension in a Portuguese population



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Introduction: Arterial hypertension is a common complex disorder, which affects 15-20% of adult population in Western societies and the most prevalent risk factor in the Portuguese population. Although it is known that the blood pressure is under substantial genetic control, the discovery of the causative genes for hypertension has been quite discouraging. Nevertheless the Renin Angiotensin Aldosterone System (RAAS) has been demonstrated to play a central role in the pathogenesis and regulation of blood pressure. **AIMS:** The objective was to study the influence of seven genetic polymorphism, five of which concerning the RAAS, in the risk of essential hypertension, in a Portuguese population. **Materials and Methods:** We evaluated, in a sample of 821 individuals with mean age 50.1±12.4 years, 233 with arterial hypertension (cases) and 588 without (controls), the following polymorphism: ACE I/D, ACE 8 AG, AT1R A/C, AGT 174 T/M and 235 M/T, and the genotype association: ACE DD+AT1R CC, ACE DD+ AT1R AA, ACE DD+ AGT 235 TT, ACE DD + ACE 8 GG, AGT 235 + AT1R CC. The respective case-controls odds ratio was calculated as well as the 95% confidence interval. Finally, we used logistics regression model to investigate which variables were significantly linked with hypertension.

Results: The AA genotype and not CC genotype of the Angiotensin II Receptor 1 polymorphism (AT1R) was significantly higher in the group of the hypertensive patients, with an odds ratio of 1.615 (1.179-2.212) p=0.003, in opposition with results previously described for most of the Caucasian populations. The remaining polymorphism and genotype associations didn't present statistical significant. On multivariate analysis (logistical regression), Age (1.07; p<0.0001), BMI (1.1; p<0.0001), Diabetes (1.8; p=0.008), Male sex (1.5; p=0.035) and AT1R AA (1.4; p=0.049) was confirmed as an independent risk predictor for Arterial Hypertension.

Conclusion: Our data suggest that AT1R AA genotype represents a risk factor of arterial hypertension, in this Portuguese population. Should these results be confirmed, an intensive primary prevention of the other changeable risk factors, can be justified in all the individuals with a such genetic profile. This concept rises the possibility that hypertensive patients with this polymorphism can answer well to drugs blocking RAAS, namely angiotensin receptor antagonists.

P733 Does brain natriuretic peptide level serve as a marker of future development of hypertension?



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Purpose: Increased brain natriuretic peptide (BNP) expression precedes the development of hypertension in spontaneously hypertensive rats. We therefore hypothesized that elevated plasma BNP levels predict future development of hypertension.

Methods: Normotensive subjects who visited our hospital for a yearly physical checkup between July, 2001 and December, 2005 (mean age, 52.4 years; women, 38.7%; n=4,331) were enrolled in this study. Subjects under antihypertensive treatment or those with cardiac disorders were excluded from the study. At enrollment, all subjects underwent a routine physical examination, electrocardiography, laboratory assessment of cardiovascular disease risk factors, and chest X-ray, and venous blood was drawn for the measurement of BNP (radioimmunoassay, Shionoria BNP kit, Shionogi). Then, subjects were followed up for 930±387 (mean±SD) days. The endpoint was development of hypertension. We evaluated the relationship between plasma BNP levels at baseline and the incidence of hypertension during the follow-up period. Hypertension was defined as systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively, or the use of antihypertensive medications prescribed by a physician.

Results: During the follow-up, hypertension developed in 20.0% and 13.1% of men and women, respectively. Risk of future hypertension increased with increasing BNP levels (Table). Multiple logistic regression analysis adjusted by the known risk factors of age, body mass index, dyslipidemia, diabetes mellitus and current smoking revealed that BNP was a significant predictor of future hypertension in men (p=0.0252) but not in women.

Hypertension development & relative risk

	Men			Women		
	BNP range (pg/ml)	Hypertension development*	Relative risk (95% CI)	BNP range (pg/ml)	Hypertension development*	Relative risk (95% CI)
Quartile 1	<3.1	57.2	1 (reference)	<7.1	37.8	1 (reference)
Quartile 2	3.2-7.2	78.6	1.283 (1.231-1.336)	7.2-13.3	55.3	1.432 (1.371-1.495)
Quartile 3	7.3-14.3	81.4	1.334 (1.280-1.390)	13.4-22.9	47.1	1.234 (1.183-1.287)
Quartile 4	14.4-	96.6	1.571 (1.506-1.639)	23.0-	68.8	1.748 (1.670-1.830)

*per 1000 person-year

Conclusions: Increased BNP levels are associated with an increased risk of future hypertension in men but not in women. The BNP levels serve as a marker of future hypertension in individuals with normal blood pressure.

P734 Patterns of alcohol consumption and blood pressure



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Background Alcohol consumption is a major cause of preventable morbidity and mortality. Hypertension is an important preventable risk factor for cardiovascular disease. We used data from the Health Survey for England (1994-2003), a series of annual population surveys designed to ascertain health and health related behaviour to examine patterns of alcohol consumption and blood pressure.

Methods Data were available for 122,809 adults. 'Sensible' weekly drinking was defined as drinking ≤14 units/week (women); ≤21 units/week (men) and binge drinking as consuming >8 units of alcohol at a single occasion for men and >6 units for women. People were grouped into four categories: a) drinking within 'sensible' weekly amount: a1) not binge drinking, a2) binge drinking; b) drinking above 'sensible' weekly amount: b1) not binge drinking, b2) binge drinking. Hypertension was defined as having blood pressure above 140/80 mmHg or taking antihypertensives.

Results Non-linear relationships were found between blood pressure and average weekly alcohol consumption in both men and women. Among men, relative to those who drank 1-7 units/week, the odds of hypertension increased with increasing weekly consumption from 1.28 (1.16-1.41) among those who consumed 22-28 units/week to 1.76 (1.58-1.96) in men who drank above 50 units/week. There was no significant increase in odds of hypertension in non-drinkers. Among women, the odds ratio was 1.17 (1.05-1.30) in those who drank 15-21 units/week, 1.67 (1.24-2.25) in women who consumed 50 units/week or more and 1.20 (1.06-1.36) in non-drinkers. The number of days on which alcohol was consumed in the previous week had little effect on the risk of hypertension in women. Among men, the odds ratio for drinking seven days a week relative to none was 1.32 (1.12-1.56), after adjusting for weekly consumption and other possible confounders. The proportions (%) of people in groups a1, a2, b1, b2 were 56.9, 6.7, 18.0, 14.6 for men and 71.8, 3.2, 13.8, 5.6 for women, respectively. The odds of hypertension were higher in both men and women who drank above the 'sensible' weekly amount; the association with binge drinking within 'sensible' weekly amount was less clear.

Conclusions: A J-shaped curve in men and a U-shaped one in women describes the association between alcohol and hypertension in this population. In men, binge drinking increases the risk of hypertension, over and above the effect of average weekly drinking. These results have important implications for health promotion and emphasise the value of screening for alcohol consumption in medical settings

P735(W) High normal blood pressure increases the risk of CHD, stroke and all-cause mortality in a large prospective study



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Definitions of so-called "prehypertension", or "high normal blood pressure (BP)", have been advanced in view of the presumed increased risk of cardiovascular disease and stroke even in those with BP below 140 and 90mm, but above desirable levels. Research is limited and it remains unclear to what extent such increased risk differs between individuals with or without other risk factors accompanying the BP level. We followed a total of 10,057 male civil servants and municipal employees, aged 40-65, with available BP measures, for 23 years, to observe mortality from these causes. We defined as "normal BP" those within the systolic 121-130 and diastolic 81-85 mmHg ranges, and as "high normal" those within the 86-90 or 131-140 range. We excluded 780 men with CHD or diabetes at baseline. The age-adjusted hazards of mortality due to CHD (N=828), relative to a desirable BP level of <120/80 mm, were 1.55 (95%CI, 1.20-2.01), 1.79 (CI 1.40-2.30) and 2.98 (CI 2.38-3.72) for those with "normal BP", "high normal" or hypertension, respectively. Further adjustment for serum cholesterol, diabetes and cigarette smoking changed the above only marginally. The corresponding adjusted hazard ratios for stroke mortality (N=303) were: normal BP, 1.20 (CI 0.74-1.96), high normal, 1.68 (CI 1.08-2.63) and hypertension, 3.72 (CI 2.52-5.48). For all-cause mortality (N=9177) the corresponding hazard ratios were 1.16 (CI 1.03-1.32), 1.23 (CI 1.08-1.39) and 1.94 (CI 1.74-2.16).

The above findings illustrate the value of carefully considering an appropriate community-wide preventive policy, aimed at monitoring individuals at elevated risk, without unduly exposing them to premature drug therapy.

P736 International trends in reaching therapeutic goals for hypertension in diabetics



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Background: Despite formal recommendations for blood pressure control in diabetic patients, the number of diabetics affected and how many achieve the target blood pressure is largely unknown.

Methods: CardioMonitor® is an annual survey from 1998-2004 (except 2002) of outpatients with cardiovascular disease (CVD) developed from records provided by primary care physicians and cardiologists around the world. In the 2004 survey, clinical data on 25,451 CVD patients were collected in six countries. To qualify for the survey, patients must have been diagnosed with at least one cardiovascular condition. In addition, physicians recorded a diagnosis of type II diabetes if present. Extrapolation of results to an entire country's population is performed using weighting methodology based on each physician as representative of the physician population and each patient based on proportion of workload and frequency of consultation.

Results: The prevalence of type II diabetes in the cardiovascular population rose markedly across several Western European countries and the United States from 1998 to 2004. In 2004, Italy had the lowest percent of diabetic CVD patients (9.6%) while Germany had the highest (24.9%) (see Fig. 1). The systolic blood pressure (BP) goal of <130 mm Hg was achieved in 41.3% of American diabetic

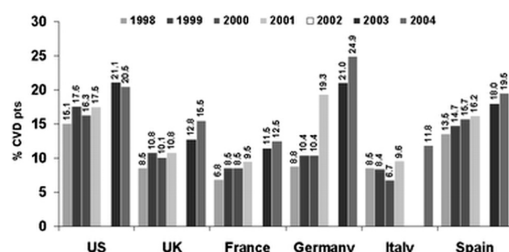


Fig. 1. Prevalence of type II diabetes in the cardiovascular population.

CVD patients and 24.3, 19.3, 18.3, 15.7, and 12.1% of patients in Britain, Germany, Spain, France, and Italy, respectively.

Conclusion: Only 1 in 5 diabetics with CVD in Europe and 2 in 5 in the US are at current BP goals. With the prevalence of diabetes steadily rising worldwide, there is an urgent need for better control of BP in this high-risk population.

GENETIC ISSUES IN CORONARY HEART DISEASE

P737 Heritability of left main coronary artery disease and future risk of fatal and non-fatal myocardial infarction in asymptomatic siblings of affected patients

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Recently, we have demonstrated in 882 CAD siblings with systematic and complete angiographic evaluation that the genetic contribution varies between specific angiographic patterns of CAD. Importantly, left main disease (LMD) and proximal stenoses in the major epicardial coronary arteries displayed a high heritability. In order to corroborate known coronary morphology of close relatives we, first, aimed to confirm the heritable component of LMD, and second, to determine whether validated occurrence of LMD in a sibling is an independent, prospective predictor of unexpected fatal and non-fatal myocardial infarction (MI) in seemingly healthy individuals.

Methods: We systematically analysed the angiograms of additional 650 CAD patients from 308 families with at least 2 siblings affected by severe CAD. LMD was defined as a luminal narrowing between the aortic origin and the bifurcation of $\geq 50\%$. Heritability was estimated using the variance component methodology. Moreover, we conducted a prospective, nested case-control study in 1369 initially healthy siblings of CAD patients with and without angiographically proven LMD. For each individual with a confirmed fatal or non-fatal MI, 4 control subjects were selected from the remaining healthy siblings who remained free of reported cardiovascular events until the point of time when the case was diagnosed. With the use of these criteria, 61 cases and 241 controls were selected. The mean follow-up period was 6.5 years.

Results: The prevalence of LMD was comparable to the initial report (11% vs. 12%). Heritability of LMD was 48% in the initial, 58% in the subsequent, and 49% in the total study sample, $p=0.007$. The relative risk for initially healthy siblings of patients with LMD to suffer fatal or non-fatal MI was 1.7 [1.1-2.9] compared to siblings of CAD patients without LMD. Multivariate adjustments did not change this risk estimate.

Conclusion: These data confirm the formerly reported heritability of LMD. Effective preventive strategies can be envisaged in healthy relatives of patients with LMD considering the high heritability of certain coronary phenotypes which go along with an increased risk for fatal and non-fatal MI in apparently healthy individuals.

P738 Role of lipoprotein(a), ApoB100 and angiotensin converting enzyme gene polymorphism in coronary artery disease in Indians

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Role of Lipoprotein (a), Apolipoprotein B100, and Angiotensin Converting Enzyme gene polymorphism in Coronary Artery Disease in Indians

Objective - Prevalence of conventional risk factors do not account for high risk of coronary artery disease (CAD) in Asian Indians. Hence there is need to look for newer risk factors. Data regarding role of ApoB100 and ACE gene polymorphism are lacking in these patients. We studied the role of Lipoprotein [Lp(a)], Apolipoprotein B100 (Apo B100) levels and Angiotensin converting enzyme (ACE) gene polymorphism in patients having CAD.

Methods - A total of 1008 subjects (540 patients of angiographically proven CAD and 468 controls with either normal coronary angiogram or negative stress test) were evaluated for Lp(a) and ApoB100 levels, with ACE deletion/insertion (DD, ID and II) genotypes being ascertained by polymerase chain reaction besides conventional risk factors.

Results - Mean age (Standard deviation SD) was 48.27 (12.07) and 49.38(12.27) years in patients with CAD and controls respectively. Prevalence of diabetes (21.8% vs. 26.3%, $p=NS$), hypertension (35.9% vs. 34.5%, $p=NS$), positive family history of premature CAD (15.7% vs. 19.1%, $p=NS$) and total cholesterol levels [180.4 (46.1) vs. 178.1 (48.1) mg/dl, $p=NS$] were similar whereas smoking (45.7% vs. 37%, $p=0.001$) and ApoB100 [>114 mg/dl] were more prevalent in patients as compared to controls (83% vs. 35.6% and 86% vs. 43.1% respectively, $p=0.001$). ACE-DD genotype was more common in patients with CAD as compared to controls (64.1% vs. 23.7%, $p<0.01$) whereas II and ID were more common in control group (43.5% vs. 16.5% and 32% vs. 19.4% respectively, $p<0.01$). On multivariate analysis, elevated Lp(a) (OR=3.89, 95% C.I.=2.42-6.27, $p<0.01$), Apo B100 (OR=7.56, 95% C.I.=5.09-11.24, $p<0.01$), triglyceride (OR=3.17, 95% C.I.=2.17-4.63, $p<0.01$), smoking

(OR=1.78, 95% C.I.=1.02-2.14, $p<0.01$) and ACE DD genotype were significant predictors of CAD.

Conclusion - Our population had similar conventional risk factors of diabetes, hypertension, family history and total cholesterol. In their presence elevated Lp(a), ApoB100 levels and ACE-DD genotypes were significantly associated with CAD. ApoB100 levels helps to further predict CAD in patients with normal LDL levels.

P739 Malmö Lp-PLA2 study - association with metabolic syndrome

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Background: Lp-PLA2 is a novel biomarker that has been shown to be an independent predictor of cardiovascular disease (CVD) events. Metabolic syndrome (MS), itself or its components, is also related to increased CVD risk. We, therefore, explored the relationship of Lp-PLA2 activity with the metabolic syndrome and the combined association of Lp-PLA2 and MS with risk of CVD.

Methods: Subjects with ($n=247$) and without ($n=4939$) CVD events during 9.6 years of follow-up in the population-based Malmö Diet and Cancer Cardiovascular Cohort were included. CVD endpoints were captured through national validated registries. Lp-PLA2 activity was measured by a radiometric assay. Twenty-one percent of subjects met the criteria for MS as defined by NECP/ATPIII. We compared risk of CVD event using Cox proportional hazards methodology for tertiles of Lp-PLA2 and for cross-classification of subjects into four groups based on having Lp-PLA2 levels $<$ or $\geq$ the median value and absence or presence of MS.

Results: Mean levels of plasma Lp-PLA2 activity were significantly higher in subjects with v. without each component of MS (waist, HDL, triglycerides, blood pressure and glucose) and in subjects with v. without MS (51.2 vs 43.7 nmol/min/mL, respectively, $p<0.001$). Moreover, Lp-PLA2 activity increased with increasing number of MS components (40.9, 43.5, 46.0, 50.3 and 52.7 for none, one, two, three and four/five components, respectively). In a proportional hazards model adjusted for age, sex, smoking status, LDL-C and the MS, subjects in the highest tertile of Lp-PLA2 activity experienced a 57% increased risk of CVD events (95% confidence interval (CI), 1.04-2.38) v. lowest tertile subjects. For the cross-classification of Lp-PLA2 and MS after adjusting for age, sex, smoking, LDL-C and hsCRP, compared to the referent group of subjects with Lp-PLA2 $<$ median and no MS, subjects with Lp-PLA2 $<$ median with MS had 1.89 times increased risk (95% CI, 1.01-3.17), and subjects with a combination of Lp-PLA2 $\geq$ median and MS had 2.59 times increased risk (95% CI, 1.74-3.85).

Conclusions: We conclude that Lp-PLA2 levels are elevated in subjects with the MS and its components, Lp-PLA2 predicts CVD risk after adjusting for the MS, and the combination of high Lp-PLA2 levels and the MS more than doubles the CVD risk. Lp-PLA2 in combination with detection of factors related to the metabolic syndrome may be useful in identifying individuals at high risk for subsequent cardiovascular disease events.

P740 Impact of ethnic background and methylenetetrahydrofolate reductase (MTHFR) genotype on age at onset of coronary artery disease among women in Israel

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An association between the C677T mutation in the MTHFR gene with the risk and age at onset of coronary artery disease (CAD) has been demonstrated in some populations with certain ethnic backgrounds. However, the specific effect of this mutation on the development of CAD in women is not well-established.

Purpose: To examine the possible effects of the MTHFR T/T (homozygous mutant) genotype and ethnic background on age at onset of CAD in women in Israel.

Methods: We studied 135 Jewish women with well-documented CAD (62 Ashkenazi, 44 oriental and 29 with other origins) in whom CAD symptoms first developed at age ≤ 65 years. DNA samples from 278 women served as control.

Results: CAD symptoms developed later in Ashkenazi than in Oriental women or women of other origins (at 51.0 ± 7.2 years, 48.3 ± 7.5 years and 46.3 ± 7.7 years, respectively, $p=0.016$, 2-way ANOVA). Among Ashkenazi women, the T/T genotype was less common in those who had CAD onset at age >50 , than either in those who had CAD symptoms earlier or the Ashkenazi control subjects (6.4% vs 25.8%, $p=0.037$, and vs 23.3%, $p=0.045$, respectively). Among women with Oriental or other origins, these differences were not significant. Logistic regression analysis showed that the T/T genotype was associated with a nearly 4-fold increase in the risk of earlier onset of CAD (at age < 50 years, OR=3.87, 95% C.I., 1.12-13.45, adjusted for risk factors and origin) and a trend towards an influence of ethnic origin ($p=0.08$). As compared to Ashkenazi women, among Oriental ones the risk of early development of CAD associated with the T/T genotype was 0.46 (95% C.I., 0.189-1.114) and among women with other origins - 5.84 (95% C.I., 1.76-19.34). An increment of one risk factor increased the risk of earlier onset of CAD by 42% (OR=1.42, 95% C.I., 1.06-1.89).

Conclusions: Among Israeli women, the age at onset of CAD is influenced by the MTHFR genotype and by the ethnic origin, in addition to the coronary risk factors. The mutation has a stronger effect on women of Ashkenazi origin than of Oriental one.

P741 RANTES G-403A gene polymorphism and its implication in the development of premature coronary artery disease in a family based study Northern Ireland



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Purpose: The development of premature coronary artery disease (PCAD) results from accelerated atherosclerosis which has a strong inflammatory component. The C-C chemokine Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES) is a potent chemoattractant for inflammatory cells and has been implicated in atherogenesis. Previous studies have demonstrated the association of RANTES A-403 with coronary artery disease. We investigated the influence of functional gene variants in the development of PCAD in our population.

Methods: A total of 1487 individuals were recruited (577 families: 798 discordant sib pairs and 67 parent/affected offspring trios) between August 1999 and August 2004. All subjects were Caucasians whose parents and grandparents were born in Ireland. Proband was defined as having PCAD with disease onset ≤ 55 years for males and ≤ 60 years for females.

Each family was required to have at least one member affected with proven ischaemic heart disease (IHD) and at least one surviving older unaffected sibling and/or both parents surviving. IHD was defined as having one or more of the following features: (1) history of myocardial infarction (MI); (2) history of unstable angina (typical chest pain, dynamic ECG changes and minor elevation of cardiac markers); (3) angiographic evidence of coronary artery disease $\geq 50\%$ stenosis. Unaffected siblings were at least 3 years older than the proband, no symptoms of angina or possible MI using the standardised 'Rose questionnaire', no history of IHD and no evidence of ischaemia on 12-lead electrocardiogram using the 'Minnesota code'.

Genotyping of RANTES G-403A was performed by restriction fragment length polymorphism (RFLP)-PCR. Linkage disequilibrium between the polymorphism and PCAD was tested using the pedigree disequilibrium test (PDT). 204 families were informative (295 discordant sib pairs and 42 trios).

Results: The PDT analyses of discordant sib pairs showed less occurrence of the A allele in affected sibs and marginally more transmission of the A allele to affected offsprings. The combined analyses of discordant sib pairs and trios showed a PDT sum test of $Z_{\text{sum}} = 0.90$ ($p = 0.37$, two tailed).

Conclusion: These data suggest that RANTES A-403 polymorphism does not influence the development of PCAD in our family cohort.

P742 Assessment of genetic risk for myocardial infarction



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Background: Although lifestyle and environmental factors influence the prevalence of myocardial infarction, genetic epidemiological studies have suggested that several genetic variants increase the risk for this condition. We have performed a large-scale association study to identify gene polymorphisms for reliable assessment of the genetic risk of myocardial infarction.

Methods and Results: The study population comprised 3483 unrelated Japanese individuals (1913 men, 1570 women), including 1192 subjects with myocardial infarction and 2291 controls. The genotypes for 164 polymorphisms of 138 candidate genes which might be expected to result in changes in the function or expression of the encoded protein were determined with an oligonucleotide ligation assay based on analysis of fluorescent microspheres with a suspension array technology. Multivariable logistic regression analysis with adjustment for age, sex, body mass index, and the prevalence of smoking, hypertension, diabetes mellitus, and hypercholesterolemia revealed that the genotypes for four polymorphisms among 164 polymorphisms examined were significantly ($P < 0.001$) associated with the prevalence of myocardial infarction. A stepwise forward selection procedure demonstrated that these four polymorphisms significantly ($P < 0.001$) affected the prevalence of myocardial infarction. Combined genotype analysis of these polymorphisms yielded a maximum odds ratio of 8.02 for predisposition to myocardial infarction.

Conclusions: The genotypes for four polymorphisms may prove reliable for assessment of genetic risk for myocardial infarction. Determination of the combined genotypes for these genes may contribute to primary, personalized prevention of this condition.

HEALTH AWARENESS AND EDUCATION

P743 Cardiovascular disease risk reduction & telehealth coaching



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Purpose: Cardiovascular disease (CVD) risk reduction, chronic disease prevention and support for self-care management have been cited as major health enhancing initiatives in the scientific literature. The Cardiovascular Health Best Practice Project (CHBPP) is a randomized clinical trial designed to test the hypothesis that CVD risk factors can be reduced using a combined intervention of telehealth support and report card feedback. This lifestyle intervention is based upon an expert patient model.

Methods: Eligibility criteria included persons with a $> 10\%$ absolute risk for CVD in ten years (based on the Framingham calculator) and aged 45 to 64, who live in the largest health region in British Columbia, Canada. Recruitment included family practice offices and work sites within Fraser Health. The intervention, the Simon Fraser Health Report Card[®], includes an annual report card for subjects and their primary physicians and tailored behavioural lifestyle counseling delivered by telehealth counselors to address smoking, exercise, nutrition, stress and medication compliance.

Results: One year follow-up data ($n=611$) support the efficacy of this CVD intervention. The mean Framingham 10-year absolute risk score for treatment subjects decreased from 12.0% to 9.4%, whereas the control group risk score decreased from 10.5% to 10.4%. The treatment/control difference over time was statistically significant after controlling for age, gender, SF-36, education, income and marital status using ANOVA ($F=4.85$, $p<.05$). Significant group differences were found for total cholesterol ($F=4.27$, $p<.05$), blood pressure ($t=-2.0$, $p<.05$), physical activity ($t=2.1$, $p<.05$) and nutrition ($F=4.85$, $p<.05$).

Conclusions: The results support the efficacy of this telehealth report card counseling approach. CVD risk factors and mean Framingham 10-year absolute risk scores were reduced significantly using this low intensity lifestyle intervention. The Simon Fraser Health Report Card System[®] results has implications for use in rural as well as urban settings as a chronic disease prevention strategy.

P744 Age and time trends in health behaviors among Swedish school age children from 1994 to 2003



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Aim: To study the importance of time and age on health behaviour of Swedish school age children

Methods: From 1993, WHO based "Health Behaviour in School Age Children" (HBSC) studies were conducted in Europe to describe health behaviours among children aged 11.5 and 13.5. A questionnaire on health habits derived from the HBSC questionnaire was in 2003 answered by 1369 12.5 year old Swedish children. The results were compared with HBSC measurements from; 1993 ($n=1225$, 1208), 1997 ($n=1294$, 1357) and 2001 ($n=1499$, 1201), enabling an analysis of time and age impact on health behaviours among Swedish schoolchildren.

Results: As described in the table there was an increase in physical activity and smoking, a decrease in sedentary behaviours and a decrease in quality of dietary variables from 1993 to 2003. An increase in 2 years of age resulted in decreased healthy behaviour (i.e. physical activity, consumption of breakfast, fruit and vegetables) and increased unhealthy behaviour (i.e. consumption of sweets, soft drink and tobacco smoking).

Table 1

Behaviour	Impact of time		p-value	Impact of age		p-value
	Boys	Girls		Boys	Girls	
Physical activity	↑	↑	<0.0001	↓	↓	<0.0001
TV-viewing	↓	↓	<0.01	↓	↓	<0.0001
Computer use	↓	↑	<0.0001	↓	↓	<0.05
Breakfast consumption	↓	↓	<0.0001	↓	↓	<0.0001
Fruit consumption	↓	↓	<0.0001	↓	↓	<0.0001
Vegetable consumption	↑	↑	<0.0001	↓	↓	<0.0001
Sweets consumption	↓	↓	<0.0001	↑	↑	<0.0001
Soft drink consumption	↓	↓	<0.0001	↑	↑	<0.0001
Tobacco smoking	↑	↑	<0.0001	↑	↑	<0.0001

Impact of time and age on health behaviours in Swedish school age children.

Conclusion: Time had a favourable impact on the proportion of physically active Swedish children while a decrease was seen in fruit and vegetable intake. Already a small increase in age influenced health behaviour negatively. Accordingly, health intervention programmes should be initiated at an early age, continued over time and structured to counteract both age and time trends to result in a long-lasting success.

P745 Self-rated health of Warsaw inhabitants between 1984-2001 - trends, determining factors. Pol-MONICA bis Warsaw Study



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Introduction: Self-rated health was a widely used indicator of the population's health.

Purpose: The evaluation of trends in self-rated health of Warsaw inhabitants between 1984 and 2001 as well as the estimation of factors influencing self-rated health.

Methods: In 1984, 1988, 1993 and 2001 cross-sectional studies of Warsaw population aged 35-64 years were carried out. The total number of respondents was 3106 men and 3182 women. Information about self-rated health, age, education level, smoking habits, anthropometric measures, blood pressure, lipids profile and dietary habits was collected for all subjects.

Results: In 1984, 43% of men and 68% of women reported their health as bad or poor, whereas in 2001, 41% and 45% respectively. In this period the improvement in self-rated health was faster among women. There weren't any differences in self-rated health changes among persons in different age groups. Higher odds ratio for poor and bad self-rated health was for persons in older age, with lower education level, lower physical activity, diabetic, persons with coronary heart disease (CHD) symptoms and persons evaluated their nutrition as improper.

Odds ratio for poor self-rated health

Factor	MenOdds ratio (95% CI)	WomenOdds ratio (95% CI)
Age (+10 yrs)	1.59 (1.45-1.76)***	1.47 (1.32-1.64)***
Education (elem, sec, univ) ¹	0.69 (0.62-0.76)***	0.65 (0.58-0.73)***
Hypertension (no, yes)	1.23 (1.04-1.44)*	1.16 (0.97-1.39)
Physical activity (high, middle, low)	1.39 (1.24-1.55)***	1.33 (1.19-1.49)***
CHD symptoms (no, yes)	2.27 (1.81-2.85)***	1.58 (1.29-1.92)***
Diabetes (no, yes)	2.45 (1.61-3.73)***	2.31 (1.32-4.05)**
Proper nutrition (yes, no)	1.39 (1.19-1.62)***	1.64 (1.40-1.92)***
Alcohol intake (+10g)	0.95 (0.91-0.99)**	0.70 (0.51-0.97)*

1- elem-elementary, sec-secondary, univ-university***-p<0.0001, **-p<0.001, *-p<0.05

Conclusion: During 17 years the improvement in self-rated health, in cardiovascular risk factors level as well as in dietary habits of Warsaw population was noticed. Analysis showed that age, education level, physical activity, symptoms of CHD, diabetes, alcohol intake and improper nutrition influenced self-rated health.

P746 Community based health education intervention is effective in increasing awareness of cardiovascular disease preventive factors and symptoms of heart attack in Kerala, India



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Purpose: Kerala State leads the rest of India in terms of low infant mortality, high literacy, morbidity and mortality due to cardiovascular diseases. The health situation in Kerala is a harbinger of what will happen to the rest of India. The objective of this study was to find out the impact of health education intervention on awareness of cardiovascular diseases (CVD) preventive factors and symptoms of heart attack. No such study has been reported from India.

Methods: Baseline data on awareness of nine CVD preventive factors (lose weight, quit smoking, regular exercise, more fish, fruits and vegetables and less fat and salt in diet) and six symptoms of heart attack (radiating chest pain, discomfort on chest, breathlessness, sweating, perspiration and coolness of extremities, vomiting/nausea and anxiety) were collected from 2635 randomly selected individuals (49.5% male, mean age 39.2years) using a pre-tested structured questionnaire in a rural community in Trivandrum district of Kerala. Health education intervention was provided to the entire village population through lectures followed by question answer sessions, posters, medical camps and distribution of leaflets on prevention and control of CVD for a period of 6 months. After the intervention data were collected from a second cross sectional sample of 2509 individuals (49.5% male, mean age 39.3 years) using the same questionnaire to find out change in the awareness of the preventive factors of CVD and symptoms of heart attack. Data were analyzed using SPSS.

Results: Awareness on all the CVD preventive factors increased significantly in the post - intervention survey. Proportion of individuals aware of all the nine CVD preventive factors increased from 29% to 64% (p < 0.001) without significant sex difference. There was strong correlation between awareness and practice of CVD preventive factors. For example, 42% of the 57 males unaware of the benefits of quitting reported smoking compared to 23% of 1160 males who were aware of the benefits (p < 0.001) in the post-intervention survey. Proportion of individuals aware of all the six symptoms of heart attacks increased from 20% to 41.5% (p < 0.001).

Conclusions: Community based intervention is an effective way to increase awareness of CVD preventive factors and symptoms of heart attack in Trivandrum district of Kerala. Such awareness is likely to result in behavioral change resulting in risk factor reduction and prevention of CVD and early detection of heart attacks.

P747 Health knowledge and it's determinants in general population. Do persons suffered from cardiovascular diseases know more about prevention?



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Purpose: Insufficient knowledge of CVD risk factors (RF), unawareness of diseases and their complications cause the significant limitation of prevention effectiveness, so the monitoring is necessary. That's why we evaluated the awareness of own CVD RF and the knowledge concerning hypertension (HT) and CVD prevention methods in relation to gender, age, education level (EL), HT, coronary artery disease history (CADH) and familial history of CVD death (FH).

Methods: Data came from the polish population sample - 14769 persons (6977 men and 7792 women), aged 20-74, screened in 2003-2005. We analyzed how many persons were familiar with their blood pressure (BP), body mass (BM), upper limit of normal BP, HT complications and CVD prevention methods.

Results: 59% of men and 69% of women declared they knew their BP (p<0.0001), but only 49% of men and 59% of women correctly classified it to the normal or high category. Out of persons that said they knew their BM, about 54% of men and 59% of women gave their BM exact to 2 kg and majority correctly classified their BM as normal or overweight/obesity. Analyzing the score of above mentioned 3 components of RF awareness, we found that more men than women knew nothing or had incorrect knowledge on their own RF (34% vs 22%). Out of 51% of men and 56% of women that said they knew the upper limit of normal BP (p<0.0001), 30% located it in normotension, 40% in the 1st grade HT and 6%-8% considered it greater than 160/100mmHg. The most often mentioned HT complications were stroke (58% men, 69% women, p<0.01) and myocardial infarction (60% and 65%, p<0.01). 32% of men and 23% of women did not know any of them (p<0.01). Higher physical activity (54% men, 58% women, p<0.0001), smoking cessation (42% and 40%, NS) and healthy life style (36% and 39%, p<0.0001) were the most often mentioned prevention methods. More men (22%) than women (18%) knew nothing about CVD prevention. Based on logistic regression we found that younger, higher educated persons and men with CADH and women with FH had greater both HT complication and CVD prevention methods knowledge.

Conclusions: Knowledge concerning awareness of own risk factors, hypertension and CVD prevention was still insufficient in polish population. Gender, age, education level and CAD history in men and family history of CVD death in women were significant modifiers of knowledge level. Hypertension status did not modify health knowledge.

P748 Impact of educational class on prevalence of cardiovascular disease risk factors in urban asian indians



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Objective: There is some evidence to suggest that the socio-economic gradient for burden of cardiovascular disease (CVD) is undergoing transition in urban India. Furthermore, lower level of education, often associated with poor socio-economic status, is likely to have adverse impact on occurrence of CVD owing to poor awareness and acquisition of adverse lifestyles characteristic of urbanization. We investigated the impact of educational class on prevalence of CVD risk factors in an urban Indian setting

Methods: We conducted a representative cross-sectional community-based study in urban Delhi, in 3050 adults (35-64 years) for comprehensive CVD risk assessment using standardised tools. Educational categories were divided into illiterate (I), education less than high school (II), high school (III), and graduate or more (IV).

Results: The mean age of the population was 47 years and ~50% of respondents were women, in all the localities. Educational status was available for 2774 adults. The prevalence of educational status was 15%, 25%, 28%, and 32% for category I, II, III, and IV respectively. While 52% women were educated less than high school, this was so for only 25% men. The prevalence of various risk factors by educational class is given in Table 1. Most of the risk factors were equally prevalence irrespective of educational class, while smoking was more prevalence in individuals with lower educational class. These results persisted even after stratifying results by sex and locality (resettlement or regular residential areas).

Table 1. Educational class and prevalence of CVD risk factors

Prevalence (%)	Class I	Class II	Class III	Class IV	p
Smoking in men	52	42	32	19	<0.001
Hypertension	27	29	28	26	NS
Diabetes	13	13	15	14	NS
Dyslipidemia	50	56	61	58	NS
Abdominal obesity	25	39	41	42	<0.01
Metabolic Syndrome (NCEP)	30	37	34	33	NS
>20% CVD risk (Framingham)	7	8	8	6	NS

Conclusion: Our results suggest that the socio-economic gradient of CVD is already reversing in urban Indians, and this has major implications for a large majority of the population as well as policy makers.

REGIONAL/ETHNIC DIFFERENCES

P749(W)



Important worldwide differences in outcomes among atherothrombotic patients: Results from Reduction in Atherothrombosis for Continued Health (REACH) Registry

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Introduction: Cardiac and vascular atherothrombotic disease has recently been recognized as the leading cause of death worldwide, however this has been explored in few contemporary global registries. We sought to compare worldwide atherothrombotic event rates in at-risk and secondary prevention populations.

Methods: The global REduction in Atherothrombosis for Continued Health (REACH) Registry includes 44 countries, and over 68,000 patients with established atherothrombosis (coronary artery disease [CAD], cerebrovascular disease [CVD], peripheral arterial disease [PAD]) or with ≥ 3 risk factors. Patients are being followed up annually for up to 4 years.

Results: Baseline characteristics for the risk factor only population are: mean age 69 years, 50% female, 75% diabetics, 42% obese (BMI >30). For the symptomatic population: mean age 69 years, 33% female, 37% diabetics, 27% obese. See Table for preliminary 1-year outcomes data for 91% of enrolled patients; 2-year data will be available for presentation in August 2006.

Regional 1-year outcomes data

	Global population	North America (NA)	Latin America (LA)	Western Europe (WE)	Eastern Europe (EE)	Middle East (ME)	Asia (As)	Australia (Au)
Total population (n)								
Risk factor only	11,318	6256	210	2625	278	122	1532	295
Symptomatic	51,066	18,737	1467	13,625	5261	691	8770	2495
CV death (%)								
Risk factor only	0.73	0.72	1.43	0.80	1.08	0.00	0.65	0.34
Symptomatic	1.82	1.96	2.18	1.90	1.97	2.75	1.29	1.52
CV death/MI/stroke(%)								
Risk factor only	2.16	2.21	3.33	1.94	2.88	1.64	2.15	2.03
Symptomatic	4.78	4.82	5.93	4.50	6.17	7.81	4.18	3.57
CV death/MI/stroke/hospitalisation (%)								
Risk factor only	5.22	5.29	6.67	5.56	10.07	5.74	3.39	4.41
Symptomatic	14.14	13.85	14.25	15.35	21.04	19.83	8.93	11.74

Conclusions: REACH Registry has identified significantly high and worldwide differences in the burden of atherothrombosis during the two-year period. Patients in regions like ME and EE experience higher event rates compared with the ROW. Global efforts are urgently needed to impact the burden of disease in both secondary prevention and at-risk populations.

P750



The distribution of hsCRP in a South-east Asian population - Singapore

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Purpose hsCRP levels are strongly related to cardiovascular risk. Available data focuses on Caucasian populations. Our objectives were to 1) describe the population distribution of hsCRP in a South-east Asian country, Singapore & 2) correlate hsCRP levels to other established markers of cardiovascular risk in this population.

Methods The Singapore National Health Survey 2004 was a cross-sectional survey conducted by the Ministry of Health. It enrolled 4168 resident Singaporeans to determine the prevalence of disease and associated risk factors. The cohort was selected by a disproportionate stratified sampling design, with oversampling of minority racial groups (Malays & Indians) to ensure sufficient sample size for reliable prevalence estimates. hsCRP concentrations were determined using latex-enhanced immunonephelometric assays (Dade-Behring).

Results 189 subjects on HRT or with on-going inflammation were excluded from analysis. Of 3979 subjects, 47.4% were males, 8.1% were obese and 27.2% were

overweight by BMI criteria. The mean age was 41.7 years (range 18-74 years). Racial composition - 65.7% Chinese, 19.8% Malays, 14.5% Indians. 21.1%, 9.8% and 20.7% had hypertension, diabetes mellitus and dyslipidemia respectively. 12.6% were smokers. 2.9% had previously documented CAD.

The distribution of serum hsCRP levels was highly skewed. The minimum value was < 0.2 mg/L and maximum value was 109 mg/L, with values of <0.2 mg/L, 0.39 mg/L, 0.93 mg/L, 2.17 mg/L & 4.04 mg/L corresponding to 10th, 25th, 50th, 75th, and 90th percentile population cut-points. There was no significant difference in the distribution by gender or age groups.

There were significant racial differences in hsCRP distribution. In Chinese, Malays & Indians, the median hsCRP was 0.8 mg/L, 1.54 mg/L & 1.98 mg/L with interquartile ranges of 0.34 - 1.88 mg/L, 0.62 - 3.17 mg/L & 0.82 - 3.86 mg/L respectively.

hsCRP distribution was significantly associated with hypertension, diabetes, obesity, cholesterol levels ($p=0.0001$ for each) & smoking status ($p=0.002$).

Conclusions: 1. Quintile cut-points of hsCRP for the Singapore population are different from the norms of middle-aged Americans.

2. There are significant differences in hsCRP means and distribution amongst the different Asian racial groups in Singapore.

P751



Comparison of coronary artery disease in circumpolar and south Tyumen regions

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The aim of this study was to test the hypothesis about more severe coronary artery disease (CAD) in patients leaving in circumpolar area compare to south area in Tyumen region of Western Siberia.

Methods: A total of 5936 symptomatic consecutive subjects underwent clinical investigation, echocardiography and coronary angiography. 2227 patients with coronary angiographic atherosclerosis (>50 of lumen) or having history of myocardial infarction were selected: 1261 from south and 966 from circumpolar north areas of Tyumen region. Groups were matched for age and sex.

Results: Higher rates of smoking (67.9 vs 48.9%, $p<0.001$), obesity (51.7 vs 39.4%, $p<0.001$), diabetes mellitus (12.8 vs 7.9%, $p<0.001$), hypertension (76.3 vs 70.2%, $p=0.004$), alcohol drinking (36.4 vs 23.0%, $p<0.001$), history of myocardial infarction (74.5 vs 64.6%, $p<0.001$), thyroid disorders (26.6 vs 14.2%, $p<0.001$) were found among north than south patients as well as higher level of blood glucose (5.34 ± 0.056 vs 5.30 ± 0.059 mmol/l, $p=0.045$).

No difference between north and south was observed for severity of heart failure. The prevalence of angina pectoris was higher in south (94.7 vs 86.9%, $p<0.001$) as well as the rate of III-IV class of angina (62.8 vs 53.3%, $p<0.001$).

According to echocardiographic measurement south patients had higher left atrial dimension (42.6 ± 0.18 vs 41.7 ± 0.18 mm, $p<0.001$), lower left ventricular ejection fraction (54.4 ± 0.26 vs 55.6 ± 0.26 %, $p=0.001$), higher extent of left ventricular wall motion abnormalities (16.2 ± 0.47 vs 14.4 ± 0.50 %, $p=0.014$). There was higher rate of patients with low left ventricular function in the south (21.8 vs 17.8%, $p=0.026$). North patients had higher aortic and right ventricle diameters (35.0 ± 0.01 vs 34.1 ± 0.10 mm, $p<0.001$; 25.5 ± 0.11 vs 24.6 ± 0.08 mm, $p<0.001$), as well as higher prevalence of atherosclerotic pattern of aorta and left ventricular thrombus (81.8 vs 74.1%, $p<0.001$; 3.2% vs 1.3%, $p=0.002$, respectively).

Conclusion: Despite more severe risk-factor profile and higher prevalence of prior myocardial infarction in north ischemic patients we revealed more severe angina and left ventricular disorders in the south.

P752



An analysis of the influence of schooling on heart failure-related mortality in the city of Rio de Janeiro

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Background: Socioeconomic status appears to have an influence on the prevalence of heart failure (HF), and some studies have suggested that HF incidence and mortality rates may be higher among economically less favored individuals.

Objectives: To evaluate the impact of schooling as a socioeconomic marker of HF-related mortality in the city of Rio de Janeiro between the years of 2000 and 2003.

Methods: We undertook a detailed analysis of all death certificates issued between January 1, 2000 and December 31, 2003, identifying all deaths caused by HF in individuals ages 20 or greater, for whom information regarding the number of years of attendance to school could be determined (NE1= less than 1 year of school attendance; NE2= 1-3 yrs; NE3= 4-7 yrs; NE4=8-11 yrs; NE5= ≤ 12 yrs; NE6= ≥ 3 yrs and NE7= ≥ 8 yrs). According to population data for the city of Rio de Janeiro 1996 Census, global mortality rates per 100,000 inhabitants (GMR/105) were calculated for each NE group and also according to age groups [20-34 yrs(AG1), 34-49 yrs(AG2), 50-59 yrs (AG3), and ≥ 60 yrs (AG4)].

Results: Between 2000 and 2003, there were 161,540 deaths for which schooling information was identifiable. Among those, 3,039 (1.9%) were due to HF. The GMR/105 were 218, 295, 105, 23 and 28 for NE1, NE2, NE3, NE4 and NE5, respectively. Analysis according to AG revealed the following (table 1)

Table 1. Odds ratio for HF death

Age group	GMR/10 ⁵ Individuals		OR	95%CI
	NE6	NE7		
AG1	8.8	0.2	44	6.2 - 326.3
AG2	32.3	3.5	9.2	6.2 - 13.1
AG3	295.6	23.3	12.7	8.35 - 19.44
AG4	688.5	206.6	3.34	2.8 - 3.8

Conclusion: HF-related mortality in the city of RJ between 2000 and 2003 was significantly higher in lower schooling segments of the population. These findings reflect the importance and impact of socioeconomic status in the morbidity and mortality associated with HF.

P753 Racial differences in high-risk patients presenting with NSTEMI ACS: results from the SYNERGY trial

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Purpose: We assessed racial differences in presentation and outcome among high-risk patients with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS).

Methods: Using data from the SYNERGY trial, we analyzed 7007 patients from North America (to limit potential biases introduced by regional differences). The primary outcome was all-cause death or nonfatal myocardial infarction (MI) through 30-day follow-up.

Results: Of the 7007 patients, 6077 were white, 586 were black, and 344 were Hispanic. The following clinical differences were observed in baseline demographics: median age in years was 68 for whites, 65 for blacks, and 63 for Hispanics (overall $p < 0.001$); the rate of hypertension was 66% for whites, 83% for blacks, and 78% for Hispanics (overall $p < 0.001$); and the rate of diabetes was 28% for whites, 43% for blacks, and 46% for Hispanics (overall $p < 0.001$). Use of angiography, revascularization procedures, and medications is shown below. In an unadjusted analysis, a significant difference in 30-day death or MI was observed: 14.1% for whites, 10.2% for blacks, and 14.5% for Hispanics (overall $p = 0.037$). After adjustment for baseline variables, the only difference between racial groups was significantly lower 30-day death or MI for black patients when compared with white patients (OR 0.74; 95% CI 0.55-0.98).

Procedures and Medications by Race

	White (n=6077)	Black (n=586)	Hispanic (n=344)	p Value
Catheterization	5543 (91%)	544 (93%)	306 (89%)	0.128
PCI	2802 (46%)	239 (41%)	155 (45%)	0.046
CABG	1241 (20%)	96 (16%)	76 (22%)	0.044
In-hospital beta-blocker	3734 (61%)	369 (63%)	241 (70%)	0.005
In-hospital ACE inhibitor	1927 (32%)	239 (41%)	164 (48%)	<0.001
In-hospital statin	1892 (31%)	184 (31%)	152 (44%)	<0.001
Discharge beta-blocker	4739 (85%)	481 (88%)	276 (87%)	0.174
Discharge ACE inhibitor	3340 (71%)	369 (76%)	242 (81%)	<0.001
Discharge statin	4303 (81%)	387 (79%)	264 (85%)	0.091

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention

Conclusions: Striking racial differences were observed in the North American patients of the SYNERGY trial. However, the impact of different revascularization rates and medication use on clinical outcomes across racial groups needs further evaluation.

P754 Cardiac and renal protection by a new mineralocorticoid receptor antagonist in salt-sensitive arterial hypertension

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Activation of the mineralocorticoid receptor (MR) via aldosterone may contribute to hypertension, end-organ damage and mortality in salt-sensitive individuals. We investigated the effect of specific MR blockade on blood-pressure control, cardiac and renal protection, and survival in two animal models of salt-sensitive hypertension.

Thirty-eight DOCA-salt (DOCA 30 mg/kg/wk s.c., 1% NaCl in drinking water) hypertensive rats were treated for five weeks with either a novel selective, non-steroidal MR antagonist (BAY, 10 and 30 mg/kg/d) or the steroidal MR antagonist Eplerenone (100 mg/kg/d), or placebo. Both BAY and Eplerenone reduced systolic blood pressure (tail cuff) to a similar extent (cf. table). However, BAY, but not Eplerenone, substantially reduced heart and kidney weight as well as proteinuria (table). In a second series, BAY was compared to Eplerenone and Spironolactone in 37 salt loaded (2% in drinking water) stroke prone spontaneously hypertensive

rats (all doses 30 mg/kg/d, treatment duration 8 weeks). Histopathological analysis (semiquantitative scoring) of the kidneys revealed substantial reduction of vascular, glomerular and tubulo-interstitial damage in the BAY group (mean grade 1.0), compared to placebo (mean grade 2.0), whereas Eplerenone and Spironolactone were not effective (mean grades 1.8 and 1.9, respectively). There was a moderate mortality in the Eplerenone and Spironolactone groups (mortality 33% each). Corresponding to the superior nephroprotection, BAY afforded a substantial survival benefit compared to placebo (mortality 0% vs. 60%).

	Placebo	BAY10 mg/kg/d	BAY30 mg/kg/d	Eplerenone100 mg/kg/d
Systolic BP mmHg	222 ± 26	180 ± 21*	175 ± 29*	186 ± 23*
Heart weight mg/g bw	3.05 ± 0.17	2.85 ± 0.15*	2.65 ± 0.15*	3.01 ± 0.4
Proteinuria mg/24 h	150 ± 80	110 ± 70	80 ± 40*	130 ± 80
Kidney weight mg/g bw	5.82 ± 0.17	5.60 ± 0.89	5.36 ± 0.49*	5.73 ± 0.53

Mean value ± SD; N=9-10/group; *, $p < 0.05$ vs. placebo

Conclusion: Pharmacological blockade of the mineralocorticoid receptor by a new non-steroidal antagonist prevents end-organ damage and improves survival in salt-sensitive hypertension.

NOVEL STRATEGIES IN HYPERTENSION

P755 Impaired diastolic function in hypertensives with Primary Aldosteronism. A tissue Doppler imaging approach

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Purpose: Primary Aldosteronism (PA) has been experimentally linked to myocardial fibrosis, while it has been further associated with left ventricular structural and functional abnormalities. The aim of our study was to assess the diastolic function by means of both conventional and tissue Doppler imaging methods in hypertensive subjects with PA.

Methods: We studied 15 subjects with established diagnosis of PA (8 males, aged 56 ± 10 years, body mass index = 30 ± 3.8 kg/m², office BP = $134 \pm 7/85 \pm 6$ mmHg) and 30 controls with essential hypertension (EH) selected from our database and matched for age, sex, body mass index, office BP and duration of hypertension (14 ± 7 vs. 12 ± 6 , $p = 0.65$). All subjects underwent 2-D echocardiography for estimation of left ventricular mass index (LVMI) and relative wall thickness (RWT). Left ventricular diastolic function was estimated by means of both transmitral inflow Doppler, estimating early and late transmitral filling peak velocities (E, A, E/A ratio), and tissue Doppler imaging (TDI), measuring early and late diastolic mitral annular peak velocities (Em, Am, Em/Am ratio) from four separate sites (septal, lateral, anterior and inferior walls), and their obtained average values (Em_{av}, Am_{av}, Em_{av}/Am_{av} ratio).

Results: Subjects with PA compared to controls had significantly increased LVMI and RWT (119.4 ± 35 vs. 96.7 ± 23 g/m², $p = 0.012$, and 0.49 ± 0.07 vs. 0.42 ± 0.06 , $p = 0.001$, respectively). Although E/A ratio appeared to be similar in both groups of PA and EH (0.92 ± 0.27 vs. 0.99 ± 0.24 , $p = 0.42$), subjects with PA compared to controls are characterized by significantly decreased values of Em_{av} (by 1.3 cm/s, $p < 0.05$) and Em_{av}/Am_{av} ratio (by 0.14, $p < 0.05$), indicating an abnormal relaxation of the left ventricle. Assessing the four walls separately, we exhibited significantly decreased Em/Am ratio only regarding the septal (0.53 ± 0.18 vs. 0.72 ± 0.23 , $p = 0.009$) and the inferior wall (0.57 ± 0.11 vs. 0.71 ± 0.23 , $p = 0.014$).

Conclusions: The altered left ventricular geometry in hypertensive subjects with PA is accompanied by impaired diastolic function, as it is indicated by means of TDI derived indices. Whether these findings have any clinical implications remain to be elucidated in future properly designed studies.

P756 Association of metabolic syndrome with hypertensive retinopathy

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Introduction: - AIM: The influence of metabolic syndrome (MS) on markers of hypertension-related target organ damage (TOD), is under research. The aim of this study is to analyze the association of MS with hypertensive retinopathy (HR), comparing with the other markers of TOD, in non-diabetic patients, with essential hypertension grade I to III (mild to severe).

Methods: 229 patients (118 men, 111 women) of an average age 47.87 years ± 7.75 , with never treated, recently diagnosed essential hypertension, were examined and analyzed with 24-hour Ambulatory Blood Pressure Monitoring (ABPM). Both retinas were examined with direct funduscopy and stereoscopic color fundus photography (in 110 subjects) and graded according to Keith - Wagener - Barker classification. Echocardiography was performed and left ventricular mass index (LVmass/BSA) was calculated. Doppler ultrasound was used to detect the intima

- media thickness (IMT) of both common and internal carotid arteries. Creatinine clearance was calculated. Metabolic syndrome was identified when 3/5 criteria, according to Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP III), were present.

Results: 42% of our study population, had MS (group B) according to NCEP/ATP III criteria. Compared with subjects without MS (group A), hypertensive patients with MS (group B), exhibited a statistically significant increased prevalence of HR (86.5% vs. 47.3%; $p < 0.0001$) however, LV hypertrophy (57.7% vs. 45.1%; $p = 0.072$), creatinine clearance disorder (36.2% vs. 29.3%; $p = 0.063$), and carotid IMT changes (62% vs. 53%; $p = 0.057$), had no statistically significant increased prevalence in patients of group B. After performing multivariate analysis, the correlation between MS with HR, remained statistically significant in adjustment of age, sex, serum cholesterol levels, mean 24h BP levels, left ventricular mass index, IMT changes, creatinine clearance disorder and positive history of smoking (partial correlation coefficients).

Conclusions: Our findings demonstrate that MS may statistically significant and independently, amplify the prevalence of hypertensive retinopathy. This finding has not been observed with the other markers of TOD. As hypertensive retinopathy is a well-known predictor of cardiovascular events, our results may partly explain the enhanced cardiovascular risk of these patients associated with MS. Our results support the importance of early screening and intervention in this population.

P757 Epidemiological profile and therapeutic control of hypertensive disease in a general medical practise within an industrially polluted region



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Introduction: According to World Health Organisation data Bulgaria occupies the seventh place in Europe and the twenty fourth in the world in mortality from Hypertensive Disease (HD) and its complications. Morbidity from it has doubled over the last 15 years.

Objective: To draw up a detailed epidemiological profile of morbidity and mortality from HD among the population in a region of proven industrial pollution and to evaluate the effectiveness of antihypertensive treatment.

Materials and Methods: The study is based on a general medical practise community of 1600 people, aged from 0 to 102 years, in a rural area with water and soil heavily polluted with Pb, Cd and Zn by a neighbouring metallurgical plant (2,5 km) and an international airport (0,9km). A detailed analysis is made of HD morbidity, complication rate, presence of concomitant diseases, therapeutic control (type, frequency and regularity of medication), mortality, diet, social and financial status of the patients. The data is collected from patients' medical records as well as from a questionnaire comprising of 24 questions regarding diet, daily routine, etc., and elaborated especially for the purpose of the study.

Results: There is a 2,5 fold increase in HD morbidity as compared to the beginning of the 5 yr period. During the 5 yr period 517 (32,2%) patients requiring regular medication are enlisted and followed up for HD. Almost 1/10 of them are below 40 years of age and 5 of them - below 18 years. Hypercholesterolemia is found in 2/3 of the hypertensive patients. The daily menu is dominated by meat (pork, home grown poultry), animal fat and conserved food. The most frequent therapeutic combinations are: ACE Inhibitor + Diuretic; ACE Inhibitor + Calcium Antagonist ± Diuretic; ACE Inhibitor + Beta Blocker ± Diuretic

Conclusions: The elevated HD morbidity, the distinct "rejuvenation" of the disease and the high complication rate despite the therapeutic control are in immediate correlation to the complex of polluted environment, extremely unwholesome dietary and motion regimen and continuous stress to provide for basic mode of life. The quality of medication is seriously limited by the low standard of living.

P758 Sildenafil and phosphodiesterase-5 augmented induction: effects on hypertensive cardiomyopathy induced by L-name



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Introduction: We recently demonstrated that chronic inhibition of phosphodiesterase 5 (PDE5) by sildenafil prevents structural and functional alterations in hypertensive cardiomyopathy induced by nitric oxide (NO) inhibition in rats. It suggests that a major cGMP bioavailability and the crosstalk between PDEs may be the responsible mechanisms for these pharmacological cardiovascular effects. Once PDE5 presence in cardiac tissue is controversial, there is a need for thorough validation concerning its distribution to differentiate haemodynamics and direct sildenafil effects.

Objective: To investigate PDE5 expression and distribution in the heart and evaluate its participation in preventing cardiovascular alterations. Material and methods: Male Wistar rats (n=15) were orally treated as follows: 1- Control; 2- L-NAME; 3- L-NAME + Sildenafil; 4- Sildenafil. After 8 weeks, haemodynamics and histological assays were performed. PDE5 distribution was evaluated by immunohistochemistry.

Results: Immunohistochemistry showed PDE-5 expression in the smooth vas-

cular muscle, myocardium vessels endothelium, and intercalated disks. Chronic administration of sildenafil increased PDE5 expression in the smooth vascular muscle and myocytes intercalated disks in a significant way. Histological (lesion areas=LA), haemodynamics (Mean Arterial Pressure=MAP; Cardiac Index=CI) and biochemical (cyclic Guanosine Monophosphate=cGMP) results are summarized in table1 (X± MSE).

Table 1

	Control	L-NAME	Sildenafil +L-NAME	Sildenafil
MAP (mmHg)	114.4 ± 16.7	180.0 ± 8.8*	157.9 ± 12.0# *	121.2 ± 19.1
CI (ml/100g/min)	0.14 ± 0.03	0.08 ± 0.01*	0.11 ± 0.01# *	0.16 ± 0.03
LA (areas, %)	7.5±0.3	44.4±2.6*	24.4±2.0# *	10.4±1.5
cGMP (mol/ml)	4.89±0.32	2.93±0.34*	4.43±0.23#	6.03±0.28*

*P<0,05 vs. Control #P<0,05 vs. L-NAME

Conclusion: Our findings suggest that PDE5 expression in smooth vascular muscle and in cardiomyocytes intercalated disks associated to sildenafil results in prevention of cardiovascular dysfunction and remodeling in this model of arterial hypertension by NO deficit.

P759 Glycine reduces blood pressure in a model of metabolic syndrome, modulating the biosynthesis of nitric oxide



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Purpose: Glycine has shown to be beneficial against hypertension induced by a sucrose diet in animal models of metabolic syndrome (MS) (1, 2). We investigated the effect of a glycine treatment on the metabolism of nitric oxide (NO), a relaxing factor involved in the regulation of vascular tone and blood pressure (BP).

Methods: Male Wistar rats aged 28 days, were randomly separated into two groups: the Control group received tap water, the experimental group (MS) 30% sucrose in the drinking water for 20-weeks to develop a significantly higher BP. Each group was divided into two subgroups: The first subgroup continued to drink water, the second subgroup received water with 1% glycine. In parallel, the sucrose group was also divided into two subgroups: one continued to receive 30% sucrose in its drinking water and the other received sucrose with 1% glycine. Glycine and sucrose treatments were continued for 4 more weeks.

Results: The concentration of NO metabolites (nitrates and nitrites) in plasma and in aortic homogenate significantly diminished in the rats with MS ($P < 0.01$), was significantly increased by glycine treatment. The decrease of the NO metabolites was associated with a decrease in the expression of NOS3 in the aorta. The treatment with glycine increased the expression of NOS3. The vasoconstriction induced by norepinephrine (NE) in the aortic rings from MS rats, was significantly higher ($P < 0.001$) in comparison with that of the Control rats. The opposite effect was observed in the vasodilation induced by accumulative doses (10-9 to 10-5 M) of acetylcholine (AC). In the group of the MS animals treated with glycine, the aortic rings developed a significant decrease in the vasoconstriction induced by accumulative doses (10-9 to 10-5 M) of NE ($P < 0.001$) and an increase in the vasodilation response ($P < 0.001$) in comparison with the aortic rings of MS animals without glycine. Glycine did not affect the reactivity of the rings from Control rats.

Conclusion: Glycine treatment rectified the alterations observed in the vascular reactivity of the rings of the MS animals. The increased concentration of the NO metabolites can be due to the increase in the expression of NOS3 or to the decrease of the oxidative stress, on account of a high concentration of reduced glutathione, which increases the availability of NO to exert its relaxing effect, thus reducing the hypertension in MS rats.

References: 1. El Hafidi et al. Curr Opin Clin Nutr Metab Care 2006, 9:26-31.

2. El Hafidi et al. Am J Physiol Regul Integr Comp Physiol 2004, 287: R1387-1393.

P760 Zinc content in the diet affects the expressional changes of Cu/ZnSOD in thoracic aorta of spontaneously hypertensive rats



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Oxidative stress induced by reactive oxygen species (ROS) plays an important role in development of hypertension. Vascular cells have a complex antioxidant system for protection against increased oxidative stress. Zinc is a cofactor of one of the most important antioxidant enzyme - Cu/ZnSOD.

The aim of the present study was to examine the effects of feeding different Zn containing diets (50, 150, 250 mg Zn/kg lab chow) on the activity and expression of Cu/ZnSOD in the thoracic aorta of spontaneously hypertensive rats (SHR). Male SHR (n=30) were studied. The diets were introduced at the beginning of the development of hypertension (2 months after birth) and the animals were

fed for 8 weeks. Cu/ZnSOD expression was analyzed by immunohistochemistry and the activity was measured by RANSOD kit (RANDOX). Atomic-absorption spectrometry was used to determine Zn and Cu concentrations in the rat sera.

Results: Cu/ZnSOD was mainly expressed in medial smooth muscle cells and it had a weak immunoreactivity in the endothelium. In the group with Zn supplementation diet (250 mg Zn/kg lab chow), Cu/ZnSOD staining was more enhanced in the smooth muscle cells and endothelium, and the systolic blood pressure was significantly decreased ($p < 0.05$) in comparison with the groups fed with other Zn diets (50 or 150 mg/kg lab chow). The change in Cu/ZnSOD activity correlates well with the protein expression and with the arterial blood pressure alterations.

Conclusions: The present data suggest that Zn concentration in the diet may play an important role in the regulation of the blood pressure and may in part be a critical nutrient for maintenance of anti-oxidative events in the endothelial cells in SHR.

P761 Heavy coffee consumption in conjunction with smoking unfavorably affects inflammatory activation and thrombosis/fibrinolysis system in essential hypertensive subjects: a dose-related harm?

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Purpose: The impact of coffee drinking on the cardiovascular system remains controversial, whereas smoking is correlated with activation of diverse proinflammatory and atherogenic pathways. In the present study, we examined the effect of heavy coffee intake on plasma concentrations of interleukin-6 (IL-6), and plasminogen activator inhibitor type 1 (PAI-1), in essential hypertensive smokers.

Methods: From our pool of smokers with newly diagnosed untreated stage I-II essential hypertension, according to a validated food frequency questionnaire we consecutively selected 30 heavy coffee drinkers (coffee intake of more than 4 cups/day) and 30 light coffee drinkers (coffee intake of less than 1 cup/day or less than 7 cups/week) matched for age, sex and pack-years. Moreover, venous blood samples were drawn for estimation of metabolic profile, IL-6 and PAI-1 concentrations according to established techniques.

Results: In hypertensive smokers, heavy compared to light coffee drinkers had increased office systolic blood pressure (BP) (154 ± 13 vs 143 ± 12 mmHg, $p = 0.001$), whereas did not differ regarding office diastolic BP, heart rate, body mass index (BMI), and metabolic profile ($p = \text{NS}$). Moreover, heavy compared to light coffee drinkers exhibited on average 120% higher IL-6 (2.01 ± 0.3 vs 0.91 ± 0.2 pg/ml, $p = 0.005$), and 84% higher PAI-1 concentrations (32 ± 8.2 vs 17.4 ± 5.7 ng/ml, $p = 0.0001$). In the entire population, IL-6 was associated with BMI ($r = 0.221$, $p < 0.05$), pack-years index ($r = 0.347$, $p < 0.001$), office systolic BP ($r = 0.372$, $p < 0.05$), triglycerides ($r = 0.253$, $p < 0.005$) and low density lipoprotein cholesterol ($r = 0.206$, $p < 0.05$), whereas PAI-1 exhibited a positive correlation with pack-years index ($r = 0.228$, $p < 0.05$), waist to hip ratio ($r = 0.204$, $p < 0.05$) and office systolic BP ($r = 0.284$, $p < 0.005$). Regarding the degree of coffee consumption, it was positively related to office systolic BP ($r = 0.242$, $p < 0.05$), IL-6 ($r = 0.475$, $p < 0.0001$) and PAI-1 levels ($r = 0.274$, $p < 0.05$). Analysis of covariance revealed that IL-6, and PAI-1 concentrations were significantly different between the two groups after adjusting for age, sex, BMI, pack-years, office BP, and lipid levels ($p = 0.013$ and $p = 0.04$, respectively).

Conclusions: Heavy coffee consumption in hypertensive smokers is associated with pronounced inflammatory involvement and dysregulation of thrombosis/fibrinolysis system, as reflected by IL-6 and PAI-1 values. These findings suggest that excess degree of coffee intake unfavorably affects subclinical atherosclerosis progression and increases cardiovascular risk in this setting.

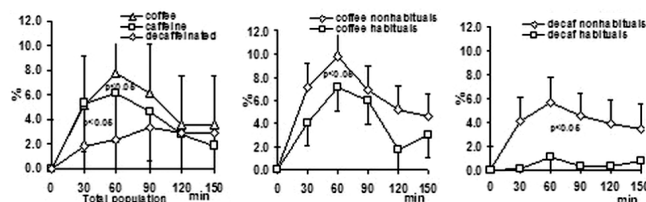
P762 Coffee has a more potent unfavorable acute effect on wave reflections than caffeine in nonhabitual compared with habitual drinkers

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Background: Arterial wave reflection (WR) are determinants of cardiovascular performance and predictors of the corresponding risk. The aim of this study was to assess whether there is a differential effect of coffee and caffeine on WR and whether this effect is related to habitual coffee consumption.

Methods: We studied 24 healthy volunteers (11 habitual-13 nonhabitual coffee consumers) on 4 separate occasions receiving: a) triple espresso, b) decaffeinated triple espresso, c) 240mg of caffeine alone (amount contained in a triple espresso) and d) placebo. Augmentation index (AIx) was measured as an index of WR using a validated system (Sphygmocor®). Higher AIx values indicate increased WR and vice versa.

Results: The effect of coffee and caffeine on WR is described as response of each variable, where response is defined as net coffee or caffeine minus placebo values at each time point. In the whole population, coffee and caffeine increased AIx, however the effect of coffee was more pronounced (left figure). Habitual and nonhabitual drinkers demonstrated similar changes with caffeine, whereas the effect of coffee (regular-middle figure- or decaffeinated-right figure) was more potent in nonhabitual compared to habitual drinkers. Pressures also increased,



however the increase was more potent in nonhabitual drinkers after both regular ($p < 0.05$) or decaffeinated ($p < 0.01$) coffee intake.

Conclusions: Both coffee and caffeine increase WR, however drinking coffee leads to a more potent response in nonhabitual drinkers. These findings indicate that substances other than caffeine are partially responsible for the unfavourable effects of coffee on the cardiovascular system.

P763 Improvement of endothelial function in diabetic subjects after consumption of flavanol-rich cocoa

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Background: Endothelial dysfunction characterized by a reduced bioavailability of nitric oxide (NO) is a key event in arteriosclerosis, and Diabetes mellitus is associated with rapidly progressive arteriosclerosis in humans. Recently, it could be shown that endothelial function in smokers was substantially improved after ingestion of a flavanol-rich diet.

Hypothesis: The consumption of a cocoa drink rich in flavanols improves endothelial function in diabetic subjects.

Methods: Ten diabetic patients received orally administered cocoa containing 90, 385 and 975 mg of total flavanols during a randomized, double-blind, cross-over study. Endothelial function was measured before and up to 6 hours after cocoa ingestion by flow-mediated dilation (FMD) of the brachial artery using high resolution ultrasound. In parallel circulating NO-species in plasma (RNO, Nitrite, Nitrate) were characterized by reductive gas-phase chemiluminescence.

Results: Endothelial dysfunction was found in every diabetic individual under control conditions (FMD $3.71 \pm 0.27\%$). Ingestion of flavanols dose-dependently increased FMD to a maximum of $5.54 \pm 0.35\%$ ($p < 0.01$) after two hours. This increase was accompanied by significant augmentations in plasma concentrations of nitrite (baseline: 173 ± 26 nM; maximum post ingestion: 293 ± 38 nM), indicating an improvement of NO-bioavailability. Endothelium-independent arterial dilation was unaffected by the intervention.

Conclusions: This study for the first time provides evidence that cocoa rich in flavanols can improve endothelial function and is associated with an increase in circulating NO-species in diabetic patients. These findings may implicate a potential use of flavanols in dietary or therapeutic interventions aimed at treating Diabetes-associated vascular diseases, including peripheral and coronary artery disease that are characterized by impaired regional NO production.

P764 The use of B-Natriuretic Peptide and ultrasonic backscatter in detecting diastolic dysfunction in hypertensive patients

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Background: Although Doppler echocardiography has been used to identify abnormal left ventricular diastolic filling dynamics, inherent limitations suggest the need for additional measures of diastolic dysfunction. We hypothesized that use of Brain-Natriuretic Peptide (BNP) levels in combination with cyclic variation of integrated backscatter could predict diastolic abnormalities in patients with normal systolic function.

Methods and Results: We studied 40 patients referred for echocardiography to evaluate ventricular function. Patients with abnormal systolic function were excluded. Cardiologists making the assessment of LV function were blinded to BNP levels and CVIBS. CVIBS values were obtained from the septal wall in the parasternal long axis view. Patients were classified as normal, stage 1 and stage 2 (pseudonormal patterns) diastolic dysfunction. Patients diagnosed with stage 1 diastolic function (n:18) had a mean BNP concentration of 71 ± 25 pg/mL and a mean CVIBS values of 6.7 ± 1.1 ; those in the normal LV group (n:12) had a mean BNP concentration of 34 ± 17 pg/mL and a mean CVIBS values of 7.1 ± 0.9 . Patients with pseudonormal patterns on echocardiography had the highest BNP levels (206 ± 75 pg/mL) and lowest CVIBS values (5.7 ± 0.9). A BNP value of 62 pg/mL had a sensitivity of 83%, a specificity of 91%, for detecting diastolic dysfunction. A CVIBS value of 7.1 dB had a sensitivity of 83.3%, a specificity of 66.7% for detecting diastolic dysfunction. A close correlation was found between the BNP and CVIBS values ($r = 0.54$, $p < 0.05$).

Conclusions: Combinative use of BNP and CVIBS can reliably detect the presence of diastolic abnormalities on echocardiography. A good correlation was found between the BNP and CVIBS values in detecting diastolic dysfunction.

P765 4a/4b-polymorphism of eNOS gene and cardiovascular remodeling in Uzbek hypertensive patients



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The aim of this study was to estimate the role of 4a/4b polymorphism of endothelial nitric oxide synthase gene (eNOS) in the development of left ventricular hypertrophy (LVH) and endothelial dysfunction (ED) in Uzbek hypertensive patients.

Methods: The study included 125 patients with essential hypertension, ethnic Uzbek males, and mean age 46.9 ± 8.1 yrs. All patients were underwent complete M-mode echocardiography to determine left ventricular mass (LVM). The LVM was indexed to the body surface area to derive the LVM index (LVMI). LVH was defined as an increase LVMI greater than 134 g/m^2 . Vascular ultrasound was performed to measure the brachial artery diameter during reactive hyperemia test and analysis of endothelium-dependent vasodilatation (EDVD). Endothelial dysfunction was diagnosed if EDVD was less than 10% ($\Delta D < 10\%$), paradoxes vasoconstriction $\Delta D < 0$. Genotyping of 4a/4b polymorphism of eNOS gene was performed by the PCR.

Results: Genotype frequencies were: 0.8% for 4a/4a; 19.2% for 4a/4b; 80% for 4b/4b genotype, and did not deviate from Hardy-Weinberg equilibrium ($p=0.000$). All patients divided into 2 group: 1st with 4a/4a+4a/4b genotype; 2nd with 4b/4b genotype. Level of LVH was similar between groups. Concentric LVH was diagnosed in 85.7% patients of the 1st group and 72.5% in patient of the second one ($p=0.78$). Baseline parameters such as systolic and diastolic blood pressure in patients with LVH were higher in 4a/4a+4a/4b than 4b/4b: SBP 165.7 ± 16.6 vs $159.218 \pm 13.548 \text{ mm Hg}$ ($p=0.055$), DBP 105.7 ± 8.1 vs $101.768 \pm 9.0 \text{ mmHg}$ ($p=0.060$) respectively. LVH also was greater in 1st group than second, without statistically significant: 189.4 ± 36.4 vs $171.0 \pm 27.3 \text{ g/m}^2$ ($p=0.09$) respectively. Both of groups characterized with damages of EDVD. Moreover, in carriers 4a/4a+4a/4b genotype were revealed more impairment of EDVD and paradoxes vasoconstriction than carriers 4b/4b: $-1.6 \pm 10.9\%$ vs $4.1 \pm 10.2\%$ ($p=0.025$) respectively.

Conclusion: Results of our study have indicated important role 4a/4a+4a/4b polymorphism of eNOS gene in vascular remodeling and associated with endothelial dysfunction in Uzbek hypertensive patients.

P766 Correlation between coronary flow reserve assessed by doppler echocardiography and left ventricular mass in hypertensive patients with angiographically normal coronary arteries



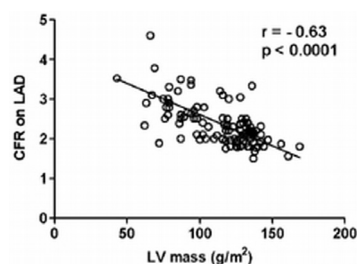
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Background: It is not clearly understood why concentric left ventricular hypertrophy (increased left ventricular mass and relative wall thickness) is associated with higher cardiovascular risk than eccentric hypertrophy (increased left ventricular mass but normal relative wall thickness). Possible reasons include a reduced coronary flow reserve in both concentric and eccentric hypertrophy. Aim. To investigate whether coronary flow reserve (CFR) assessed with transthoracic Doppler 2D-echo in the left anterior descending coronary artery (LAD) territory, is affected to left ventricular (LV) mass in hypertensive patients.

Methods: 109 hypertensive patients (61 men; 60 ± 13 years), 65 of whom having LV hypertrophy (LV mass $> 104 \text{ g/m}^2$ in women and $> 116 \text{ g/m}^2$ in men) on resting echo, were selected on the basis of a normal coronary angiogram. Using 0.44 as relative wall thickness (diastolic septum + diastolic posterior wall to cavity ratio) cut-off value, 33 patients had both concentric and 32 eccentric hypertrophy. All patients underwent transthoracic dipyridamole (0.84 mg/kg in $10'$) stress echo. CFR, defined as the ratio between maximal vasodilation and rest peak diastolic flow velocity, was assessed by pulsed Doppler.

Results: Significant inverse correlation ($r=-0.63$, $p<0.0001$) was found between CFR and LV mass in the whole population (Figure). CFR was similar in subjects with concentric and eccentric hypertrophy (2.11 ± 0.29 vs 2.13 ± 0.40 , $p=0.76$).



Conclusions: In hypertensive patients without organic coronary artery disease, a significant inverse correlation exists between CFR, assessed by transthoracic echo, and LV mass. However, the pattern of LV geometry does not affect CFR.

P767 Maternal total vascular resistance and left ventricular concentric geometry: a new echocardiographic classification to assess the risk of complications in gestational hypertension



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Background: The classifications of gestational hypertension (GH) that we use in clinical practice are important for research and epidemiological purposes, but might reveal to be unsatisfactory for the identification of patients who will develop complications. This study was designed to evaluate the prognostic impact on the outcome of pregnancy of elevated total vascular resistance (TVR) in early mild GH (EMGH).

Methods: 268 EMGH patients (systolic and diastolic blood pressure [BP] $140-150 \text{ mm Hg}$ and $90-99 \text{ mm Hg}$, respectively) referred to our outpatient clinic were submitted to an echocardiographic examination within 24 hours from the diagnosis. BP was recorded at the time of the examination and TVR was calculated. Patients were followed until term to detect subsequent fetal/maternal adverse outcomes (preeclampsia, preterm delivery, abruptio placentae, other maternal medical problems, fetal distress, neonatal low birth weight, admittance to Neonatal Intensive Care Unit, perinatal death). At the end of pregnancy EMGH was classified as complicated or uncomplicated.

Results: Ninety-two out of 268 pregnancies were classified as complicated (34.33%). The best independent predictor for maternal and fetal complications was TVR (OR 64.41, CI 95% 25.90-160.13). The cut off value was 1340 dyn s cm with a sensitivity and a specificity of 90% and 91%, respectively. Concentric geometry of the left ventricle was also an independent predictor (OR 4.72, CI 95% 1.85-12.04).

Conclusions: Echocardiography could help in identifying GH patients who subsequently develop maternal and fetal complications allowing a classification in high risk (TVR $> 1340 \text{ dyn s cm}$, concentric geometry of the left ventricle) and low risk patients (TVR $< 1340 \text{ dyn s cm}$, non concentric geometry of the left ventricle) for adverse outcomes of pregnancy.

P768 Endothelial dysfunction and plasma nitroso compounds



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Objective: We investigated whether plasma nitros(yl)ated species (RXNOs) that mediate systemic nitric oxide (NO) bioactivity are depleted in individuals with cardiovascular risk factors and endothelial dysfunction.

Background: Endothelium-derived NO acts not only as regional messenger but exerts significant systemic effects via formation of circulating RXNOs delivering NO to sites of impaired production.

Methods: Endothelial function was assessed in 68 patients with 1-4 major cardiovascular risk factors (RF) and 39 healthy control subjects (C) by measurement of flow-mediated dilation (FMD) of the brachial artery using high resolution ultrasound. In parallel, plasma RXNOs were determined by reductive gas phase chemiluminescence.

Results: Increasing numbers of risk factors were accompanied by a progressive decrease in FMD: $6.5 \pm 0.4\%$ (C), $4.7 \pm 0.5\%$ (1 RF), $2.8 \pm 0.4\%$ (2 RF), $2.2 \pm 0.4\%$ (3 RF), and $1.0 \pm 0.3\%$ (4 RF). Progressively impaired vascular function was associated with a concomitant decrease in plasma RXNOs ($p<0.01$): $39 \pm 2 \text{ nmol/L}$ (C), $30 \pm 2 \text{ nmol/L}$ (1 RF), $24 \pm 3 \text{ nmol/L}$ (2 RF), $22 \pm 3 \text{ nmol/L}$ (3 RF), and $15 \pm 2 \text{ nmol/L}$ (4 RF), with univariate correlation between FMD and RXNO ($r=0.41$, $p<0.001$). In a multivariate regression model RXNO was an independent predictor of endothelial function.

Conclusions: Endothelial dysfunction in patients with cardiovascular risk factors is associated with decreased levels of circulating RXNOs. Plasma RXNOs may be diagnostically useful markers of NO bioavailability and a surrogate index of endothelial function. Whether the observed decrease in concentration reflects impaired NO formation, accelerated decomposition and/or consumption of RXNOs and whether these processes play a causal role in the pathophysiology of arteriosclerosis remains to be investigated.

P769 The interplay between left ventricular hypertrophy, inflammatory process and arterial stiffness in essential hypertensive subjects: a new approach to target organ damage



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Purpose: Subclinical inflammation and arterial stiffening are markers of cardiovascular risk, while left ventricular (LV) hypertrophy is an independent risk

factor. In this study we examined the interrelationship between augmented LV mass, high-sensitivity C-reactive protein (hs-CRP), serum amyloid-A (SAA), tumor necrosis factor- α (TNF- α) and arterial stiffness in essential hypertensives.

Methods: Our population consisted of 295 newly diagnosed untreated non-diabetics with stage I to II essential hypertension [192 men, mean age= 50 years, office blood pressure (BP)=148/95 mmHg] that underwent echocardiographic examination and according to gender-specific criteria were divided into those with LV hypertrophy (n=104) and those with normal LV mass (n=191). A arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP).

Results: Patients with LV hypertrophy compared to those without LV hypertrophy were older (54 ± 4 vs 45 ± 7 years, $p < 0.005$) and had greater 24-h systolic and diastolic BP (138 ± 10 vs 132 ± 14 mmHg and 90 ± 8 vs 86 ± 10 mmHg, respectively; $p < 0.001$ for both cases). In the total population hs-CRP was associated with body mass index ($r = 0.281$, $p < 0.0001$), 24-h systolic BP ($r = 0.144$, $p < 0.05$), SAA ($r = 0.425$, $p < 0.0001$), TNF- α ($r = 0.191$, $p < 0.05$) and PWV ($r = 0.233$, $p < 0.0001$). Moreover, PWV was associated with age ($r = 0.399$, $p < 0.0001$), 24-h systolic BP ($r = 0.250$, $p < 0.0001$), SAA ($r = 0.249$, $p < 0.05$), and TNF- α ($r = 0.286$, $p < 0.0001$). Although the two groups did not differ regarding body mass index, smoking status and lipid levels ($p = \text{NS}$ for all), hypertensives with LV hypertrophy as compared to those without exhibited higher levels of hs-CRP (2.9 ± 0.7 vs 2.1 ± 0.4 mg/l, $p < 0.05$), SAA (9.0 ± 5.3 vs 6.1 ± 4.6 mg/dl, $p < 0.05$), TNF- α (2.74 ± 0.57 vs 1.71 ± 0.4 pg/ml, $p < 0.001$) and PWV (8.9 ± 1.2 vs 7.8 ± 1.4 m/sec, $p < 0.05$). Analysis of covariance revealed that inflammatory markers levels and PWV values remained significantly different between groups after adjustment for confounders ($p < 0.05$).

Conclusions: LV hypertrophy in essential hypertensives is accompanied by pronounced inflammatory activation and impaired arterial compliance. These findings may partially explain the cardiovascular risk associated with LV hypertrophy in this setting.

P770 Mechanisms underlying functional and structural cardiac alterations associated with b-adrenergic chronic stimulation. Role of aldosterone



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Background: Chronic b-adrenergic receptor stimulation produces ventricular hypertrophy and heart failure. Aldosterone is a profibrotic factor involved in the development of ventricular hypertrophy and heart failure. This factor can participate in cardiac damage through stimulation of different mediators including connective tissue growth factor (CTGF), a potent profibrotic agent. However, the participation of aldosterone in cardiac alterations produced by chronic stimulation of b-adrenergic receptors is not known. Whether or not the role of aldosterone involved CTGF mediation is not well established.

Aim: To evaluate the role of aldosterone in functional and structural cardiac alterations induced by chronic stimulation of b-adrenergic receptors. The possible role of CTGF in aldosterone participation in cardiac damage.

Material and methods: Male Wistar rats (250g) were treated with either isoproterenol (ISO; 3mg/kg/day s.c.) or vehicle for 15 days. Half of the animals from each group was treated with spironolactone (SPIRO; 200mg/kg/day s.c.). At the end of the treatment, heart rate (HR) was measured. Systolic arterial pressure (SAP), diastolic (DAP) and mean arterial pressure (MAP), left ventricle final diastolic pressure (pDf), + dP/dt and - dP/dt were measured through a catheter inserted into the right carotid artery. Also, cardiomyocytes diameter and collagen content present in the myocardium was evaluated with optical microscopy techniques. CTGF protein expression by western blot analysis was also measured. As index of cardiac hypertrophy, heart/body weight ratio was calculated.

Results: Neither ISO nor SPIRO were able to modify SAP, DAP, MAP, HR, + dP/dt y - dP/dt. However, the pDf was higher ($p < 0.001$) in rats treated with ISO as compared with controls. Treatment with SPIRO normalized these values ($p < 0.001$). Relative heart weight was greater in rats treated with ISO ($p < 0.001$) than in controls. Treatment with SPIRO reduced heart weight ($p < 0.01$) without normalizing. No differences in cardiomyocytes diameter were observed in any group. Collagen content in the myocardium of rats treated with ISO was greater ($p < 0.001$) than in control rats. Treatment with SPIRO reduced collagen content ($p < 0.05$) without normalizing. No differences in CTGF protein expression were observed in any group.

Conclusions: 1) Aldosterone participates in functional and structural alterations associated with b-adrenergic stimulation.

2) It seems that CTGF is not involved in the cardiac fibrotic process associated with b-adrenergic stimulation.

P771



Ascending aortic pulsatility and pulsatility index are better predictors of event-free survival compared to systolic, diastolic, mean and pulse pressure. The results from the ABPS Study

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Ascending aortic BP-derived indices were shown to be related to the extent of coronary atherosclerosis. However, their prognostic significance is still unknown. Therefore, the aim of the study was to evaluate the relationship between baseline aortic BP-derived indices (pulsatility - the ratio of pulse pressure [PP] to mean BP; pulsatility index - the ratio of PP to diastolic BP) and major cardiovascular complications.

Methods: The study group consisted of 1109 patients (821 M and 288 F; mean age: 57.5 ± 10.1 years; mean EF: $56.4 \pm 12.4\%$) undergoing coronary angiography. Invasive ascending aortic BP during catheterization was taken at baseline. The duration of follow-up was 55.0 ± 17.2 months. The primary end point was defined as: cardiovascular death, myocardial infarction, stroke or myocardial revascularization.

Results: At baseline, ascending aortic systolic BP was 135.4 ± 23.0 mmHg, diastolic BP 71.6 ± 10.9 mmHg, mean BP 92.9 ± 13.5 mmHg, PP 63.8 ± 18.2 mmHg, pulsatility 0.68 ± 0.15 and pulsatility index 0.90 ± 0.27 . The primary end point occurred in 246 (22.2%) patients over. The crude and adjusted hazard ratios are given in the table. When pulsatility or pulsatility index were added to models together with systolic, diastolic, mean or pulse pressure only pulsatility or pulsatility index but not the other indices were related to the event-free survival. The findings did not differ significantly when the study group was divided according to age, EF, presence of CAD, revascularization procedures or risk factors.

Table 1

Hemodynamic variable	Crude HR (95% CI)	Adjusted HR * (95% CI)
Invasive ascending aortic blood pressure		
Systolic blood pressure per SD	1.05 (0.93-1.19)	1.11 (0.96-1.29)
Diastolic blood pressure per SD	0.92 (0.81-1.04)	0.93 (0.81-1.07)
Mean blood pressure per SD	0.98 (0.87-1.12)	1.02 (0.88-1.16)
Pulse pressure per SD	1.12 (0.99-1.27)	1.24 (1.06-1.45)
Pulsatility per SD	1.17 (1.03-1.32)	1.29 (1.11-1.50)
Pulsatility index per SD	1.18 (1.05-1.33)	1.29 (1.12-1.49)

* adjustments were made for age, gender, ejection fraction, extent of coronary atherosclerosis, NYHA class, heart rate, creatinine level, risk factors and treatment.

Conclusion: Aortic pulsatility and pulsatility index are independently related to the risk of major cardiovascular complications in coronary patients.

P772

Impact of blood pressure on admission on the in-hospital and post-discharge prognosis in patients with acute coronary syndromes

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Introduction: There is a correlation between systolic and diastolic blood pressure (BP) values on admission for an acute coronary syndrome (ACS) and prognosis. In this also true in an unselected population of ACS patients?

Aim: To evaluate, in an ACS population, if there is a correlation between systolic and diastolic BP values on admission and the in-hospital and 6-month prognosis.

Population and methods: Retrospective analysis of a database with 15982 ACS patients. This population was divided according to the systolic and diastolic BP values, considering 10 mm Hg intervals.

Results: There was a progressive decrease in the in-hospital mortality rates as the systolic BP on admission increased from 40-49 mm Hg until 130-139 mm Hg, and then the mortality rates stabilized (3-5%), increasing again for values above 250 mm Hg. The in-hospital morbidity showed a similar trend, but without the increase for very high systolic BP values. The correlation between systolic BP on admission and 6-month mortality was similar, not reached statistical significance ($p = 0.08$) and the event rate increased above the 230 mm Hg. There was no correlation between the systolic BP and 6-month morbidity. Regarding diastolic BP, trends were similar to those of systolic BP for all the endpoints.

Conclusion: In unselected ACS patients, there is a correlation between systolic and diastolic BP values on admission and in-hospital and post-discharge mortal-

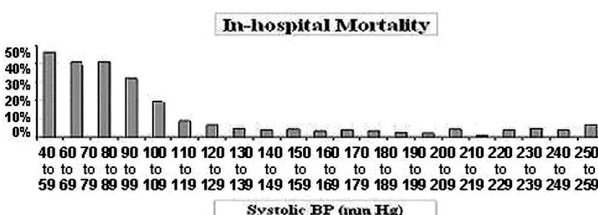


Fig. 1. Results

ity, which is higher in patients with very low and very high BP. In-hospital morbidity is higher in hypotensive patients (but not in hypertensive ones), but BP on admission cannot predict 6-month morbidity.

P773 Genotyp of matrix metalloproteinase-2 relates to value of aortic pulse pressure



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A wide pulse pressure (PP) is a marker of increased artery stiffness and represents a well established independent predictor for cardiovascular morbidity and mortality. The increasing value of aortic PP is connected to more severe atherosclerosis of coronary vessels. Pulse pressure is increasing with stiffness of large arteries. Elevated content of collagen fibres at the expense of elastin in the extracellular matrix (ECM) tends to arterial stiffness. Activation of proteolytic enzymes known as the metalloproteinases (MMP) contribute to ECM remodelling. MMP-2 (gelatinase A) degrades elastin.

Aim: To assess the possible effect of functional four polymorphism in matrix metalloproteinase 2 (MMP-2) gene promoters (-1575 G/A, -1306C/T, -790T/G and -735C/T) on the value of aortic PP.

Methods: We included 80 stable patients, age >50 years without anamnesis of myocardial infarction and without left ventricle systolic dysfunction. Echocardiography, coronary angiography, left ventriculography and invasive intra-aortic BP were measured. The value of pulse pressure was corrected on age. Polymorphism was detected by PCR following RFLP.

Results: Patients were distributed according to median of pulse pressure corrected on age. The relation between polymorphism of MMP-2 (-790T/G) and value of PP corrected on age was established. We found a relation in distribution of genotypes of this polymorphism ($P=0.05$) with significant rise of genotype with at least one G (TG+GG) in patients with lower PP ($P=0.01$). There was only trend in frequency of alleles ($P=0.06$) between the groups. We did not find any other significant relations for the rest polymorphism in MMP-2 gene promoters.

Conclusion: Polymorphism MMP-2 gene promoters (-790T/G) significantly contribute to variability of aortic pulse pressure. The data suggest some genetic predisposition of value of PP.

P774 Role of arterial stiffness in hypertensive heart failure



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Purpose: Arterial hypertension is associated with stiffening of large arteries and enhanced pressure wave reflection. These abnormalities are known to increase systolic pressure and left ventricular afterload and reduce diastolic pressure and coronary perfusion. Whether arterial stiffness plays a role in worsening heart failure (HF) is still unknown. We studied aortic stiffness, reflected pressure waves and their relations with left ventricular (LV) structure and function in hypertensive patients with HF.

Methods: We studied 56 patients with essential arterial hypertension (HTN), 8 of whom had symptoms and signs of heart failure, and were free of coronary artery disease (HTN-HF). All patients were black, enrolled and studied in Mozambique and under pharmacological treatment. HTN-HF were in NYHA class II (85%) or III (15%) and had ejection fraction (EF) <45%. Doppler-echocardiography was used to measure LV mass (LVM), EF, total peripheral resistance (TPR) and LV elastance (Ees, end-systolic LV pressure/volume ratio, mmHg/ml). Calibrated carotid applanation tonometry was used to calculate the amplitude of the pressure reflected wave (augmentation pressure, AP). PWV, effective arterial elastance (Ea, end-systolic pressure/stroke volume, mmHg/ml) and Ea/Ees (an index of arterial-ventricular coupling) were also measured.

Results: There were no significant differences between HTN-HF and HTN in age (48 ± 16 vs 50 ± 12 yrs), systolic blood pressure (152 ± 21 vs 155 ± 27 mmHg), PWV (8.5 ± 0.9 vs 9.4 ± 2.9 m/sec) and AP (14.6 ± 7.7 vs 17.5 ± 13.1 mmHg). Compared to HTN, HTN-HF had lower EF (37 ± 6 vs $67 \pm 8\%$, $p<0.01$) and CO (3.09 ± 0.9 vs 5.2 ± 0.3 L/min, $p<0.01$) and higher LV diameter (59 ± 9 vs 50 ± 4 mm, $p<0.01$), LVM (142 ± 30 vs 98 ± 24 g/m², $p<0.01$) and TPR (2813 ± 282 vs 1837 ± 456 dynes/cm⁵, $p<0.01$). Ea/Ees was three fold higher in HTN-HF (1.64 ± 0.94 vs 0.51 ± 0.20 , $p<0.01$) revealing an excessive arterial load on the failing LV in spite of treatment. There were no significant relationships of AP and PWV with EF and LVM in HTN-HF.

Conclusions: Aortic stiffness (PWV) and intensity of reflected pressure waves (AP) were not significantly different in HTN-HF compared to HTN, suggesting that they don't play a major role in systolic heart failure. However, as revealed by the abnormal arterial-ventricular coupling (increased Ea/Ees), arterial load is too high for the impaired inotropic state of hypertensive failing heart.

P775 Early detection of hypertensive heart disease by measuring regional myocardial diastolic dysfunction assessed by color Doppler myocardial imaging



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Purpose: Doppler echocardiography of the mitral valve and pulmonary veins inflow often reveals global diastolic dysfunction in hypertensive patients. The assessment of regional diastolic function is crucial in understanding the pathophysiological process and diagnosing subclinical myocardial changes. Therefore, we sought to analyze segmental myocardial relaxation using Color Doppler Myocardial Imaging (CDMI) in hypertensive patients without fulfilled criteria for first grade diastolic dysfunction in conventional Doppler.

Methods: The study comprised 32 treated hypertensive pts. (48 ± 7.3 years, normal myocardial thickness and normal systolic function) with well regulated blood pressure according to values from previous 24h BP monitoring and 11 healthy age matched normals. All subjects underwent DMI (E', A' at annulus, base and middle segment (s.) of each wall (w.) in longitudinal views) as well as Doppler echocardiography (IVRT, PFVE, PFVA, DtE, Adur, PVA, PVAdur) at baseline, 3- and 6-month follow up. The non-parametric Mann-Whitney test was used for statistical analysis. P value <0.05 *vs. control group, #vs. baseline.

Results: CDMI revealed global and regional impairment of relaxation: at baseline: 1. regional E'/A' <1 was found in 2/18 s. or 11% (in basal s. of posterior and septal w.). 2. All segments mean was: E'/A' = 2.01 ± 0.77 , n.s. 3-mo follow up: 1. regional E'/A' <1 was found in 5/18 s. or 28% (in basal s. of posterior, inferior, septal and lateral w. as well as middle s. of posterior w.) 2. All segments mean was: E'/A' = 1.6 ± 0.7 , $p<0.05^*$. 6-mo follow up: 1. regional E'/A' <1 was found in 6/18 or 33% of all s. (in basal s. of posterior, lateral, inferior and septal w. and middle s. of posterior and inferior w.) 2. All segments mean: E'/A' = 0.98 ± 0.17 , $p<0.01^*$, $p<0.05^{\#}$.

Conclusion: CDMI parameters in these patients revealed regional diastolic dysfunction at baseline while standard Doppler parameters were normal. Regional diastolic changes were the earliest sign of hypertensive heart disease in our patients, followed by CDMI parameters of global diastolic dysfunction in 6-month follow up. These data might have significant clinical value in diagnosis of subclinical hypertensive heart disease and follow up of the treatment.

P776 Altered coronary flow velocity reserve and aortic elastic properties in hypertension: an echocardiographic study



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Background: The structures and functions of large conduit arteries and coronaries are frequently affected by hypertension. The aim of the present study was to determine the clinical usefulness of stress transoesophageal echocardiography (STEE) for the simultaneous evaluation of the coronary flow velocity reserve (CFVR) and aortic elastic properties in hypertensive patients with normal epicardial coronary arteries.

Patients and methods: Aortic elastic properties (elastic modulus [E(p)] and Young's circumferential static elastic modulus [E(s)]) and CFVR were evaluated during the same STEE examination. The following patient populations were compared: 17 normotensive subjects with negative coronary angiograms (Group 1) and 21 hypertensive patients with normal epicardial coronary arteries (Group 2). Patients with diabetes mellitus were excluded from the present study. Elastic moduli were calculated from descending aortic diameter and intima-media thickness data and blood pressure values. The CFVR was calculated as the ratio of the average peak diastolic flow velocity during hyperaemia to that at rest. Aortic morphology was also evaluated using a five-grade scale.

Results: Data are presented in the table.

Parameter	Group 1 (n = 17)	Group 2 (n = 21)
Age (years)	52.3±8.3	52.1±13.4
CFVR	2.73±0.53	2.25±0.73*
E(p)	0.42±0.20	0.73±0.42*
E(s)	4.23±2.24	7.81±4.39*
Average grade of aortic atherosclerosis	0.87±0.64	0.87±0.99

* $p<0.05$ vs Group 1.

Conclusions: Altered aortic distensibility and coronary vasoreactivity (CFVR) have been demonstrated during the same STEE in hypertensive patients with a negative coronary angiogram.

P777 Adiponectin and resistin levels in patients with masked hypertension



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Introduction: Recent evidence demonstrates that masked hypertension (MH) is

a significant predictor of cardiovascular disease, while hypoadiponectinemia and hyperresistinemia may contribute to chronic inflammatory process, insulin resistance, endothelial dysfunction and accelerated atherogenesis.

Aim of our study was to examine the adiponectin and resistin plasma levels in patients with MH and compare the findings to those of healthy normotensives matched for age, sex, body mass index and the rest of risk factors.

Patients and methods: One hundred-thirty (60 M, 70 F) healthy subjects mean age 45 ± 12 yrs who had clinic blood pressure $< 140/90$ mmHg were studied. The whole study population underwent 24 hour ambulatory blood pressure monitoring (ABPM). According to the ABPM recordings, 24 individuals (8M, 16 F) had MH (daytime systolic blood pressure ≥ 135 mmHg or daytime diastolic blood pressure ≥ 85 mmHg - group A) and the remainder 106 subjects (52 M, 54 F) had normal ABPM recordings, group B. Adiponectin and resistin plasma levels were determined in both groups (ELISA method).

Results: Our findings and the comparisons between the two groups are shown in table 1.

	Group A (n=24)	Group B (n=106)	p
Adiponectin ($\mu\text{g/ml}$)	6 ± 2.3	11 ± 2.7	< 0.001
Resistin (ng/ml)	12 ± 4	6.8 ± 3.6	< 0.001

Table 1

Conclusions: Our findings suggest that subjects with masked hypertension have significantly lower adiponectin levels and significantly higher resistin levels compared to healthy individuals. This observation may have prognostic significance for future cardiovascular events in subjects with masked hypertension and needs further investigation.

P778 Inhibitor of differentiation Id2 is involved in the pathogenesis of angiotensin II-induced end-organ damage



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The helix-loop-helix transcription factor inhibitor of differentiation (Id) 2 has a pivotal role in determining cell lineage choice and differentiation. Id2 deficient mice (Id2^{-/-}) lack Langerhans, splenic CD8 α^+ dendritic, and natural killer cells. Id2^{+/-} mice appear to be normal. We observed earlier that dendritic and other immune cells are important mediators of angiotensin (Ang) II-induced renal damage. The aim of this study was to elucidate the role of the Id2 gene in cardiac and renal damage in transgenic mice over expressing the rat angiotensinogen gene (TGM). The mice are known to develop Ang II-induced cardiac hypertrophy and blood pressure increases. We mated Id2^{-/-} with TGM. We compared TGMxId2^{+/-} with TGMxId2^{-/-} and the respective non-transgenic strains (WTxId2^{+/-} and WTxId2^{-/-}). Transgenic TGMxId2^{+/-} showed significantly increased heart weight, cardiac hypertrophy index (5.4 ± 0.2 mg/g), cardiac fibrosis, and left ventricular brain natriuretic peptide (BNP) expression. Albuminuria (235 ± 40 $\mu\text{g/d}$), renal fibrosis, and cell infiltration were also significantly elevated. TGMxId2^{+/-} showed media hypertrophy, extracellular matrix deposition, and tubular changes in the outer medulla. In contrast, cardiac hypertrophy (4.3 ± 0.2 mg/g), albuminuria (25 ± 10 $\mu\text{g/d}$), renal and cardiac fibrosis, macrophage and T-cell accumulation in the kidney and heart, were all significantly reduced in TGMxId2^{-/-}. Albuminuria in WTxId2^{+/-} and WTxId2^{-/-} was 18 ± 2 and 22 ± 5 $\mu\text{g/d}$, respectively. No histopathological changes were observed in TGMxId2^{-/-} and the non-transgenic groups. Our results demonstrate that Id2 plays a major role in the pathogenesis of Ang II-induced renal and cardiac damage.

P779 Diverse associations of sustained, white-coat and masked hypertension with C-reactive protein, adiponectin and arterial stiffness: linking blood pressure status to subclinical atherosclerosis



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Purpose: The clinical significance of "masked" hypertension (MHT) and "white-coat" hypertension (WCHT) is controversial, while inflammatory and proatherosclerotic processes are associated with adverse outcome. In this study we investigated the relationships of MHT, WCHT and sustained hypertension (SHT) with high-sensitivity C-reactive protein (hs-CRP), adiponectin, and arterial stiffness.

Methods: 335 consecutive untreated non-diabetic subjects who referred to our outpatient clinic for 24-h ambulatory blood pressure (BP) monitoring, were classified as subjects with sustained normal BP (office BP $< 140/90$ mmHg and daytime BP $< 135/85$ mmHg, n=44), MHT (office BP $< 140/90$ mmHg and daytime BP $\geq 135/85$ mmHg, n=32), WCHT (office BP $\geq 140/90$ mmHg and daytime BP $< 135/85$ mmHg, n=81) and SHT (office BP $\geq 140/90$ mmHg and daytime BP $\geq 135/85$ mmHg, n=178). Moreover, in all hypertensive subjects, arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by

means of a computerized method (Complior SP) and venous blood samples were drawn for estimation of hs-CRP and adiponectin levels.

Results: Patients with SHT compared to WCHT and MHT had higher 24-h systolic BP (138 ± 10 vs 119 ± 7 vs 129 ± 15 mmHg, respectively; $p < 0.0001$) and left ventricular mass index (118.3 ± 17 vs 111.2 ± 13 vs 101.4 ± 17 g/m², respectively; $p < 0.05$). Although groups did not differ regarding sex, body mass index and metabolic profile ($p = \text{NS}$ for all), patients with SHT as compared to those with WCHT and MHT had increased hs-CRP (2.8 ± 0.7 vs 2.2 ± 0.6 vs 1.9 ± 0.4 mg/l, respectively; $p < 0.05$), lower adiponectin (8.4 ± 1.5 vs 10.5 ± 1.8 vs 10.2 ± 1.6 $\mu\text{g/ml}$, respectively; $p < 0.05$) and heightened PWV levels (8.2 ± 1.4 vs 7.8 ± 1.2 vs 7.3 ± 0.9 m/sec, respectively; $p < 0.05$). However, there was no difference between the MHT and WCHT group regarding hs-CRP, adiponectin and PWV values ($p = \text{NS}$ for all cases). In the hypertensive population, hs-CRP was associated with body mass index ($r = 0.285$, $p < 0.0001$) and PWV ($r = 0.232$, $p < 0.0001$), whereas adiponectin was negatively related to 24-h systolic BP ($r = -0.203$, $p = 0.001$), hs-CRP ($r = -0.192$, $p = 0.001$) and PWV ($r = -0.247$ $p < 0.0001$).

Conclusions: Patients with MHT and WCHT did not differ regarding hs-CRP, adiponectin and PWV levels. These findings suggest that although SHT is associated with activated inflammatory and proatherogenic pathways, masking and white coat effect may be associated with lower vascular disease burden.

P780 Endothelial nitric oxide synthase Glu298Asp and T-786C gene polymorphisms do not affect post challenge insulin levels in non diabetic hypertensive men



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Background: The endothelial nitric oxide synthase (eNOS) gene has been suggested to modulate nitric oxide production and to regulate muscle blood flow by inducing vasodilation. Throughout this mechanism eNOS may play an important role in the regulation of insulin induced blood flow and glucose uptake. A decrease in local blood flow has been reported to favor insulin resistance. In both non diabetic and type 2 diabetic subjects from Japan both the Glu298Asp and the T-786C eNOS gene polymorphisms have been associated with insulin resistance but no data are available in Caucasian populations.

Methods: We examined the association of those polymorphisms with fasting and post-challenge glucose and insulin levels in 278 caucasian non diabetic men with essential hypertension. A 75g glucose tolerance test was performed and blood sampling were obtained at baseline and at 30', 60', 90', 120' and 180' after glucose loading. Blood glucose and insulin (RIA method) were measured. Genotypes of both Glu298Asp and T-786C mutations were examined by the PCR-RFLP method.

Results: The percentages of the EE298, ED298 and DD298 genotypes were 45.0, 42.1 and 12.9%, respectively. The correlative features for TT786, TC786 and CC786 were 21.4, 48.2 and 30.4%. Genotypes did not differ in age, BMI, waist-to-hip ratio, systolic and diastolic blood pressure and lipid profile. Fasting and post-challenge glucose and insulin levels did not differ by genotypes. No significant differences by genotypes were observed in homeostasis model assessment for insulin resistance (HOMA-IR: EE298D: EE 3.0 ± 1.9 ; ED 3.6 ± 3.2 ; DD 2.8 ± 1.2 , $p = 0.10$; T786C: TT 3.3 ± 2.7 ; TC 3.3 ± 2.7 ; CC 3.2 ± 1.7 , $P = 0.98$) as well as in areas under the curve (AUC) for both glucose and insulin, or in insulinogenic index (DI30/DG30: EE298D: EE 98 ± 58 ; ED 135 ± 132 ; DD 100 ± 69 , $p = 0.22$; T786C: TT 112 ± 83 ; TC 116 ± 113 ; CC 120 ± 99 , $P = 0.91$). No interaction between the two polymorphisms was observed: fasting and post-challenge glucose and insulin, AUC for glucose and insulin, HOMA-IR and the insulinogenic index did not differ by haplotypes.

Conclusions: The present study suggest that in non diabetic hypertensive caucasian men the eNOS Glu298Asp and T-786C polymorphism does not affect insulin sensitivity as measured by oral glucose tolerance test.

P781 Urotensin II may impair left ventricular systolic function in essential hypertension



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Urotensin II (UII) is one of recently discovered vasoactive peptides. Preliminary studies indicate important role of UII in blood pressure homeostasis, in etiopathogenesis of essential hypertension and in hypertensive target-organ damage such as left ventricular (LV) hypertrophy and arterial remodeling. We sought to determine the relationships between plasma level of UII and LV function assessed using echocardiographic strain/strain rate technique in essential hypertension.

Material and methods: Studied group consisted of 48 untreated hypertensive patients aged 55.3 ± 9.2 yrs. In each patient echocardiographic study with strain/strain rate imaging was performed. Analysis of LV longitudinal deformation data included assessment of systolic strain (Ss), peak systolic strain rate (SRs) and peak early diastolic strain rate (SRe) obtained from the basal, mid and apical segments of LV septal, lateral, anterior and inferior wall. Plasma level of UII was measured by radioimmunoassay method.

Results: We found out significant inverse correlations between plasma UII and parameters of LV systolic function - Ss and SRs from segments of lateral ($r = -0.55$,

$p < 0.01$ and $r = -0.56$, $p < 0.01$, respectively) and anterior wall ($r = -0.51$, $p < 0.05$ and $r = -0.47$, $p < 0.05$, respectively). No associations were noted for diastolic function parameter -SRe and UII. No significant correlations were shown for UII and other echocardiographic indices including LV ejection fraction, LV mass index and mitral inflow indices.

Conclusions: Demonstrated relationships may suggest the adverse effect of UII on LV systolic function in hypertensive pts. Strain/strain rate imaging seems the most useful tool in evaluation of interdependence between plasma UII and LV function.

P782 NT-pro-BNP relates to systolic blood pressure load and diastolic dysfunction in newly diagnosed hypertensive patients



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Background and Aim: The N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is a cardiac neurohormone secreted from the ventricles in response to volume expansion and pressure overload. We hypothesized that NT-pro-BNP is an early marker of ventricular dysfunction related to cardiac target organ damage in hypertension, and therefore assessed its relationship with variables derived by ambulatory blood pressure (BP) monitoring and echocardiographic indices of systolic and diastolic dysfunction in newly diagnosed hypertensive patients (pts).

Methods: A cohort of 100 recently (<6 months) diagnosed, and untreated hypertensive pts underwent ambulatory BP monitoring. Measurements were made at 15-min intervals during daytime and at 30-min intervals during night time. All subjects were evaluated by echo for systolic and diastolic function. NT-proBNP was assessed by enzyme immunoassay.

Results: Patients' age (mean±SD) was 56±8 y; 63% of pts were male; body mass index was 28±5 kg/m². Significance of correlations for uni- and multivariate analysis between NT-pro-BNP and both BP [systolic (S) BP, diastolic (D) BP, SBP variability, DBP variability and SBP load (% of values >140 mmHg) and ventricular function [E/A ratio (E/A), deceleration time (DT), iso-volumetric relaxation time (IVRT)] variables are listed in the Table.

NT-pro-BNP vs BP and Diastolic Variables

	Univariate	Multivariate
E/A	0.05	NS
DT	0.002	0.04
IVRT	0.032	NS
SBP	0.04	NS
DBP	0.038	NS
SBP Variability	0.045	NS
DBP Variability	0.05	NS
SBP Load	0.002	0.04

Conclusions: In newly diagnosed hypertensive pts, NT-pro-BNP levels correlate with a number of left ventricular diastolic dysfunction and BP variables and, more closely, with deceleration time at echo and systolic blood pressure load at ambulatory blood pressure monitoring.

P783 Prognostic value of reflected pressure waves compared with aortic stiffness in a general population



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Purpose: Previous studies have shown the independent prognostic role of pulse wave velocity and augmentation index in hypertension and end-stage renal disease. The aim of our study was to compare the prognostic value of aortic stiffness with indices of amplitude and timing of pressure wave reflection in a general population.

Methods: 244 patients with at least a major risk factor were prospectively evaluated. Indices of both intensity and timing of RPW were obtained by calibrated carotid tonometry. Augmentation pressure (AP), a measure of the contribution of RPW to systolic pressure, was calculated from the carotid waveform as the difference between the peak pressure and pressure at the foot of RPW (Inflection point, Pi); AP was considered equal to 0 if Pi followed the peak systolic pressure and RPW had no effect on peak pressure. Timing of RPW was measured by transit time (TT; time interval from the foot of carotid waveform to the inflection point) divided by left ventricular ejection time (TT/ET). Aortic stiffness was assessed by carotid-femoral pulse wave velocity (PWV). All new fatal and non fatal cardiovascular events were the primary endpoint. In order to evaluate the impact of aortic stiffness and pressure wave reflection on the primary endpoint, population was divided in tertiles of PWV (1st 4.7-7 m/s; 2nd 7-8.4 m/sec; 3rd 8.4-18 m/sec), AP (1st 0-6 mmHg; 2nd 7-13 mmHg; 3rd 14-61 mmHg) and TT/ET (1st 72-45%; 2nd 44-34%; 3rd 33-18%). Relative risks of developing a new cardiovascular event were compared among groups.

Results: Patients were 48±10 year old; 10% had a previous cardiovascular event, 31% hypertension, 12% diabetes, 48% familial hypercholesterolemia. During the follow-up (mean 85±27 months), 49 new cardiovascular events occurred. The relative risk for 3rd tertile of AP vs 1st was 2.45 (CI 95% 1.21 to 4.97), for 3rd

tertile of TT/ET vs 1st was 3.84 (CI 95% 1.69 to 8.72). The 3rd tertile of PWV did not identify subjects with a greater incidence of new cardiovascular events.

Conclusions: In a general population, intensity and timing of pressure wave reflection, expressed as AP and TT/ET respectively, are predictors of cardiovascular events. This likely reflects the atherosclerotic burden related to risk factors. Surprisingly, PWV was not associated to higher incidence of new cardiovascular events in our population. Since PWV is highly dependent by age and blood pressure, this result probably reflects the young mean age and the relatively low prevalence of hypertensive subjects in this study.

P784 Aliskiren as add-on to amlodipine provides significant additional blood pressure lowering without increased oedema associated with doubling the amlodipine dose



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Purpose: The calcium channel blocker (CCB) amlodipine is widely used in the treatment of hypertension (HTN). However, effective blood pressure (BP) control may be limited by poor tolerability at higher doses. Aliskiren, a novel renin inhibitor, is an effective and well tolerated antihypertensive. In the present study, the effects of adding aliskiren 150mg to amlodipine 5mg in patients (pts) with inadequate BP control on this treatment was compared with continuing amlodipine 5mg monotherapy or increasing the dose to 10mg, in a 6-wk, randomized parallel-group study.

Methods: Pts with mild-to-moderate HTN (mean sitting diastolic BP [MSDBP] 95-109mmHg) underwent 2 wks' washout followed by 4 wks' single-blind treatment with amlodipine 5mg once daily. Pts with MSDBP remaining ≥90mmHg on this regimen were randomized to double-blind treatment with amlodipine 5mg monotherapy (n=180), amlodipine 10mg (n=178) or aliskiren 150mg plus amlodipine 5mg (n=187) for 6 wks. Outcome measures included change from baseline (end of single-blind amlodipine treatment) in MSDBP and mean sitting systolic BP (MSSBP), responder rates (proportion of pts achieving MSDBP <90mmHg and/or ≥10mmHg reduction from baseline), and control rates (pts achieving BP <140/90mmHg).

Results: Adding aliskiren 150mg to amlodipine 5mg provided statistically significant additional reductions in MSDBP and MSSBP, and led to superior responder and control rates, compared with continuing on amlodipine 5mg alone. Combination therapy was numerically, but not significantly, superior to amlodipine 10mg in each of these parameters. The overall incidence of adverse events (AEs) was comparable across treatment groups; however, there was a higher incidence of oedema with amlodipine 10mg monotherapy than with combination therapy and amlodipine 5mg.

	Aliskiren/amlodipine 150/5mg	Amlodipine 5mg	Amlodipine 10mg
MSDBP (mean change mmHg)	-8.46*	-4.84	-8.04*
MSSBP (mean change mmHg)	-10.98*	-4.96	-9.63*
Responder rate (%)	64.2*	45.2	59.9*
Control rate (%)	42.8*	22.6	37.9*
Overall AEs (%) [‡]	31.6	28.5	30.9
Oedema (%)	2.1	3.4	11.2 [‡]

* $p < 0.005$ vs amlodipine 5mg; [‡] $p < 0.001$ vs combination; [‡] significance not tested.

Conclusion: Aliskiren, at the starting dose of 150mg, provided significant additional BP lowering when added to amlodipine 5mg in pts not at goal on this treatment. The additional efficacy was at least comparable to that achieved by doubling the amlodipine dose to 10mg, but was not associated with the increased incidence of oedema seen with high-dose CCB treatment.

P785 Chronotherapy with nifedipine in hypertensive patients: Reduction of secondary effects after bedtime administration



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Several studies have shown that the circadian pattern of blood pressure (BP) remains unchanged after either morning or evening dosing of several CCB, including amlodipine, isradipine, verapamil, nitrendipine, and cilnidipine. While peripheral edema seems to be more prevalent with dihydropyridine CCB as compared to other antihypertensive drugs, the incidence of this secondary effect might be reduced with evening as compared to morning dosing. Accordingly, we investigated the antihypertensive efficacy, safety, and regulation of the circadian BP pattern after treatment with nifedipine GITS administered at different times according to the rest-activity cycle of each patient. We studied 130 previously untreated patients with grade 1-2 essential hypertension (62 men), 52.3±10.9 years of age, randomly assigned to receive nifedipine GITS (30 mg/day) as a monotherapy for 2 months either upon awakening or at bedtime. BP was measured by ambulatory

monitoring at 20-min intervals from 07:00 to 23:00 hours and at 30-min intervals at night for 48 hours before and after treatment. Physical activity was simultaneously monitored every minute by wrist actigraphy. The BP reduction after 2 months of therapy with 30 mg/day nifedipine GITS was similar at both treatment times (9.5 and 6.4 mm Hg reduction in the 24-hour mean of systolic and diastolic BP after nifedipine GITS on awakening; 10.5 and 6.4 mm Hg after bedtime dosing; $P > 0.349$ between groups). Efficacy was slightly but not significantly higher after bedtime dosing on the nocturnal mean of BP (7.4 and 4.7 mm Hg reduction after nifedipine GITS on awakening; 10.6 and 7.0 mm Hg after bedtime dosing; $P > 0.113$). The day/night BP ratio (nocturnal decline of BP relative to the diurnal mean) was slightly reduced after morning treatment, but increased after bedtime dosing, mainly for diastolic BP. Most important, bedtime administration of nifedipine GITS significantly reduced the incidence of edema from 18.8 to 1.6% and the total number of secondary effects from 20.3 to 4.7% as compared to morning dosing ($P = 0.009$). Independently of the circadian time of administration, a single daily dose of 30 mg/day of nifedipine GITS efficiently reduces BP for the whole 24 hours of the day. The added efficacy on the nocturnal BP mean without any loss in 24-hour or diurnal efficacy, the slight increase in day/night ratio, and, most important, the markedly improved safety profile of bedtime as compared to morning administration of nifedipine GITS, all indicate that this CCB should preferably be administered at bedtime in patients with essential hypertension.

P786 The beneficial effect of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins is in part due to their effect on inflammation



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Aim: The aim of the study was to compare the effect of renin-angiotensin system (RAS) inhibitors and statins on blood pressure, albuminuria, and C-reactive protein (CRP) and fibrinogen (FIB) as pro-inflammatory markers.

Patients and methods: A total of 314 hypertensive type 2 diabetics (58.55 ± 10.9 yrs. old; diabetes duration 10.2 ± 7.7 yrs.) were studied over a 1-yr follow-up period. Patients were randomized to receive either angiotensin-converting enzyme (ACE) inhibitor lisinopril (group I, n=69), angiotensin receptor blocker (ARB) losartan (group II, n=48), lisinopril/losartan combination (group III, n=36), atorvastatin (group IV, n=59), or simvastatin (group V, n=64). The control group included 39 patients. CRP, FIB, atherogenic index of plasma (AIP), pulse pressure (PP) and albumin excretion rate (AER) were determined at the beginning and at the end of the study. The patients were assigned to groups based on AER (mg/24h) (<30, 30-300, >300) and PP (<45, 45-50, 50-65, >65). Wilcoxon signed ranks test and Kruskal-Wallis test were used in the statistical analysis.

Results: Significant differences were found in initial CRP, FIB and AIP ($p = 0.01$, $p = 0.004$ and $p = 0.041$, respectively) according to AER, and in FIB and AIP (both $p < 0.001$) according to PP. Initial SBP, DBP, PP and AER were significantly reduced in the groups I, II and III (generally $p < 0.05$), while PP also fell in the groups IV and V ($p = 0.009$ and $p = 0.002$, respectively). CRP decreased significantly in Group I ($p < 0.001$) and III ($p = 0.030$), but not in Group II ($p = 0.432$), whereas FIB was significantly reduced in the groups I and IV ($p = 0.040$ and $p = 0.001$, respectively). At the end of the study CRP was also significantly reduced in the groups IV and V ($p < 0.001$ and $p = 0.049$, respectively), as was AIP ($p < 0.001$). Among-group comparison showed that the reduction in PP and SBP was most pronounced in Group III (both $p < 0.001$), while a difference in DBP reduction was not observed among the groups I-III ($p = 0.147$). Group III, followed by Group I, was the most effective in AER reduction. Group I and III did not differ in their effect on CRP ($p = 0.134$), and the reduction was most pronounced in Group IV ($p < 0.01$).

Conclusion: Diabetic patients with hypertension and albuminuria are at a considerable risk from vascular events. Increased CRP and FIB increase this risk additionally. In addition to their effect on AER, PP and AIP through reducing CRP and FIB, RAS inhibitors and statins can have a beneficial effect on the inflammation and consequently on vascular disease.

P787(W) PPAR(gamma)-activating angiotensin type-1 receptor blocker telmisartan in treatment of arterial hypertension with metabolic disturbances



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Aims: To estimate clinical efficiency of telmisartan, an antihypertensive agent with evidence of partial peroxisome proliferators-activated receptor activity-gamma (PPAR γ) activating angiotensin type-1 receptor blocker and enalapril, angiotensin converting enzyme inhibitor in hypertensive patients with metabolic disturbances (glucose intolerance, hypercholesterolemia).

Design and methods: 50 patients (men and women of 18-65 years) with mild-to-moderate hypertension (mean 150/92 mm Hg) were randomized to telmisartan, 40-80 mg daily (n=25) or enalapril 10-20 mg daily (n=25) for 8 weeks, according to a prospective, open-label, blind end point, parallel-group design. At the end of 2-week washout period and after 8 weeks of active treatment, seated trough systolic and diastolic blood pressure (SBP and DBP), 24-h noninvasive mean blood pres-

sure (BP) monitoring was performed, clinic BP and fasting plasma glucose (FPG), fasting plasma insulin (FPI), homeostasis model assessment of insulin resistance (HOMA-IR), glycosylated hemoglobin (HbA_{1c}) and lipid profile (plasma total cholesterol-TC, low density lipoprotein cholesterol-LDL-C, triglycerides-TG concentration) were evaluated.

Results: After 8 weeks' treatment, a 24-h mean diastolic BP of <85 mm Hg was observed in 72% of the telmisartan-treated patients but in only 48% of the enalapril-treated patients ($P < 0.05$). Telmisartan produce greater reduction in SBP and DBP during the last 8 h of the dosing interval in patients than enalapril-treated patients ($P < 0.05$). Changes in metabolic parameters were observed at the end of treatment compared with baseline. Telmisartan reduced FPG by 7% ($P < 0.05$), FPI by 8% ($P < 0.05$), HOMA-IR by 21% ($P < 0.05$) and HbA_{1c} by 8% ($P < 0.05$). Levels of FPG and FPI following oral glucose tolerance test were also significantly reduced by telmisartan compared with enalapril. Telmisartan significantly improved plasma TC (-17%, $P < 0.01$), LDL-C (-13%, $P < 0.01$) and TG (-25%, $P < 0.05$). Enalapril did not have a meaningful effect on these parameters. The incidence of adverse effects was lower in the telmisartan group (5% vs 12%, $P < 0.05$), with the absence of cough (0 vs 4%, $P < 0.01$).

Conclusions: As well as providing superior 24-hour blood pressure control including during the last 8 h of the dosing interval, a highly selective angiotensin type-1 receptor blocker telmisartan, unlike enalapril, may improve insulin sensitivity and lipid profile in hypertensive patients with metabolic disturbances, which may be explained by its partial PPAR γ activity.

P788 Chronotherapy in resistant hypertension: Improved renal function associated to the increase in the diurnal/nocturnal blood pressure ratio



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Patients with resistant hypertension present high prevalence of a non-dipper blood pressure (BP) pattern. Against the usual therapeutic strategy of administering all drugs in a single morning dose, recent results have indicated that the prevalence of non-dipping in resistant hypertension is markedly reduced from 82 to 57% in patients receiving at least one drug at bedtime [Hypertension. 2005;46:1053-1059]. Moreover, previous results have also indicated a significant correlation between the increase in diurnal/nocturnal BP ratio and a decrease in urinary albumin excretion (UAE) after chronotherapy with valsartan [Hypertension. 2005;46:960-968]. Accordingly, we have prospective evaluated the potential beneficial effects of chronotherapy on renal function in patients with resistant hypertension. We studied 213 (114 men), 59.8 ± 12.0 years of age, who were receiving 3 antihypertensive drugs in a single morning dose. Patients were randomly assigned to one of two groups according to the modification in their treatment strategy: 1) Changing one of the drugs, but keeping all 3 in the morning. 2) The same approach but prescribing the new drug to be taken at bedtime. BP was measured at 20-min intervals from 07:00 to 23:00h and at 30-min intervals at night for 48h at baseline and after 3 months of treatment with the new scheme. Physical activity was simultaneously monitored every minute by wrist actigraphy. The patients collected their urine during the first 24h of ambulatory monitoring. The diurnal/nocturnal BP ratio was slightly reduced with all drugs on awakening (-0.9 and -1.6 for systolic and diastolic BP; $P = 0.019$), but significantly increased in patients receiving one of the antihypertensive drugs at bedtime (7.1 and 7.3 for systolic and diastolic BP; $P < 0.001$). The percent decrease from baseline in UAE and the percent increase in glomerular filtration rate after treatment were independent from the changes in diurnal and 24-hour means of BP ($P > 0.237$). There were, however, significant correlations between the increase in diurnal/nocturnal BP ratio and both the decrease in UAE ($r = -0.329$ and 0.301 for systolic and diastolic BP ratio; $P < 0.001$) and the increase in glomerular filtration rate ($r = 0.257$ and 0.326 for systolic and diastolic BP ratio; $P < 0.001$). Chronotherapy allows increasing the diurnal/nocturnal BP ratio towards a more dipper profile. This change in the circadian BP pattern is correlated with a decrease in UAE and an increase in glomerular filtration rate, indicating the improvement of renal function associated to reverting the high-risk non-dipper pattern into a dipper BP profile.

P789 Aliskiren, a novel renin inhibitor for treatment of hypertension, enhances renin system suppression by reducing plasma renin activity alone or in combination with ramipril in patients with diabetes



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Purpose: Chronic activation of the renin system puts patients with hypertension, particularly those with comorbidities such as diabetes, at risk of end-organ damage. Renin system blockade is beneficial in the management of hypertension in patients with diabetes; however, monotherapy is often insufficient to achieve the stringent blood pressure (BP) control required in this population. Inhibition of the renin system stimulates compensatory renin release which can induce a reac-

tive rise in plasma renin activity (PRA; the capacity of circulating renin to form angiotensin I). The renin inhibitor aliskiren overcomes this by targeting the renin system at its point of activation. Effects on PRA and renin concentration (RC) of aliskiren and the angiotensin converting enzyme (ACE) inhibitor ramipril, alone and in combination, were investigated in patients with diabetes and hypertension. **Methods:** Patients with type 1 or 2 diabetes and hypertension (mean sitting diastolic BP 95-109 mmHg) were randomized to treatment with aliskiren 150 mg (n=282), ramipril 5 mg (n=278) or aliskiren/ramipril 150/5 mg (n=277) once daily for 4 weeks, followed by forced titration to aliskiren 300 mg, ramipril 10 mg or aliskiren/ramipril 300/10 mg for a further 4 weeks. In an exploratory analysis, PRA and RC were measured in blood samples taken from a subgroup of patients at baseline and on study completion, and percentage change from baseline was calculated based on geometric means.

Results: Aliskiren, ramipril and combination therapy reduced systolic/diastolic BP by 14.7/11.3, 12.0/10.7 and 16.6/12.8 mmHg, respectively. RC increased in all groups; the increase was greater in the aliskiren group (115%; n=84) than in the ramipril group (68%; n=72), and the increase seen with combination therapy exceeded the sum of the two monotherapies (315%; n=77). Consistent with the reactive rise in RC, PRA increased by 111% in the ramipril group (n=79); however, PRA was reduced by 68% in the aliskiren group (n=74). In combination therapy, aliskiren counteracted the ramipril-induced increase in PRA, leading to an overall reduction of 44% (n=75).

Conclusions: Aliskiren and ramipril demonstrated effective renin system blockade, as indicated by compensatory increases in RC, with apparent synergy in combination. Increases in RC were functionally countered by aliskiren, leading to overall reduction of PRA with aliskiren alone and in combination with ramipril. Aliskiren offers enhanced renin system suppression corresponding to additional antihypertensive efficacy when added to ramipril in patients with diabetes and hypertension.

P790 Aliskiren, a novel renin inhibitor, provides long-term suppression of the renin system, when used alone or in combination with hydrochlorothiazide in the treatment of hypertension

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Purpose: Aliskiren has previously demonstrated reduction of plasma renin activity (PRA; the capacity of circulating renin to form angiotensin I) in trials up to 8 wks long. Aliskiren also prevents PRA increases induced by other antihypertensive drug classes. Here we report the effects of long-term aliskiren treatment (Tx), alone or with hydrochlorothiazide (HCTZ), and the effects of aliskiren withdrawal, on PRA and renin concentration (RC) in patients (pts) with hypertension.

Methods: 1955 pts with mean sitting diastolic blood pressure (BP) 90-109mmHg received 11-12 mths' open-label Tx with aliskiren up to 300mg once daily, with optional addition of HCTZ in pts with inadequate BP control after Mth 2. A subset of pts had PRA and RC measured at baseline, Mth 6 and final open-label visit. Of the overall pt population, 261 pts remaining on aliskiren monotherapy (mono) at Mth 11 entered a 1-mth double-blind withdrawal phase and were randomized to continued aliskiren or placebo. PRA and RC were evaluated at Wks 1, 2 and final visit.

Results: Open-label Tx led to sustained BP reduction of 18.0/12.7mmHg overall at endpoint, with no rebound on withdrawal. PRA was also substantially reduced, to a similar extent with aliskiren mono and combination therapy, despite increases in RC that were greater with combination than mono. Changes were apparent after 6 mths and were sustained for the remainder of open-label Tx. Despite elevated RC for at least 2 wks after Tx withdrawal, PRA remained suppressed during withdrawal and was still >50% below baseline levels after 4 wks' placebo. RC returned to approximately baseline levels by the end of the withdrawal period.

Open-label Tx	PRA [†]		RC [†]	
	Mono n=138	Combination n=159	Mono n=100	Combination n=131
Mth 6	-73.2	-65.3	+148	+390
End	-68.0	-65.4	+176	+411
Withdrawal period*	Aliskiren n=15	Placebo n=11	Aliskiren n=11	Placebo n=9
Wk 1	-70.5	-61.7	+267	+56.5
Wk 2	-68.4	-60.2	+154	+19.9
End	-76.1	-55.9	+82.8	-1.6

[†]Geometric mean % change from start of open-label Tx; *Pts on aliskiren mono at open-label Mth 11.

Conclusion: Long-term (1-yr) aliskiren Tx, alone and in combination with HCTZ, is associated with sustained suppression of the renin system, as indicated by similar PRA reductions at 6 mths and endpoint. This was consistent with sustained BP reduction throughout the year. Following acute aliskiren withdrawal, PRA reductions persisted despite continued RC elevation, suggesting continued renin inhibition far beyond the drug's plasma half-life.

P791 Arterial stiffness is related to ventricular diastolic function and cardiovascular risk in older adults

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Objectives: We assessed the relationship between arterial stiffness and left ventricular (LV) diastolic function, and compared the utility of various indices of arterial stiffness for cardiovascular risk stratification.

Background: There is limited information regarding the relationship between arterial stiffness and LV diastolic function, and the performance of non-invasive indices of arterial stiffness as markers of cardiovascular risk.

Methods: In 188 subjects of age ≥ 65 years (mean 75 ± 5 years; 71% men), LV diastolic function was quantitated with echo-Doppler and left atrial (LA) volume. Indices of arterial stiffness [brachial and aortic pulse pressure (PP), carotid-femoral pulse wave velocity (PWV), and augmentation pressure (AP)] were measured using applanation tonometry. Risk for new cardiovascular events was estimated using a validated clinical-echocardiographic risk algorithm.

Results: LA volume was positively associated with aortic and brachial PP, AP, PWV, diastolic function grade, LV mass and heart rate, and negatively associated with LV ejection fraction. One standard deviation increase in aortic PP (p=0.001), brachial PP (p=0.002), AP (p=0.03) and PWV (p=0.03) was associated with 6%, 6%, 4% and 4% increase in indexed LA volume, respectively, after adjusting for significant covariates (Table). PWV, aortic and brachial PP were superior to AP in identifying subjects with highest cardiovascular risk (area under receiver operator characteristic curve 0.67, 0.70, 0.67, respectively versus 0.56; p<0.05).

Relationship between LA volume and Arter

	Indexed LA volume									
	Brachial PP* model (R ² =0.25)		Aortic PP* model (R ² =0.26)		AP* model (R ² =0.23)		Alx ₇₅ * model (R ² =0.21)		PWV* model (R ² =0.23)	
	effect	p-value	effect	p-value	effect	p-value	effect	p-value	effect	p-value
LVEF	-4%	0.03	-4%	0.04	-3%	0.11	-3%	0.07	-3%	0.06
LVMI	+2%	0.24	+2%	0.22	+3%	0.15	+3%	0.14	+4%	0.06
Grade I DD	+9%	0.12	+9%	0.13	+11%	0.05	+11%	0.05	+10%	0.10
Grade II-IV DD	+30%	<0.0001	+30%	<0.0001	+34%	<0.0001	+37%	<0.0001	+34%	<0.0001
IAS*	+6%	0.002	+6%	0.001	+4%	0.03	+0%	0.90	+4%	0.03

IAS = Index of Arterial Stiffness.

Conclusion: In elderly patients at high-risk for cardiovascular events clinically, increased arterial stiffness was associated with more severe diastolic dysfunction. Central and brachial PP and PWV, but not AP, were comparably useful for further risk stratification.

P792 The presence of mitral L wave in patients with systemic hypertension indicates severe diastolic dysfunction

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Purpose: Diastolic mitral flow velocities obtained by pulse wave Doppler echocardiography consists of two velocity peaks in sinus rhythm: early diastolic peak from early rapid filling rate (E wave) and late filling peak from atrial contraction (A wave). In some patients (pts) a third mid-diastolic filling wave (L wave) is encountered.

The aim of this study was to evaluate the clinical implication of the presence of triphasic mitral inflow in patients with arterial hypertension.

Methods: 38 patients with systemic hypertension grade 2 and 3 (18 men, 20 women, mean age 54 ± 9 years) were evaluated. All patients were in sinus rhythm. Mitral L wave was defined as a mid-diastolic wave, with velocity > 0.2 m/s. We evaluated the following parameters: peak velocity of E, L and A filling, deceleration time (DT) of E velocity, left atrial (LA) volume, ejection fraction (EF), diastolic annular mitral E' velocity, measured by Doppler tissue imaging in the lateral mitral ring, mean left ventricular (LV) mass. Clinical data were collected from clinical notes. Pts were classified into two groups: group A (n=12), which included pts with L wave and group B (n=26), which included pts without L wave.

Results: In group A pts, the heart rate was significantly lower (56 ± 6 vs 66 ± 10 , p<0.001). A clinical history of severe heart failure (NYHA III or IV) was more frequent in group A pts (22% vs 8%, p<0.001). LV mass and LA volume index were higher in group A pts (258 ± 72 g vs 188 ± 64 g, p<0.001 and 42 ± 11 vs 34 ± 10 ml/m², p<0.01) EF was not significantly different between the two groups ($56\% \pm 14$ vs $58\% \pm 10$, p=NS). E/A ratio was higher and DT was lower in group A pts (1.2 ± 0.4 vs 0.8 ± 0.3 , p<0.001 and 168 ± 42 vs 226 ± 58 ms, p<0.001). E' was significantly lower in group A pts (5.6 ± 2.8 cm/s vs 7.8 ± 1.6 cm/s) and the E/E' ratio was higher (17 ± 7 in group A pts vs 14 ± 8 in group B pts, p<0.01).

Conclusions: The presence of L wave in patients with hypertension is more frequent associated with severe heart failure and with diastolic echocardiographic parameters compatible with elevated LV filling pressures.

P793 Regression of left ventricular mass and its impact on pulsed Doppler tissue imaging variables in hypertrophic hypertensive cardiopathy



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Background: The Doppler tissue imaging (DTI) method in its pulsed modality has the unique capacity to perform a quantitative analysis of the left ventricular (LV) segmental myocardial wall function, an aspect of LV function that is dependent on LV hypertrophy (LVH) regression.

Purpose: The objective of this study was to assess the effect of LVH regression on several pulsed DTI parameters in a group of patients with LVH secondary to hypertensive heart disease.

Methods: We studied a group of 22 patients (pts) with LVH secondary to hypertensive heart disease, mean age 57±10 years (37-75 years), 72.7% male gender, all with concentric LVH type, normal global LV systolic function, and no LV regional wall motion abnormalities, with a reduction of the LVM>10%. In each case, we calculated by conventional transthoracic echocardiography the left atria (LA-mm), LV end-systolic (ESD-mm) and end-diastolic (EDD-mm) diameters, LV ensystolic (EDV-ml) and end-diastolic (EDV-ml) volumes, LV percent fractional shortening (LV%FS-%) and ejection fraction (LV%EF-%), interventricular septum (IVS-mm) and posterior wall (PW-mm) thickness, LV mass (LVM-g) and LVM index (LVMi-g/m²). By pulsed DTI we calculated the mean and maximal velocities (V-cm/s) of the systolic contraction s'wave, the diastolic early e'and late a'relaxation waves, and its Vmax e/a'ratio. LVH was defined as LVM>200 g and LVMi>134 g/m² (♂) and >120 g/m² (♀). These parameters were evaluated during a mean follow-up time of 13±3 months, each case being its own control.

Results: In this period of time, we observed a reduction of -12.5±3.2 g and -12.5±3.2 g/m² in the basal LVM (p=0.02) and LVMi (p=0.02) values, respectively. The mean values of the Vmax of the systolic s' and diastolic e' waves increased +7.3±3.2 cm/s (p=0.02) and +8.2±2.5 cm/s (p=0.01), respectively, and its e/a'ratio increased +15.6±4.2 g., when compared with basal values.

Conclusions: The LVM reduction has a direct impact on the maximal velocities of the systolic contraction s' wave and mainly on the early e' relaxation wave of the pulsed DTI pattern, revealing a significant improvement on the diastolic segmental myocardial wall function as the first target on the process of LVH regression.

P794(W) Additive beneficial effects of fenofibrate combined with candesartan in the treatment of hypertriglyceridemic, hypertensive patients



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Background: Biological mechanisms underlying fibric acid (PPARα ligand) and angiotensin II type 1 receptor blocker therapies differ. Experimental studies demonstrated cross-talking between PPARα and RAS system. We investigated vascular and metabolic responses to these therapies either alone or in combination in hypertriglyceridemic, hypertensive patients.

Methods: This was a randomized, double-blind, placebo-controlled cross-over trial with three treatment arms (each 2 months) and two washout periods (each 2 months). Forty-four patients were given fenofibrate 200 mg and placebo, fenofibrate 200 mg and candesartan 16 mg, or candesartan 16 mg and placebo daily during each 2 month treatment period.

Results: Fenofibrate, combined therapy, or candesartan significantly reduced systolic and diastolic blood pressure after 2 months administration compared with baseline. However, combined therapy significantly reduced blood pressure more than fenofibrate or candesartan alone (P<0.001 by ANOVA). When compared with candesartan, fenofibrate or combined therapy significantly improved the lipoprotein profile. All three treatment arms significantly improved flow-mediated dilator response to hyperemia. Combined therapy significantly decreased plasma malondialdehyde (MDA), hsCRP, and soluble CD40L levels relative to baseline measurements. Importantly, these parameters were changed to a greater extent with combined therapy when compared with monotherapy (P<0.001, P=0.002, P=0.050, and P=0.032 by ANOVA, respectively). Fenofibrate, combined therapy, and candesartan significantly increased plasma adiponectin levels and insulin sensitivity (determined by QUICKI) relative to baseline measurements. However, the magnitude of these increases were not significantly different among three therapies (P=0.246 and P=0.153 by ANOVA, respectively).

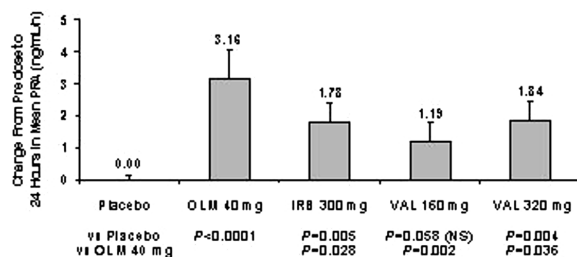
Conclusions: Fenofibrate combined with candesartan improves endothelial function and reduces inflammatory markers to a greater extent than monotherapy with either drug in hypertriglyceridemic, hypertensive patients.

P795 Effects of Olmesartan Medoxomil (OLM), Irbesartan (IRB), and Valsartan (VAL) on the Renin-Angiotensin-Aldosterone System (RAAS) in healthy normal subjects



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Angiotensin II (Ang II) receptor blockers (ARBs) inhibit the binding of Ang II to the AT1 receptor, thus lowering blood pressure. Blockade of the RAAS and the concurrent fall in blood pressure induced by ARBs causes a compensatory rise in plasma renin activity (ΔPRA). ΔPRA can be used as an indirect measure of the degree and persistence of AT1 receptor blockade. This 5-way crossover study compared, in 20 healthy normal subjects, ΔPRA for 24 hours following single doses of placebo, OLM 40 mg, IRB 300 mg, VAL 160 mg, and VAL 320 mg. There was a 7-day washout period between doses. The primary endpoint was ΔPRA from pre-dose to 24 hours. Subjects' ages ranged from 20-65 years; 14 were male and 6 female; 12 were Black, 5 Caucasian, and 3 Hispanic. PRA levels increased with each dose of active treatment. There was a rapid rise (2 hours) and peak (4 hours), followed by a slow fall between 8 and 24-hours. The 24-hour area under the curve for PRA was significantly greater than with placebo for all drugs and doses, but no differences between active treatments were observed. At 24 hours post-dose, ΔPRA was significantly greater compared with placebo for OLM 40 mg, VAL 320 mg, and IRB 300 mg but not VAL 160 mg (Figure).



At 24 hours post dose ΔPRA was significantly greater for OLM 40 mg compared to IRB 300 mg, VAL 160 mg, and VAL 320 mg but did not differ among IRB 300 mg, VAL 160 mg, or VAL 320 mg. As expected from the ΔPRA results, 24-hour urine aldosterone excretion rates were significantly reduced with OLM 40 mg, IRB 300 mg, and VAL 320 mg, but not VAL 160 mg, compared with placebo. The results of this study suggest that OLM may provide more prolonged AT1 receptor blockade than VAL or IRB at the doses tested.

P796 Short term fish oil supplementation increases arterial elasticity in patients with obese hypertension



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Background: Clinical studies showed that omega-3 fatty acid intake decrease the risk of cardiovascular disease in patients with essential hypertension. Mechanisms underlying this effect are unknown, but could involve arterial elasticity.

Objective: We tested the hypothesis that omega-3 fatty acid supplementation ("fish oil") would ameliorate arterial elasticity in obesity-related hypertension independently of any effect on blood pressure and heart rate.

Design: Patients with obese hypertension (n=43) were randomly assigned to receive 3 g/day fish oil capsules (contained EPA 540 mg, DHA 360 mg) (experimental group, n = 23), or 3 pills/day placebo capsules (control group, n = 20) in a 8-wk parallel, double-blind, controlled clinical trial.

Outcome measures: Arterial elasticity was measured with CVProfilor DO-2020 before(PRE) and after(POST) the interventions. Serum FFA were determined by high performance liquid chromatogram, insulin and leptin by radioimmunoassay.

Statistical analyses: Differences in baseline subject characteristic were determined by t test, and repeated measures ANOVA was used to determine effects of the intervention.

Results: – Serum n3 polyunsaturated fatty acids levels significantly increased POST than PRE in the experimental (79.4±23.5 vs. 65.1±14.5 mL/mmHg) group and was comparable POST than PRE in control (56.0±23.0 vs. 56.8±20.5 mL/mmHg) subjects.

– Large arterial elasticity (C1) at rest significantly increased POST than PRE in experimental (15.49±1.46 vs. 12.8±3.74 mL/mmHg) subjects and was comparable POST than PRE in control (12.97±3.39 vs. 13.35±3.82 mL/mmHg) subjects.

– Small arterial elasticity (C2), blood pressure level, heart rate, serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides levels did not show significant difference POST than PRE between experimental and control group.

Conclusion The data indicated that 8 weeks of fish oil supplementation in patients with obese hypertension increase large artery elasticity independently of any effect on blood pressure and heart rate.

P797 Aliskiren, a novel renin inhibitor, is well tolerated and has sustained BP-lowering effects alone or in combination with HCTZ during long-term (52 weeks) treatment of hypertension



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Purpose: The long-term efficacy and tolerability of the novel potent renin inhibitor aliskiren, with optional addition of hydrochlorothiazide (HCTZ), were assessed in a 12-month, open-label study in patients with hypertension, including a randomized, placebo-controlled withdrawal period.

Methods: Patients with mean sitting diastolic blood pressure (MSDBP) 90-109 mmHg were randomized to aliskiren 150 mg (n=1178) or 300 mg (n=773) once daily, after washout and a 2-4 week drug-free period. Dose titration (aliskiren 150 mg titrated to 300 mg) or addition of HCTZ (12.5 mg titrated to 25 mg if required) to aliskiren 300 mg was permitted in patients with BP $\geq$ 140/90 mmHg after Month 2. A subgroup of patients remaining on aliskiren monotherapy at Month 11 were randomized to continued aliskiren (n=132) or placebo (n=129) during a 4-week double-blind withdrawal phase. MSDBP and mean sitting systolic BP (MSSBP) were measured at intervals throughout open-label treatment and withdrawal; ambulatory BP monitoring (ABPM) was performed in a subset of patients at the start and end of the withdrawal period.

Results: A total of 1625 patients (83%) completed the open-label treatment period. Mean BP reductions (MSSBP/MSDBP) at endpoint were 17.5/12.4 and 18.8/13.3 mmHg in aliskiren 150 and 300 mg groups, respectively. 868 patients (45%) required addition of HCTZ; BP reductions at study end were comparable in these patients (18.7/12.1 mmHg) and those responding adequately to monotherapy (17.4/13.3 mmHg). In the withdrawal period patients on placebo had a gradual increase in mean sitting BP, while BP reductions were maintained in patients remaining on aliskiren. At the end of the withdrawal period there was a statistically significant difference between the two groups (5.99/3.87 mmHg; $p < 0.0001$ for MSSBP and MSDBP). ABPM at Month 12 also showed significantly increased BP with placebo versus continued aliskiren (treatment difference 4.14/3.87 mmHg; $p < 0.0001$ for systolic and diastolic BP), with clear separation at most hourly time-points. There was no evidence of dose-dependent side-effects during open-label treatment with aliskiren alone or with HCTZ. During the withdrawal period, AE rates were similar in patients on aliskiren (15.9%) and placebo (14.7%).

Conclusion: Aliskiren, as monotherapy and in combination with HCTZ, is effective and well-tolerated in the long-term treatment of hypertension. Aliskiren continues to demonstrate significant BP lowering efficacy, sustained over 24-hours, after 12 months' treatment. Following treatment withdrawal, BP rose gradually with no evidence of rebound.

P798 Cardiorenoprotective effect of fasudil, a specific Rho-kinase inhibitor, in malignant hypertensive rat



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Rho/Rho-kinase pathway is known to function as a molecular switch in various cellular functions. Recent studies have shown that Rho/Rho-kinase pathway is involved in the pathophysiology of various cardiovascular disease such as arteriosclerosis, pulmonary hypertension, myocardial infarction. However, few studies have investigated the role of Rho/Rho-kinase in hypertensive target organ damage. The present study was examined whether Rho/Rho-kinase pathway is involved in pathogenesis of left ventricular hypertrophy (LVH) and glomerulosclerosis in malignant hypertensive rats and if so, we investigated the long-term effect of fasudil.

Method: We studied the following four groups: control; Wistar Kyoto rats (WKY, n=8), untreated deoxycorticosterone acetate-salt spontaneously hypertensive rat (D-SHR, n=8), low dose fasudil-treated D-SHR (30mg/kg/day, n=8), and high dose fasudil-treated D-SHR (100mg/kg/day, n=8). After 3 weeks, we measured blood pressure, renal function, neurohumoral factors, gene expressions, and histological examinations.

Result: D-SHR was characterized by increased LV weight, decreased kidney function, abnormal cardiac and renal morphological findings, and increased urinary 8-isoprostane excretion and gene expressions in left ventricle and renal cortex compared with WKY. Chronic high-dose fasudil treatment significantly improved LV weight (-10%), renal function (serum Cre: -26%, Cr: +42%, TproV: -24%), renal histological findings (GIS: -49%, AAIS: -17%), and without changing systolic blood pressure compared to untreated DS. Long-term high-dose fasudil treatment did not change plasma renin or aldosterone, but decreased ANP. Furthermore, fasudil significantly decreased urinary 8-iso-prostane excretion and mRNA expressions levels of TGF-beta, collagen I, collagen III and NADPH oxidase subunits in LV and renal cortex. However, there were still significant differences in above parameters between WKY and high dose fasudil treated D-SHR.

Conclusion: Long-term inhibition of Rho-kinase pathway may be a new therapeutic approach for prevention of hypertensive organ damage partly via inhibition of oxidative stress.

P799 Usefulness of renal frame count to identify the good responder of renal artery stent placement in patients with atherosclerotic renal artery stenosis with hypertension



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Background: The efficacy of renal artery stenting on blood pressure in patient with atherosclerotic renal artery stenosis (ARAS) remains controversial. Therefore, there is a considerable need and interest to define the clinical predictors to identify the response of renal artery stenting. Recent data suggest that renal frame count (RFC) method using renal angiography represent the renal perfusion status. We evaluate the patient with ARAS after renal artery stenting by using RFC. And we investigate the usefulness of RFC to identify the good responder of this therapy.

Methods: A total of 50 patients with hypertension were evaluated. They underwent successful renal artery stenting for angiographically $> 70\%$ stenosis and did not show restenosis. We divided subjects into the two groups by reaction to this treatment, and clinical factors including RFC were compared. Good responder group is categorized by cure or improvement of hypertension using guideline criteria (Circulation. 2002 Sep 17;106(12):1572-85) at 4months later. RFC was measured as previously described (Mulumudi MS et al. Catheter Cardiovasc Interv. 2005 Jun;65(2):183-6).

Results: Good responder was observed in 25pts (50%). High pre-procedural blood pressure, lower pre-serum creatinine level and lower post RFC numbers were more frequently seen in good responder group.

	Good responder	Poor responder	P value
pre systolic blood pressure (mmHg)	154 $\pm$ 21	134 $\pm$ 17	0.001
pre diastolic blood pressure (mmHg)	83 $\pm$ 10	74 $\pm$ 11	0.003
pre number of anti-hypertensive drugs(n)	2.7 $\pm$ 1.3	2.2 $\pm$ 1.4	ns
pre serum creatinine(mg/dl)	1.4 $\pm$ 0.8	2.1 $\pm$ 1.5	0.04
resistive index > 0.8	36.0%	45.4%	ns
RFC immediately after stenting (n)	22.2 $\pm$ 7	26.8 $\pm$ 8	0.05
post systolic blood pressure (mmHg)	123 $\pm$ 14	136 $\pm$ 17	0.005
post diastolic blood pressure (mmHg)	74 $\pm$ 10	74 $\pm$ 11	ns
post serumcreatinine (mg/dl)	1.2 $\pm$ 0.5	1.9 $\pm$ 1.1	0.02
post number of anti-hypertensive drugs(n)	2.3 $\pm$ 1.3	2.2 $\pm$ 1.3	ns

Conclusion: Well perfused kidney may contribute to reduction of renal hypertension and preservation of renal function. RFC may be useful tool to identify the good responder of this therapy.

P800 Home-based structured exercise training program as a therapeutic intervention for reducing cardiovascular risk profile in mild hypertension



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Aims: This study aims at evaluating the effects of exercise training on blood pressure (BP) and on cardiovascular risk factors (CVRF) in patients with mild hypertension (grade I ESH/ESC 2003).

Methods: At baseline, forty-six hypertensive patients (30M/16F) underwent CVRF evaluation (Total Cholesterol, LDL-C, HDL-C, Triglycerides, BMI), echocardiography and exercise stress test. Patients were randomly assigned into two groups: Group A patients (n=23) were enrolled in the study protocol including health education, dietary and behavioural recommendations, and home-based exercise training program. Group B patients (control group) were seen at 3 months follow-up. Exercise training in Group A was performed for 30 minute on a bike-ergometer at 60-70% of the maximal heart rate (HR) achieved at the initial exercise stress test at least 5 times/week. This exercise protocol was performed with a gradual increase of both workload and duration of exercise sessions. Patients were also instructed to fill in a diary, reporting the date, hour, duration, and radial pulse HR achieved at the end of each exercise session. After 3 months, all patients repeated CVRF evaluation, echocardiography and exercise stress test.

Results: After 3-months, in Group A patients we observed a significant improvement in systolic and diastolic BP (from 144.9 to 137.5 ($p < 0.05$) and from 100.2 to 89 mmHg ($p < 0.001$), respectively), in resting and peak HR (from 72 to 58 ($p < 0.05$) and from 179.8 to 172.8 beats/min ($p < 0.001$), respectively), in total Cholesterol (from 235.3 to 206.8 mg/dL, $p < 0.001$), and in Triglycerides (from 195.3 to 156.2 mg/dL, $p < 0.05$), but no significant changes in BMI, LDL-C, HDL-C and Doppler-echocardiographic parameters.

Conclusions: This study confirms the beneficial effects of aerobic training on CVRF and BP, representing a valid strategy and/or therapeutic option for approaching mild hypertension according to 2003 ESH/ESC Guidelines.

P801 Morphological and functional pattern of vascular responses after AT1 receptor blockade started at prehypertensive period of SHR



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We evaluated the effect of angiotensin II AT1 receptor antagonist losartan (Los) on systolic blood pressure (sBP), heart weight/body weight ratio (HW/BW), morphological and functional parameters of thoracic aorta (AT) of SHR and Wistar rats. We used 4-week-old rats: 1) Wistar rats, 2) SHR, 3) Wistar rats+Los and 4) SHR+Los. Los was administered 20 mg/kg/day in drinking water by gavage. Experiment lasted 5 weeks. BP was measured on the tail artery using the plethysmographic method. For functional study AT was excised (from 6 rats of each group), cut into rings and mounted in organic bath for measurement of endothelium dependent relaxation (EDR) and contractile response to noradrenaline (NA). For morphological study cardiovascular system (11 rats of each group) was perfused with glutaraldehyde fixative (120 mm Hg) via cannula placed in the left ventricle. Heart was excised and HW/BW (cardiac hypertrophy) was estimated. AT was processed according to standard electron microscopical procedure. Geometry of AT - wall thickness (WT), inner diameter (ID), cross sectional area - tunica intima + tunica media (CSA) and WT/ID ratio were evaluated in light microscope. In comparison to age matched Wistar rats we observed: (i) in 4-week-old SHR: cardiac hypertrophy (+79%), unchanged sBP and EDR, and decreased contractile response to NA (-28%), and contrary to other conduit arteries (1) decreased WT (-26%), ID (-10%), CSA (-35%), and WD (-17%); (ii) in 9-week-old SHR: cardiac hypertrophy (+26%), increased sBP (+37%), contractile response to NA (+68%), inhibition of EDR (-22%), and decreased WT (-7%), CSA (-9%), and no differences in ID and WT/ID ratio. Administration of Los to (i) Wistar rats (compared to untreated Wistar rats) evoked: cardiac hypotrophy (-65%), decrease of sBP (-7%) and WT (-18%), CSA (-21%), WT/ID ratio (-16%), and no changes in ID; (ii) SHR (compared to untreated SHR) resulted in: decrease of cardiac hypertrophy (-28%), sBP (-9%), contractile response to NA (-63%), and increased EDR (+29%), in geometry decrease WT/ID ratio (-15%), increase of ID (+9%), and unchanged CSA and WT. In conclusion: Cardiac hypertrophy opposite to hypotrophy of AT wall was observed in prehypertensive period of SHR. Similar effect on cardiovascular system of Wistar rats and SHR was observed after 5 weeks long administration of Los. Beneficial effect of Los treatment on functional parameters was observed in SHR.

P802 Effects of swimming training on cardiac remodelling in young and adult spontaneously hypertensive rats



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Background: Left ventricular hypertrophy (LVH) is a cardiac adaptation observed in the time-course of hypertension, with important participation of the renin-angiotensin system (RAS). Aerobic exercise is prescribed as non-pharmacological therapy to manage hypertension and it induces cardiac remodelling in experimental animal models.

Aim: To investigate the effects of swimming training (ST) and age during the development of hypertension in SHR over hemodynamic parameters, LVH and RAS.

Methods: Male SHR (1 and 3 months old) were divided into 3 groups: sedentary young (SY n=13), sedentary adult (SA n=12) and trained adult (TA n=13). ST consisted in 60-min swimming sessions for 8 weeks, 5days/week with 5% body weight tail overload. Hemodynamic parameters, LVH (LV weight/BW, mg/g), myocytes diameter (μm), collagen volume fraction (CVF, %), ACE and plasma renin (PRA) activities were evaluated.

Results: TA (149±2mmHg) and SY (145±2mmHg) showed similar mean blood pressure levels (MBP). MBP was decreased in TA when compared to SA (149±2 vs. 161±2mmHg; p<0.001). Resting HR was lower in SA (294±5bpm) and TA (278±5bpm) than in SY (339±4bpm, p<0.05). The +dP/dt improved 9% in SA, 69% in TA when compared to SY (p<0.05) and 55% in TA when compared to SA (p<0.05). The -dP/dt improved 57% in TA when compared to SY (p<0.05). LVH increased 9% in SA and 23% in TA when compared to SY (p<0.05) and increased 13% in TA when compared to SA (p<0.05). The myocytes diameter were larger in SA (18.2±0.5μm) and TA (25.1±0.5μm) when compared to SY (12.5±0.24μm) and it was 37% larger in TA when compared to SA (p<0.05). The CVF increased 179% in SA and 183% in TA when compared to SY, however there was no change between TA and SA. Cardiac ACE activity decreased in SA (1010±86UF/min) and TA (892±67UF/min) when compared to SY (1579±107UF/min; p<0.05). Serum ACE activity decreased 11% in TA when compared to SY and SA. PRA was increased in SA (200%) and TA (82%) when compared to SY, however swimming training prevented the increase in TA when compared to SA in 40%.

Conclusion: ST lowers MBP and HR. While age attenuates HR, ST assured that TA kept MBP at similar values of SY. ST improved LV function, induced LVH and increased myocyte diameter, however it did not change CVF, that was modified only by age. Moreover, biochemical results suggest that exercise training induced LV remodelling with collagen reduction, in part, mediated by reduction of the local RAS and decrease of blood pressure levels.

P803 Clinical importance of the completeness of revascularization and long-term outcome in patients with hypertension and multivessel coronary artery disease treated with balloon angioplasty



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Background: the completeness of revascularization in multivessel coronary artery disease (MVD) achieved with angioplasty is still under debate. There is no sufficient data regarding long-term prognosis in patients (pts) with incomplete revascularization.

Aim: To evaluate the influence of completeness of revascularization on long-term outcome in hypertensive MVD pts treated with angioplasty.

Material and methods: 409 consecutive hypertensive pts (79% males, 30-83years) with MVD treated with balloon angioplasty between 1988 and 1997 were included. Pts have been followed-up for 8-16 years (median 11years). Complete revascularization (CR) was defined as successful angioplasty (residual stenosis<50%) of all significant (≥70%) lesions. Incomplete revascularization (IR) was recognized in case of unsuccessful or not attempted angioplasty in any significant lesion. Left ventricle (LV) dysfunction was defined as ejection fraction<40%. Information regarding cardiovascular events was obtained in 97.5% subjects. In statistical analysis, chi-square test, analysis of variance, Kaplan-Meier analysis with long-rank test and proportional hazard stepwise regression were processed.

Results: the CR was achieved in 143 pts. The subgroups of pts with CR and IR did not differ as for age, gender, BMI and smoking. Patients with IR more frequently had previous myocardial infarction (38.1 vs 27.5%, p<0.05), hyperlipidemia (58.4 vs 37.1%, p<0.0001), family history of coronary artery disease (53 vs 9.3%, p<0.0001), at least one chronic coronary occlusion (50.8 vs 25.9%, p<0.0001) and LV dysfunction (50.9vs10.5%, p<0.0001). In contrast, the prevalence of diabetes was more common in CR-subgroup (34.9 vs 13.9%, p<0.0001). The completeness of revascularization had no impact on total (19.1% in CR and 19.8% in IR- subgroup, p=ns) or cardiovascular mortality (12.3vs11.5% respectively, p=ns.). The prevalence of myocardial infarction was also comparable (23.2 in CR vs 24.2% in IR subgroup, p=ns.). Patients with IR required more re-hospitalizations (53.3 vs 32.6%, p<0.0005) and re-PTCA (28.4 vs 15.9%, p<0.05) during the follow-up period. However, the only independent predictor of long term mortality was LV dysfunction (HR 1.93, 95%CI 1.1-3.4).

Conclusions: the left ventricle ejection fraction but not the completeness of revascularization was the independent predictor of long-term mortality in hypertensive patients with multivessel coronary artery disease treated with angioplasty.

ENDOTHELIAL FUNCTION AT THE BEDSIDE

P804 Inhibition of Interleukin-1 activity improves coronary flow, endothelial function and arterial wall properties: a randomized cross-over, placebo-controlled, trial



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Background: Interleukin-1 plays an important role in the pathophysiology and progression of inflammation and may be involved in regulation of coronary vasomotor tone. Anakinra, a human recombinant interleukin-1a receptor antagonist, has been used as an anti-inflammatory agent in patients with rheumatoid arthritis. We investigated the effects of anakinra on endothelial function, arterial wall properties and coronary flow.

Patients: Eleven patients (8 female, 3 male, mean age 49±5 yrs) with rheumatoid arthritis were randomized to receive a single injection of anakinra (150mg sc) or placebo and after 48 hours (drug's 5 half lives) the alternative treatment (placebo or anakinra respectively). Before and 3 hours after each s.c. injection, we assessed a) the time integral of the coronary flow velocity (CF-VTI), the coronary flow reserve (CFR) of the LAD after adenosine infusion, and aortic strain, by means of echocardiography, b) flow mediated endothelial-dependent dilation of the brachial artery (FMD) by ultrasonography c) carotid to femoral artery pulse wave velocity using the Complior apparatus and d) plasma levels of high sensitivity C-reactive protein. All patients continued treatment with anakinra and were reassessed one month later.

Results: During the acute phase of the study (pre- and 3 hours post injection), a significant improvement in FMD and in CF-VTI and aortic strain was observed in the anakinra arm, while no significant differences were observed in the placebo arm (table, p<0.05). After one month treatment with anakinra, a further improvement in FMD and CF-VTI was demonstrated. In addition, C-reactive protein, arterial stiffness and aortic distensibility were significantly improved. No significant differences were observed in CFR.

	Baseline	3h Post	p	Post Month	p
hsCRP (mg/L)	17,1±24,5	11,5±10	NS	2,6±2,1	0,028
FMD (H-B/B×100%)	5,6±3,4	10,5±4,5	0,008	13,7±4,9	0,018
CF-VTI (cm)	14,9±11,7	18,4±10,7	0,008	20,3±11,1	0,018
PWV (m/sec)	7,8±2,2	8,2±2,1	NS	7,1±1,9	0,034
Aortic Strain (%)	4±1,8	7±3,6	0,033	11±7	0,028

Conclusion: IL-1a receptor antagonism improves coronary flow, endothelial function and arterial wall properties through reduction of inflammation.

P805 Differential elevation of endothelial microparticles and their binding to leukocytes in acute coronary syndromes

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Background: EMP are small membrane vesicles released by activated or apoptotic endothelial cells. Recent studies indicate that different species of EMP reflect different biologic processes and exert different biologic functions. Furthermore, some species bind and activate leukocytes. We examined different phenotypic species of EMP and EMP-leukocyte (EMP-L) conjugates among patients with ACS.

Methods: We studied 40 patients with ACS and compared them to 22 controls. Using flow cytometry, we measured EMP identified by E-selectin (EMP62E), CD51 (EMP51) and CD54 (EMP54). EMP62E- and EMP54-leukocyte conjugates were measured by the detection of E-selectin (CD62E) or CD54, respectively, co-expressed with CD45 in leukocytes.

Results: Patients with ACS had elevated levels of free EMP51 (Table) but normal levels of EMP54 and EMP62E. However, levels of EMP54-monocyte, -neutrophil and -lymphocyte conjugates were higher among patients with ACS than in controls. Patients with ACS also demonstrated elevated levels of CD62E-lymphocyte and EMP62E-monocyte conjugates.

	ACS	Controls	P value
Free EMP (counts/ μ L)			
EMP51 (IQR)	332 (174-452)	119 (101-230)	0.02
EMP62E (IQR)	105 (55-207)	98 (60-143)	0.65
EMP54 (IQR)	75 (36-110)	76 (24-192)	0.97
EMP-Leukocyte Conjugates (FLIU)			
EMP54-Lymphocyte (IQR)	1.26 (1.20-1.37)	1.21 (1.14-1.26)	0.02
EMP54-Monocyte (IQR)	1.99 (1.55-2.50)	1.19 (1.09-1.43)	<0.0001
EMP54-Neutrophil (IQR)	2.00 (1.60-2.25)	1.46 (1.28-1.85)	0.003
EMP62E-Lymphocyte (IQR)	1.20 (1.07-1.31)	1.14 (1.06-1.18)	0.03
EMP62E-Monocyte (IQR)	1.85 (1.51-2.17)	1.32 (1.21-1.56)	<0.0001
EMP62E-Neutrophil (IQR)	1.88 (1.54-2.17)	1.67 (1.39-2.11)	0.20

IQR=Interquartile Range; FLIU=Fluorescence Intensity Units

Conclusions: Increased formation of EMP-L conjugates occurs in ACS, resulting in normal levels of the free form of some EMP species. Analysis of free EMP is therefore limited and concomitant assessment of EMP-L conjugates is important. Formation of EMP-L conjugates may promote thrombosis and inflammation through their effects on leukocyte activation and tissue-factor activity.

P806 Glu298Asp eNOS gene polymorphism is associated with decreasing exercise-induced muscle vasodilation in humans

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Background: Nitric oxide (NO), an endothelium-derived relaxing factor synthesized by the constitutively endothelial nitric oxide synthase (eNOS) isoform, plays an important role in the exercise-induced muscle vasodilation.

Objective: We tested the hypothesis that G to T nucleotide transition at position 894 in the gene encoding eNOS, resulting in Glu298Asp polymorphism of the protein, would be associated with decreasing in basal muscle blood flow and impaired muscle vasodilatory response during exercise.

Methods: We studied 33 healthy individuals selected to represent three genotypes: Glu/Glu (n=15, age=41 $\pm$ 3 yr, BMI=23.6 $\pm$ 0.4 kg/m²), Glu/Asp (n=9, age=39 $\pm$ 3 yr, BMI=24.6 $\pm$ 1.2 kg/m²) and Asp/Asp (n=9, age=38 $\pm$ 4 yr, BMI=24.3 $\pm$ 0.9 kg/m²). Heart rate (HR), mean blood pressure (MBP) and forearm blood flow (FBF, plethysmography) were recorded for 3-min at baseline and 3-min during handgrip exercise (30% MVC).

Results: Baseline HR, MBP, FBF and forearm vascular conductance (FVC) were not different among genotypes. During exercise, FBF and FVC did not significantly increase in Asp/Asp individuals. The comparisons among groups showed that FBF responses were significantly lower in Asp/Asp individuals when compared with Glu/Glu and Glu/Asp individuals (0.31 $\pm$ 0.1 vs. 0.87 $\pm$ 0.1 and 0.89 $\pm$ 0.2 ml.min⁻¹.100 ml⁻¹, P=0.001 respectively). Similarly, FVC responses during exercise were significantly lower in Asp/Asp individuals than in Glu/Glu and Glu/Asp individuals (0.07 $\pm$ 0.14 vs. 0.57 $\pm$ 0.1 and 0.64 $\pm$ 0.2 units, P=0.008 respectively).

Conclusion: These findings show an association between Glu298Asp eNOS polymorphism with blunted vasodilatory response to exercise, suggesting an impaired NO bioavailability in Asp/Asp genotype during physiological maneuvers.

P807 5-methyl-tetrahydrofolate acid improves endothelial function and decreases superoxide production in vessels from patients with coronary artery disease

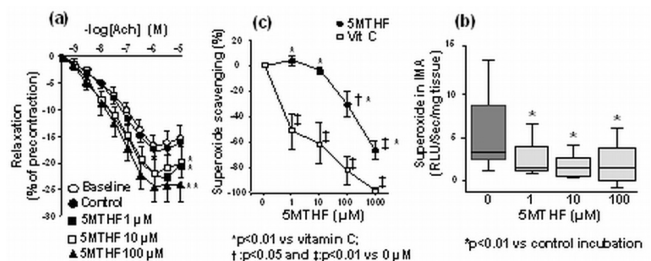
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5-methyltetrahydrofolate (5MTHF), the active form of folic acid, may have anti-atherogenic properties by reducing homocysteine, but its direct effects on vascular function are unclear.

Aim: We evaluated the direct effect of 5MTHF on endothelial function and superoxide (SOO) production in saphenous veins (SV) and internal mammary arteries (IMA) of patients undergoing CABG.

Methods: Vasomotor responses to acetylcholine (ACh) were evaluated in an ex vivo model in vessel segments from 35 patients at baseline and after 45 minutes incubation with 5MTHF 0, 1, 10 and 100 μ M. Vascular superoxide (SOO) was measured using lucigenin chemiluminescence, in paired segments (SV and IMA) of the same vessel, in the presence of 5MTHF 0, 1, 10 and 100 μ M respectively. The direct SOO-scavenging capacity of 5MTHF was quantified using a xanthine/xanthine oxidase system, and similar concentrations of vitamin C as positive control.

Results: All the used concentrations of 5MTHF similarly improved the vasomotor responses of SV to ACh (Figure a). Whereas 5MTHF at high concentrations (100 and 1000 μ M) had direct SOO scavenging effect, no direct scavenging was observed with concentrations <10 μ M (Figure b). Vitamin C had SOO scavenging properties even at concentration 1 μ M (Figure b). 5MTHF rapidly decreased SOO in both SV and IMA compared to control, but there was no difference in SOO production between vessels exposed to 1, 10 and 100 μ M 5MTHF (Figure c).



Conclusions: 5MTHF improves endothelial function and decreases superoxide production in vessels from patients with CAD, by a mechanism other than direct superoxide scavenging. Therefore, 5MTHF may be useful for the treatment of coronary atherosclerosis, by decreasing vascular superoxide and improving NO bioavailability in human vessels.

P808 Plasma nitrite reserve predicts endothelial dysfunction in humans: preserved baseline but reduced post exercise levels with aging

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Objective: We investigated whether the capacity of endothelial NO-synthase (eNOS)- activity is reduced in human age-related endothelial function.

Background: Aging is associated with endogenous alterations of the vessel wall promoting atherosclerosis and vascular dysfunction. NOS-activity is impaired in endothelial dysfunction. Plasma nitrite sensitively reflects acute and chronic changes in eNOS-activity and declines with dependence of cardiovascular risk factors.

Methods: In 28 young and 29 old healthy individuals (25 $\pm$ 1 years and 58 $\pm$ 2 years; p<0.001) without major cardiovascular risk factors, endothelial function was defined by flow-mediated dilation (FMD) of the brachial artery via ultrasound. Plasma nitrite was measured before and 10 minutes after ergometric exercise using reductive gas-phase-chemiluminescence and nitrite reserve as change in plasma nitrite levels after ergometric exercise was determined.

Results: Older subjects had significant impaired endothelium-dependent dilation of the brachial artery (5.4 $\pm$ 0.4% vs. 6.7 $\pm$ 0.3%; p<0.05), suggesting endothelial dysfunction. Baseline levels of plasma nitrite did not differ significantly (82 $\pm$ 10 nmol/L vs. 107 $\pm$ 8 nmol/L, old vs. young; n.s.). Ergometric stress, as quantified by rate-pressure-product, was similar in both groups (17371 $\pm$ 703 vs. 16621 $\pm$ 710 mmHg*bpm; young vs. old, n.s.). In young subjects, ergometric exercise led to a significant increase in plasma nitrite concentration (107 $\pm$ 8 to 143 $\pm$ 11 nmol/L; p<0.001) compared to older people (82 $\pm$ 10 to 101 $\pm$ 14 nmol/L; n.s.), corresponding to a nitrite reserve of 34% and 23%, respectively. Multivariate analysis showed that nitrite reserve is independently influenced by endothelial function.

Conclusion: eNOS activity is preserved in age-related endothelial dysfunction at rest. Exercise reveals an impaired eNOS capacity in old subjects, which is reflected by a reduction in plasma nitrite reserve. This biochemical approach may open new avenues in the diagnosis of vascular dysfunction.

P809 Endothelial function in patients with ischemic heart disease

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The early phase in the development of atherosclerosis is the injury of the endothelium, which can be identified by noninvasive examination tools with adequate sensitivity. We conducted a noninvasive examination to specify the range velocity of the pulse wave (PWV) which shows the flexibility of the aortic wall; as well as the augmentation index (AIx), which varies proportionately with the resistance of the small arteries (arterioles).

Objectives: Specification of the above mentioned parameters in healthy volunteers (control group, n = 82), verification of endothelial dysfunction in patients with hypertension (HT) (n = 87), and in patients with ischemic heart disease (IHD) diagnosed using quantitative coronary angiography (QCA) (n = 115). In the case of 15 patients, we compared the AIx and PWV parameters gained simultaneously through invasive and noninvasive examination methods.

Method: We conducted a total of 284 noninvasive examinations, by means of TensioClinic Atrierigraph using oscillometric principles. The coronarography and QCA tests were performed with the Philips Integris 5000 system.

Findings: The AIx and PWV values did not show pathological difference in the control group (-38.6 ± 3.8 and 8.6 ± 0.2). Compared to these values, we found the AIx and PWV data significantly (p < 0.01) higher in the IHD and HT groups (AIx: -10.7 ± 2.7 and -10.8 ± 3.3; PWV 9.6 ± 0.2 and 9.5 ± 0.3 respectively). Based on the QCA data, we separated three stages to describe the seriousness of the coronary disease: IHD score 1-2 (n = 32), IHD score 3-5 (n=35) IHD score > 6 (n = 40). The AIx and PWV values were above the normal level by a different margin in each group (AIx: -4.4, -12, -16; PWV: 9.3, 9.4, 9.9), but there was no significant difference between the three groups. As a result of the invasive and noninvasive measurements conducted simultaneously in the brachial artery, we found a strong correlation both in the respect of the AIx and PWV parameters (R = 0.92 and R = 0.88 respectively).

Conclusion: Our results show that the AIx and PWV values gained through a noninvasive measurement method are appropriate to verify the existence of endothelial dysfunction.

MECHANISMS OF ENDOTHELIAL (DYS)FUNCTION

P810 Coronary endothelial dysfunction as a consequence of chronic in-vivo proteasome inhibition

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Background: Future therapeutic modalities for atherosclerosis remain to be defined with the proteasome being one potential target. The current study was designed to assess the cardiovascular effects of chronic proteasome inhibitor treatment in a porcine model.

Methods: 3 months-old female pigs were randomized to a normal diet without (N) or with twice weekly SC injections of the proteasome inhibitor MLN-273 (0.08 mg/kg, N+MLN273) for a period of 12 weeks (n=5 per group). Peripheral WBC proteasome activity was measured at study beginning, myocardial perfusion and coronary microvascular permeability index response to adenosine and dobutamine by EBCT after 11 weeks, and serum concentrations of LDL and oxLDL after 12 weeks. Subsequent ex vivo studies assessed coronary artery vasorelaxation by organ chamber experiments in response to bradykinin (log-10.5 to -6.5 M) and sodium nitroprusside (log-9 to -5 M), expression of eNOS and p47phox by immunoblotting, and superoxide content by DHE oxidative fluorescent microscopy.

Results: A single dose of 0.08 mg/kg of MLN-273 resulted in 68±4 and 40±9% inhibition of the proteasome within 1 and 24 hours after SC injection. Study results as per Table 1.

Table 1

(mean ± SEM) *p<0.05 for group comparison	N	N+MLN273
Serum LDL [mg/dL]	28±4	37±7
Serum oxLDL [mg/dL]	12.5±1.6	11.1±0.8
Myocardial perfusion response to adenosine [% increase from baseline]	52.6±7.3	9.3 ±16.7*
Myocardial perfusion response to dobutamine [% increase from baseline]	138.1±26.8	3.4±11.6*
Coronary microvascular permeability index response to adenosine [% increase from baseline]	4.9±5.1	50.4 ±22.4*
Coronary microvascular permeability index response dobutamine [% increase from baseline]	3.4±11.6	138.1±26.8 *
Coronary vasorelaxation to bradykinin, log -6.5 M [%]	90±2	57±6 *
Coronary vasorelaxation to sodium nitroprusside, log -5 M [%]	56±7	69±7
eNOS/beta-actin densitometric ratio	0.58±0.05	0.85±0.08*
p47 phox/beta-actin densitometric ratio	0.45±0.07	0.69±0.03*
DHE fluorescence [% intima area]	0.6±0.5	6.0±1.7*

Conclusion: Chronic proteasome inhibition at the current study dose leads to coronary endothelial dysfunction in association with increased vascular oxidative

stress in a large animal model of early atherosclerosis. These findings attribute a functional role to the proteasome for coronary vascular biology.

P811 Curcumin protects TNF alpha-induced inflammatory responses through inhibition of nuclear factor kappa B and STAT-3 in endothelial cells

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Background: Curcumin, a yellow pigment of turmeric in curry, is reported to interfere with NF-κB. NF-κB is a well known transcription factor responsible for inflammatory responses. This study was designed to investigate the underlying pathway of anti-inflammatory action of curcumin on endothelial inflammation.

Methods: Human umbilical vein endothelial cell (HUVEC) was stimulated with TNF-α (10 ng/mL) in the presence or absence of curcumin (10 μM). The activation of signal transducer and activator of transcription (STAT)-3, and c-Jun N-terminal kinase (JNK) were examined. Cytokine expressions were analyzed by RT-PCR, western blot, or ELISA.

Results: Intracellular ROS level, monocyte adhesion, and phosphorylation of JNK and STAT-3 were increased by TNF-α. TNF-α also increased the expressions of vascular cell adhesion molecule (VCAM)-1, intracellular cell adhesion molecule (ICAM)-1, monocyte chemoattractant protein (MCP)-1, and interleukin (IL)-8 at both transcription and translation level. Pretreatment of curcumin reduced intracellular ROS (79.6%) and monocyte adhesion (46.6%), as well as the phosphorylations of JNK and STAT-3. Curcumin also reduced mRNA levels of VCAM-1, ICAM-1, and MCP-1, and protein levels of VCAM-1 and ICAM-1 in a dose-dependent manner. Nuclear translocation of p65 by TNF-α was inhibited in curcumin treated cell.

Conclusions: Curcumin inhibited the NF-κB pathway to control the inflammatory response, which play a leading role in atherogenesis, through JNK and STAT-3 in endothelial cell.

P812 Enhanced vascular superoxide production and impaired endothelium-dependent smooth muscle relaxation in Bkb1 knockout mice

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Objective: Nitric oxide (NO)-induced vasorelaxation involves the activation of large conductance Ca²⁺-activated K⁺ channels (BK). A regulatory subunit, Bkb1, confers Ca²⁺-, voltage- and NO/cGMP-sensitivity to the BK channel. We investigated whether the NO-dependent control of arterial tone was affected by a deletion of the b1 subunit.

Methods: Vascular superoxide production in Bkb1^{-/-} and wild-type (WT) mice and NO/cGMP signaling were analyzed in aortic tissue. To detect superoxide production we used the oxidative fluorescent microtopography method and lucigenin enhanced chemiluminescence. NO formation in aorta was quantified using electron paramagnetic resonance (EPR), and expression of the NADPH oxidase subunits p67phox, Nox1 and phosphorylation of the vasodilator-stimulated phosphoprotein (P-VASP) were assessed by Western blotting.

Results: The expression of the endothelial NO synthase, soluble guanylyl cyclase, cGMP-dependent protein kinase-I, as well as acetylcholine-induced NO production were unaltered in Bkb1^{-/-} animals. In contrast, endothelium-dependent relaxation to acetylcholine and the activity of the cGMP-dependent protein kinase (P-VASP:VASP ratio: 0.61±0.04 vs. 1±0.07 in WT) were reduced. At the same time vascular O₂⁻ formation was increased and the expression of the NADPH oxidase subunits p67phox and Nox1 were almost doubled. Increased superoxide production in Bkb1^{-/-} was inhibited by the protein kinase C (PKC) inhibitor, chelerythrine and impaired endothelial dependent relaxations were normalized using the NADPH oxidase inhibitor apocynin. KCl-induced depolarization mimicked the effect of Bkb1-deletion by increasing vascular O₂⁻ formation, which was blocked by apocynin.

Conclusion: Deletion of Bkb1 interferes with endothelium-dependent relaxation in the mouse aorta by increasing O₂⁻ formation, presumably via increased vascular NADPH oxidase activity and expression.

P813 Accelerated re-endothelialization in an eNOS transduced iliac artery following gene delivery from an adenoviral eluting stent

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Introduction: Anti-proliferative drug eluting stents represent a useful strategy to prevent in stent restenosis. However these drugs share the liability of impairing

endothelial recovery, thereby increasing the risk of stent thrombosis. Gene therapy has the potential to regenerate denuded endothelial cells following PCI. We tested the hypothesis that adenovirus encoding eNOS gene could accelerate re-endothelialization when delivered from a gene eluting stent.

Methods: New Zealand White rabbits were used for the study. Balloon angioplasty of right external iliac was performed by a 2.5 x 14 mm balloon (6 ATM x 60 sec x3). Following angioplasty an adenovirus coated stent (5 x 109 pfus per stent) encoding eNOS or LacZ was deployed at injury site (6 ATM x 30 sec). Gene delivery was assessed by x-gal staining for LacZ at 14 days. For re-endothelialization AdeNOS (n=4) and Ad β gal (n=4) were used. Stents were retrieved at 14 days and assessed for re-endothelialization with evans blue staining. eNOS expression was also assessed by immunohistochemistry.

Results: Gene delivery of LacZ was demonstrated in the stented vessel at 14 days (mean 5.06%). eNOS overexpression was confirmed by immunohistochemistry 6 days post stent deployment. There was a significant acceleration of re-endothelialization of stents in the eNOS treated arteries as compared to control stents. Re-endothelialization was 85.34% in the eNOS treated arteries as compared to 62.66% in the Ad β gal group (p<0.05).

Conclusion: Adenovirus- coated stents can be used to deliver therapeutic genes to the vessel wall. eNOS gene delivery represents an alternative approach to accelerate re-endothelialization following angioplasty and therefore reduce the incidence of acute stent thrombosis.

P814 Telmisartan, an angiotensin II receptor blocker, modulates endothelial inflammation in human umbilical vein endothelial cells



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Background: Increased intercellular adhesion molecule (ICAM)-1 expression by activated endothelial cell initiates vascular inflammation that, in turn, promotes atherosclerotic disease progression. Telmisartan (TEL), a lipophilic AT1-specific Angiotensin II (All) receptor blocker (ARB), may modulate vascular inflammation through pleiotropic mechanisms unrelated to All receptor antagonism.

Methods: To test that hypothesis, we evaluated the effect of TEL (10-7 to 10-4 M) in human umbilical vein endothelial cells (HUVEC). In-vitro ICAM-1 expression was induced by All-receptor unrelated inflammatory stimuli such as tumor necrosis factor (TNF)- α (200 U/ml) and lipopolysaccharide (LPS, 1 μ g/ml). Losartan (LOS, 10-7 to 10-4M), another ARB, and dexamethazone (DEX), a steroid with well known anti-inflammatory effects, were used as controls for TEL. Cell-surface ICAM-1 expression was measured by ELISA (absorbance units, AU); % decrements from TNF- α and LPS-stimulated levels were the study variable.

Results (means $\pm$ SD): After 4-hr stimulation, TNF- α (from 0.29 $\pm$ 0.08 to 0.65 $\pm$ 0.1 AU, +137 $\pm$ 34%, n=25, p<.001) and LPS (from 0.29 $\pm$ 0.08 to 0.55 $\pm$ 0.01 AU, +91 $\pm$ 58%, n=20, p<.001) increased ICAM-1 expression. Albeit ineffective at 10-7M (-7 $\pm$ 8%), higher concentrations of TEL reduced TNF- α induced ICAM-1 expression (10-6M:-20 $\pm$ 11%, 10-5M:-19 $\pm$ 12%, 10-4M:-22 $\pm$ 7%, n=10 at least, p<.01) in a dose-independent manner. LOS behaved similarly (10-6M:-14 $\pm$ 12%, 10-5M:-14 $\pm$ 10%, 10-4 M:-15 $\pm$ 9%, p<.05, n=10 at least) but its inhibitory effect at equimolar concentrations was significantly lower than that of TEL (p<.04 at least). TEL but not LOS (10-4M for both) inhibited LPS-stimulated ICAM-1 expression (-17 $\pm$ 8% vs +4 $\pm$ 13%, p<.001, n=8 at least) and the inhibition of TNF- α induced ICAM-1 expression was comparable to that of DEX (-22 $\pm$ 7% vs -24 $\pm$ 7% respectively, n=10, 10-4M for both). In additional experiments aimed at evaluating the time-course profile, TEL decreased TNF- α stimulated ICAM-1 expression at 2 (-20 $\pm$ 5%, p<.01, n=5), 4 (-16 $\pm$ 4%, p<.005, n=7) but not 16 (-5 $\pm$ 3%, n=4, NS) hrs.

Conclusions: TEL inhibits ICAM-1 expression in HUVEC activated by both TNF- α and LPS, two inflammatory stimuli independent of All receptor stimulation. The All-independent anti-inflammatory potential of TEL was greater than that of LOS, a control ARB, and equipotent to that exerted by DEX, a steroid with well known anti-inflammatory effects. Thus, TEL modulates endothelial inflammation through mechanisms unrelated to All receptor blockade in HUVEC, and that pleiotropic effect may perhaps contribute to its clinical actions.

P815 Differential expression analysis induced by ANP and its molecular variants in HUVEC



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Background: Previous studies have demonstrated a contributory effect of ANP gene molecular variants to increased susceptibility to develop stroke. In particular, a Val/Met transposition at position 7 of proANP (within the LANP) and a 30 (instead of 28) aminoacid long a ANP, as a result of a stop codon mutation, were significantly associated to an increased risk of stroke in human populations.

Aim: In the attempt to gain insights on the disease mechanisms directly dependent from ANP gene structural alterations, we investigated the differential expression profiles of human endothelial cells exposed to either normal or variant proANP/ANP. Genes involved in the processes of proliferation, metastasis and angiogenesis were considered.

Methods: AT1-20 cells were transfected with either regular or mutant ANP cDNA (both ANP gene molecular variants were tested). Forty-eight hrs after transfection the media was collected, the proANP concentration was measured by ELISA and the peptide levels produced by all constructs were normalized to reach a physiological concentration (2400 fmol/ml). HUVEC were then exposed for 12 hrs to each peptide preparation. Media obtained from cells transfected with the empty vector was used as control. RNA was then extracted from endothelial cells for the macroarray analysis. Levels of genes expression were normalized by GAPDH as housekeeping gene.

Results: Among the genes tested (n=300) only 16 were significantly modulated by ANP and the results were confirmed by RT-PCR. In particular, the wild type ANP stimulated the expression of metalloproteinase 16, integrin α -1 and integrin α -5, FGF, and laminin β -2 vs control, whereas both ANP molecular variants were able to significantly increase the levels of metalloproteinases 15 and 16 and to significantly decrease the levels of integrins and laminins as compared to wild type ANP.

Conclusions: Our findings are consistent with a role for ANP, and particularly for its molecular variants, in the modulation of key genes involved in cellular proliferation, and particularly in the maintenance of cellular integrity and stability within the endothelium.

P816 Shear stress-dependent connective tissue growth factor expression in endothelial cells can be modulated pharmacologically: possible implications for atherogenesis



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Background: Shear stress plays an important role in the pathogenesis of atheroma, especially where flow conditions are disturbed. We used novel flow-through bifurcating cell culture slides which mimic in vivo vessels, to analyse the modulation of atherogenic protein expression under disturbed versus laminar flow.

Methods and Results: Human umbilical cord endothelial cells were exposed to laminar or turbulent flow conditions at physiologic arterial shear stress (10 dyne/cm²). Connective tissue growth factor (CTGF) and adhesion molecules were determined by immunofluorescence as markers of endothelial dysfunction, and quantified using MetaVue software for image analysis. Protein levels were expressed as relative fluorescence units.

Endothelial expression of CTGF was significantly reduced by 18 h of laminar flow (0.48 $\pm$ 0.06; n=9; p<0.001) as compared with areas of turbulent flow (1.41 $\pm$ 0.2) or static conditions (1.68 $\pm$ 0.2). In cells treated with 1 μ M simvastatin during flow, CTGF expression was barely detectable both under laminar and turbulent flow conditions. Pre-treatment with simvastatin for 48h before starting the flow resulted in overall CTGF downregulation. However, when simvastatin was removed prior to the flow, significant CTGF induction occurred anew in areas of turbulent flow. As RhoA pathway seems to be the major link between mechano-sensing and gene expression, we investigated the modulation of CTGF expression by RhoA-associated kinase inhibitor, fasudil. Pre-treatment of cells with 20 μ M fasudil for 48h prior to the flow reduced CTGF induction in the areas of turbulent flow. Moreover, in cells transfected with actin mutant not polymerizing into F-actin, CTGF induction by turbulent flow was suppressed, further pointing to an active role of endothelial cytoskeleton rearrangement in atherogenesis-related protein expression.

In accordance with in vivo studies, moderate upregulation of VCAM-1 and ICAM-1 expression was observed in areas of turbulent flow. Laminar flow suppressed LPS-stimulated expression of adhesion molecules.

Conclusions: In conditions resembling in vivo vessel, turbulent flow increases pro-atherogenic protein expression, underscoring the importance of hemodynamic forces in early atherosclerosis. The pharmacological inhibition of cytoskeleton-dependent gene expression in endothelial cells may prove a promising possibility to impede atherosclerosis progression.

P817 Antiphospholipid antibodies induce severe endothelial dysfunction in murine model



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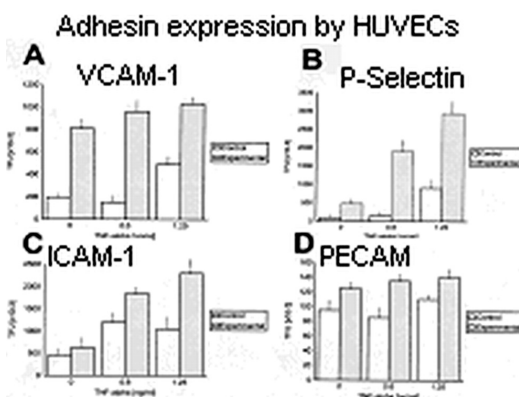
Antiphospholipid antibodies syndrome (APS) is associated with an increased risk of severe cardiovascular events in young people, suggesting a proatherogenic effect. Several mechanisms have been suggested to explain this effect, such as superoxide production (Sherer Y, Immunobiology. 2003;207:13-6); interferences with paroxonase activity (Delgado Alves J. Arthritis Rheum. 2002;46: 2686-94), or with anti oxidized LDL antibodies, or even an endothelial dysfunction. Whether antiphospholipid antibodies (aPLA) may per se induce endothelial dysfunction is unknown. The purpose of the study was thus to analyse if aPLA exert an influence on the endothelial reactivity in a murine model. In a first set of experiments, 9 groups of CD1 mice received one single intraperitoneal injection of solvent or a purified murine IgG aPLA mAb (8 different mAb) derived from a male (BXSB x NZW)F1 mouse which develops a lupus-like disease associated with an antiphospholipid antibodies syndrome (APS).

pholipid syndrome. One week later, first order mesenteric arteries (diameter 220-260 μ m) were isolated and mounted in a small vessel myograph for the recording of isometric tension. Relaxing responses to acetylcholine (ACh) and the NO donor nitroprusside were assessed in arteries precontracted by phenylephrine. As seen, one antibody called the 4b7 mAb has a particular behavior: since it markedly diminished the relaxation comparing to controls. In contrast, no changes in the response to nitroprusside were observed. Further experiments performed with 4B7 mAb showed that the impairment was maintained after 3 weeks of treatment (control 84 ± 2 ; 4B7 64 ± 3 , $p < 0.01$) and was dose dependent (25mg 89 ± 1 ; 50mg 83 ± 2 , 100mg 58 ± 1 , $p < 0.01$; 200mg 77 ± 1 , $p < 0.05$; 400mg 76 ± 2 , $p < 0.05$). The NO synthase (NOS) inhibitor L-NA markedly reduced the response to ACh in control (from 86 ± 2 to 46 ± 2 , $p < 0.05$) and 4B7 mAb (from 60 ± 3 to 30 ± 2 , $p < 0.05$), while the cyclooxygenase inhibitor diclofenac had no effect. 4 hydroxy -tempo had no effect on vascular relaxation. We conclude that some aPLA mAb may directly and markedly alter endothelial function, and this effect might contribute to their proatherogenic and prothrombotic effects.

P818 Newborn Human Umbilical Vein Endothelial Cells with backgrounds of strong familial heart infarction overexpress adhesion molecules and react differently to pro-atherogenic molecules

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Atherosclerosis is a human complex disease involved in major fatal events such as myocardial infarction and stroke. It is commonly accepted that atherosclerotic plaque is the result of interactions between metabolic, dietetic or environmental risk factors acting on a genetic background. Endothelial susceptibility is part of this genetic background that is poorly studied in humans. We aimed at determining potential differences in cell membrane expression of adhesion molecules and phosphatidylserine between Human Umbilical Vein Endothelial Cells (HUVECs) isolated from healthy newborns born to parents with a strong background of familial heart infarction (four or more close relatives with myocardial infarction history) in basal and TNF- α or oxLDL stimulated conditions. Compared to control HUVECs, experimental cords showed a four-fold increase in VCAM-1 expression under basal conditions which did not multiply with the pro-atherogenic factors; basal P-selectin expression was two-fold higher but it reached a ten-fold increase with any of the pro-atherogenic factors used. ICAM-1 expression behaved similar to P-selectin but the increase induced by the stimuli was fewer. PECAM-1 expression was similar in control and experimental HUVECs. Unexpectedly, phosphatidylserine expression was importantly increased in experimental cords HUVECs (211,817 vs 3,354 TFU) but the percentage of dead cells induced by TNF- α treatment was very low (0.55 vs 9.87%). T cell adherence to HUVECs was highly upregulated in the genetically predisposed samples.



The analysis of non-pooled, individual cord derived HUVECs from newborns to family-predisposed persons might represent a useful strategy to identify phenotypical and functional alterations, and hopefully, to take early prevention actions.

P819 Local delivery of a soluble dimeric platelet collagen receptor glycoprotein VI prevents thrombosis after injury in an experimental animal model

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Background: Pharmacological developments that are directed against very early events of platelet adhesion may prevent not only thrombosis, but also be a key

factor to prevent platelet-mediated pro-atherogenic alterations of the arterial wall and thus atherosclerosis. Only recently, the platelet glycoprotein VI (GPVI) has been identified as the major platelet collagen receptor. GPVI is a 60-65-kDa type I transmembrane glycoprotein that belongs to the Ig superfamily. Since GPVI is critically involved in platelet-mediated arterial thrombosis, this makes the receptor a promising target for antiplatelet treatment.

Methods: In this study a new concept of antiplatelet therapy was studied. The hypothesis was that a local application of GPVI to injured, collagen-exposing vessels would prevent thrombus formation. We used the newly developed GENIE[®]-application device that allows for homogenous drug transfer to the whole vessel wall without being restricted to stent coatings as drug carrier. Basically this system consists of a percutaneous balloon having a distal and proximal segment with occlusive function and a central segment that allows for drug transfer. We induced arterial injury in the right carotid arteries of White New Zealand rabbits by denudation resulting in a stable thrombus formation at the site of injury. Consequently the right coronary artery was treated with local delivery of Fc-GPVI using the GENIE[®] device or Fc alone as control. The same treatment (Fc-GPVI or Fc locally) was repeated in the left uninjured carotid arteries as control (n=6 in each group). Vessels were excised and prepared for immunohistochemistry and en-face thrombus analysis.

Results and conclusion: Immunohistological staining against GPVI showed homogenous drug uptake after local delivery in all injured vessels, limited to the areas where the GENIE[®]-catheter had been used. Thrombus formation was significantly reduced in these vessels from 11% (relative area) to less than one third in GPVI-treated animals. No thrombus formation was detected in healthy control vessels after local delivery. In conclusion, this initial study of a completely new therapy concept showed local drug delivery of Fc-GPVI to be effective and detectable by immunostaining in this animal model of profound thrombus formation. These data may contribute to an advanced local intracoronary pharmacotherapy in near future. Independent of stent coatings, the combination of early antithrombotic and antiatherosclerotic mechanisms may be a realistic and effective approach to minimize postinterventional thromboischemic events.

P820 CD40 expression and function in human umbilical vein endothelial cells (HUVECs) from healthy newborns with strong family background of heart infarction. Hyper-reactivity to pro-atherogenic stimuli

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Complications of atherosclerosis such as heart infarction are the leading cause of death worldwide. Recent findings indicate that atherogenesis starts early in life, during childhood and perhaps even before birth. It is considered that the members of families with a positive history of myocardial infarction are more prone to develop fatal events at early ages. The concept of atherogenesis has changed, and now is conceived not only as metabolic alteration, but mainly as inflammatory process, perhaps immunologically initiated. Under this renewed perception, prominent pro inflammatory molecules such as CD40 have been implicated in the pathogenesis of atherosclerosis. To examine the endothelial cell status of neonates, clinically healthy newborns (day 0, at birth) were rigorously grouped according to the presence or absence of a strong familial heart infarction background (four or more close relatives affected) in order to assess their HUVECs for: a) CD40/CD40-Ligand expression and function, and b) adhesion of monocytic and lymphocytic cells; both in basal conditions and after stimulation with TNF α . CD40 expression in non-stimulated HUVECs was low but detectable in experimental cords but, upon stimulation with TNF α , increased only in the experimental group. Essentially the same, albeit at lower level, was found for CD40-Ligand expression. Binding of CD40 with a monoclonal antibody enhanced the intracellular expression of IL-8 and MCP-1 in experimental HUVECs. Adhesion of lymphocytic and monocytic cells to HUVECs was high in non-stimulated endothelium from experimental cords and augmented considerably upon TNF α stimulation.

HUVECs	No Treatment		TNF-alpha 48 hs.	
	% + Cells	Mean Fluorescence	% + Cells	Mean Fluorescence
Control	4.0 $\pm$ 0.3	2.20 $\pm$ 0.8	0.65 $\pm$ 0.2	0.70 $\pm$ 0.1
Experimental	4.5 $\pm$ 0.5	10 $\pm$ 1.1	45 $\pm$ 3.2	17 $\pm$ 2.0

Differences in CD40 Expression with and without TNF-alpha stimulus.

This approach, comparing HUVECs with different heart infarction backgrounds uncovered so far unknown pathological properties of endothelial cells from otherwise healthy neonates: their apparent hyper-sensitivity to a key pro-atherogenic factor like TNF α in the context of lymphocytes/monocytes adhesion and CD40 expression and function, thus revealing to the endothelial susceptibility as a potential active player during early atherogenesis.

P821 Sustained inhibition of mitochondrial respiration increases lipid uptake by endothelial cells



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Purpose: Concentrations of nitric oxide (NO) present during inflammatory processes are capable of inhibiting mitochondrial respiration and thus modulate cellular bioenergetics. Adaptation under ATP-deprived conditions involves the activation of AMP-activated protein kinase (AMPK), which acts as a metabolic master switch. Although it is generally accepted that endothelial cells generate most of their ATP through anaerobic glycolysis, there is growing evidence of the role of the oxidative mitochondrial pathway. We have analyzed the effects of partial inhibition of mitochondria respiration with exogenous nitric oxide on the activation of AMPK and lipid uptake.

Methods: Human umbilical vein endothelial cells (HUVEC) were incubated with the NO donor DETA-nonoate (1 μ M, 1-4h) in presence of long chain fatty acids labeled with the BODIPY[®] fluorophore, and their uptake was measured by fluorescence (Fluoroskan). The effects of NO on vascular reactivity were evaluated in rings of rat aorta by organ bath. The inhibition of mitochondrial respiration in HUVEC was analyzed with a Clark electrode, while activation of AMPK was evaluated by western blot and glucose uptake and glycolysis were measured via an enzymatic assay. Results are mean $\pm$ SEM (n $\geq$ 4).

Results: DETA-nonoate (1 μ M) caused a 50% relaxation in precontracted rat aortic rings and inhibited mitochondrial respiration by 20-30%. When HUVEC were incubated for 4h with a similar concentration of this NO donor they increased their uptake of long chain fatty acids by 15 $\pm$ 5%, and exhibited a substantial increase of phosphorylated AMPK, the activated form of this enzyme. This increase was not observed during shorter incubation periods (1h). There were no changes in glucose uptake and glycolysis.

Conclusions: There is an increased uptake of lipids by endothelial cells in response to a sustained inhibition of mitochondrial respiration, probably involving activation of AMPK. If sufficiently prolonged, this response could lead to lipid accumulation and may be involved in processes such as endothelial dysfunction or the initial phases of atherosclerotic disease.

P822 Molecular mechanisms involved in enoxaparin effect on hydrogen peroxide exposed human endothelial cells



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Purpose Enoxaparin, a low molecular weight heparin (LMWH) is well recognized for its antithrombotic effects. Recent data revealed the antioxidative potential of heparins (both unfractionated and LMWH) in various pathological conditions such as diabetes and ischemia/reperfusion but the underlying mechanisms are not very well understood. Given that vascular endothelium is implicated in many oxidative stress associated pathologies, in this study we questioned the antioxidant capacity of enoxaparin on human endothelial cells (HEC) exposed to an oxidant stimulus.

Methods Cultured human endothelial cell, line, EAhy926, were exposed to non-toxic concentrations of H₂O₂ in the presence or absence of enoxaparin and the adhesion of monocytes (adhesion tests), expression of cell adhesion molecules ICAM-1 and P-selectin (cellular Elisa), protein tyrosine kinase and transcription factors NF- κ B and AP-1 activation (Western Blot) were tested.

Results: Exposure of HEC to H₂O₂ resulted in an 2 fold increase in monocyte adhesion, enhanced surface expression of ICAM-1 by 2 fold and P-selectin by 1.2 fold, augmented tyrosine phosphorylation of protein bands of ~ 65, 55 and ~36 kDa, and increased nuclear levels of c-Jun and p65 proteins. Addition of enoxaparin together with the oxidant stimulus to the culture medium abolished monocyte adhesion to HEC and induced a 30% reduction in ICAM-1 expression and inhibition of P-selectin expression. Furthermore, enoxaparin diminished tyrosine phosphorylation of ~65 and ~55 kDa proteins while no decrease in tyrosine phosphorylation of the band of ~36 kDa was detected. In addition, enoxaparin reduced the nuclear levels of c-Jun and p65 proteins.

Conclusion: Together, our data demonstrate the protective, antioxidant effect of enoxaparin directly on human endothelial cells and reveal that the mechanism of drug action involves cell adhesion molecules (ICAM-1 and P-selectin), and the transcription factors NF- κ B and AP-1.

P823 Effects of vitamin D2 supplementation on aortic valvular and vascular endothelial functions in a rabbit model of aortic stenosis



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Aortic stenosis (AS) is associated with systemic endothelial dysfunction but the relationship between the development of AS and aortic valve (AV) endothelial dysfunction has not been explored. Animal studies (porcine and canine models)

have demonstrated that AV endothelium releases nitric oxide (NO) and prostacyclin, which exert local anti-thrombotic effects and reduce leaflet tone. In a rabbit model, we have documented that high dose vitamin D2 (VitD-hd) supplementation for 8 weeks (25000 IU/4 days weekly) induces AS (confirmed histologically and by echocardiography), while low dose (VitD-ld, 5000 IU/4 days weekly) does not. In this model we examined the effects of VitD supplementation (with or without cholesterol) on valvular and vascular endothelial function. Rabbits were given either normal chow/drinking water (n=8, control), or supplemented with VitD-ld (n=4), VitD-hd without (n=5) and with 0.5% cholesterol (Chol/VitD-hd, n=3). AV endothelial function was examined using bio-assay where AV fragments were co-incubated with human whole blood or platelet-rich plasma and the effects on ADP-induced platelet aggregation and intra-platelet content of cGMP and cAMP were assessed. Vascular endothelial function was assessed as relaxant responses to acetylcholine (ACh, 0.001-100 μ M), sodium nitroprusside (SNP), and isoprenaline (ISO, 0.001-10 μ M) in phenylephrine pre-constricted aortic rings. AV tissue from control rabbits inhibited platelet aggregation in whole blood by 48 $\pm$ 4% (p<0.01). In VitD-ld, VitD-hd and Chol/VitD-hd groups inhibition was 64 $\pm$ 5%, 64 $\pm$ 7%, and 73 $\pm$ 12%, respectively (p<0.05 vs control in all groups). To determine whether this anti-aggregatory effect was attributed to the valvular release of NO or prostacyclin, we assessed intraplatelet cGMP and cAMP content. There was no significant increase in cGMP content. cAMP content was increased in the presence of AV tissue (p<0.05) but did not differ between the experimental groups. Maximum relaxation to ACh in aortic rings was significantly impaired in the VitD-hd group compared to control (70.9% $\pm$ 1.5 vs 18.2% $\pm$ 9.4, p<0.001), whereas relaxations by SNP and ISO were not different from control. In Chol/VitD-hd and VitD-ld groups, responses to ACh, SNP, and ISO were not significantly different from control.

Conclusions: In this model of AS, there is a dissociation between VitD-hd induced impairment of vascular endothelial function and enhancement of AV anti-aggregatory effects, together with no reduction in autocoid release from AV, which suggests that AV endothelial dysfunction is not a primary pathogenetic mechanism in AS.

P824 Red blood cells express a functional endothelial nitric oxide synthase



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Nitric oxide (NO) is a signalling molecule of major importance modulating not only the function of the vascular wall but also that of blood cells, such as platelets and white blood cells. NO originates via the oxidative L-arginine pathway catalyzed by a family of enzymes termed NO-synthase (NOS) isozymes. Recently, we provide biochemical, molecular and functional evidence for a constitutive blood-born NO synthesis in mammals. Erythrocytes express eNOS isoform stimulated by L-arginine but not endothelium-dependent vasodilators. In vivo L-arginine induced NO formation exceeds the acetylcholine-induced endothelium-derived intraluminal NO formation severalfold given comparable flow increases in forearm vasculature. Erythrocyte-derived NO formation serves important regulatory functions essential for adequate passage of blood through the vasculature. Export of bioactive NO from erythrocytes modulates tone of arteries with reduced NO bioactivity in vivo and in vitro. L-arginine stimulated erythrocyte NO synthesis compensates lack of endothelium-derived NO describing beneficial effects upon L-arginine application in a variety of cardiovascular disorders. The discovery of a constitutive NO synthesis in erythrocytes shifts the paradigm of understanding vascular homeostasis and may help to develop new approaches in diagnosis and treatment of NO deficiency inherent to many vascular diseases.

P825 Is telomerase regulated by nitric oxide in endothelial cells?



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Background and Purpose: Telomerase, a reverse transcriptase involved in the maintenance of telomere function and cellular replicative capacity, is thought to be regulated by nitric oxide (NO) in normal endothelial cells (EC). NO has been claimed to counteract the loss of telomerase activity which occurs as a function of replicative age and to delay the onset of cellular senescence (Vasa et al. 2000 Circ. Res. 87:540). We have previously shown that in cells grown with fibroblast growth factor-2, telomerase is up-regulated and that the cells attain a normal replicative age (Kurz et al. 2003 Arterioscler. Thromb. Vasc. Biol. 23:748). In contrast, in cells grown with vascular endothelial growth factor-A, which is known to increase NO levels, telomerase remains depressed and the cells undergo senescence prematurely, suggesting that the involvement of NO in telomerase regulation and cellular senescence warrants further study. Here we have investigated whether manipulation of NO levels by pharmacological and genetic approaches affects levels of telomerase activity and EC senescence.

Methods and Results: Treatment of EC for 24 hours or during serial passage in

culture, either with the NO synthase (NOS) inhibitor NG-mono-methyl-L-arginine (L-NMMA, 1 mM) or with the NO donors diethylenetriamine/NO (DETANO, 12.5–50 μ M) and S-nitroso-penicillamine (SNAP, 25 μ M) which at those concentrations generated NO in the 20–125 nM range, respectively reduced (L-NMMA) or increased (NO donors) c-GMP levels but had no effect on telomerase activity compared to untreated cells. Infection of EC with a lentiviral vector expressing a small hairpin (sh)RNA targeted against endothelial NOS reduced the expression level of the corresponding protein by >80% and abrogated the calcium-induced increase in c-GMP, but did not affect telomerase activity. Furthermore, none of the above treatments affected the accumulation of senescent cells as determined by senescence-associated beta-galactosidase staining. Withdrawal of ascorbate from the EC growth medium increased intracellular levels of reactive oxygen species (determined by oxidation of DCFDH), accelerated the loss of telomerase activity and increased the accumulation of senescent cells upon serial passage in culture. However, the shift to a more oxidative redox state did not unmask the putative capacity of NO to modulate telomerase or the onset of senescence.

Conclusions: Our findings suggest that in cultured endothelial cells NO at physiological concentrations does not modulate telomerase levels or cellular replicative capacity, regardless of the oxidative status of the cells.

P826 Potentiation of platelet responsiveness to nitric oxide by angiotensin-(1-7) is mediated by its specific receptor and is associated with the suppression of superoxide release

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Angiotensin II (Ang II) and Ang-(1-7) exert physiological antagonism in vasculature. Recently we showed that Ang II potentiates platelet aggregation, while Ang-(1-7) potentiates the anti-aggregatory action of nitric oxide (NO) donor sodium nitroprusside (SNP), and may therefore counteract platelet NO resistance that accompanies cardiovascular disease and is associated with increased levels of superoxide (O₂⁻). In the current study, we investigated the putative role of a specific Ang-(1-7) receptor in mediating the effect of Ang-(1-7) and tested whether this effect is associated with the modulation of O₂⁻ release.

We studied effects of SNP (1–10 μ M), Ang-(1-7) (0.1 nM – 1 μ M) and the Ang-(1-7) receptor antagonist D-ala⁷-Ang-(1-7) (1 μ M) on ADP(2.5 μ M)-induced platelet aggregation and lucigenin (5–12 μ M)-derived chemiluminescence (LDCL) in whole blood (WB), platelet-rich plasma (PRP) and isolated polymorphonuclear leukocytes (PMN) obtained from normal subjects.

In WB, SNP inhibited ADP-induced platelet aggregation by 21±8% ($p<0.02$). Ang-(1-7) did not directly affect platelet aggregation, but potentiated (2-fold, on average) the inhibitory action of SNP ($n=12$), in accordance with our previous observations with U46619 as an inducer of aggregation. This effect of Ang-(1-7) was bimodal, with maximal increase in SNP-induced inhibition of aggregation by incremental 18±2% ($p<0.01$) at 10–100 nM Ang-(1-7) (C_{max}), and was abolished at higher concentrations of Ang-(1-7). Platelet aggregation was accompanied by O₂⁻ release (assessed via LDCL); SNP suppressed this O₂⁻ release. Ang-(1-7) at C_{max} augmented (by incremental 23±8%, $p<0.03$) the SNP-induced suppression of O₂⁻ release during the aggregation ($n=12$). The Ang-(1-7) receptor antagonist completely eliminated the potentiating effects of Ang-(1-7) ($n=11$); in the absence of Ang-(1-7), the antagonist had no effects. In order to examine possible association of Ang-(1-7) receptor with platelets, we performed experiments in PRP. In PRP, however, Ang-(1-7) did not potentiate the anti-aggregatory action of SNP ($n=7$). Furthermore, in isolated PMN, a major source of O₂⁻ in blood, Ang-(1-7) did not modify O₂⁻ release (after stimulation of PMN with fMLP or ADP), either in the absence or presence of SNP ($n=9$). Thus, Ang-(1-7) effects occurred only in WB.

Conclusions: Ang-(1-7) potentiates the anti-aggregatory effects of NO donor, presumably via a specific Ang-(1-7) receptor. This potentiation is associated with the suppression of O₂⁻ release during aggregation and arises via an interaction between platelets and PMN.

P827 Direct measurement of Nitric Oxide release from vagus nerve stimulation in the isolated heart

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We have previously shown that the protective effect of vagus nerve stimulation (VNS) against ventricular fibrillation is blocked by inhibiting Nitric Oxide (NO) production. Direct evidence that VNS releases NO is lacking. We have developed a new technique to measure NO using Fluorescence (F) dye, 4-5 Diaminofluorescein (DAF-2) in a novel innervated isolated rabbit heart preparation ($n=5$). Left ventricular pressure (LVP) was monitored. Epicardial F was measured with excitation at 480, 490 and 500nm and emission at 535nm. DAF-2 was loaded with a bolus injection (1 μ mol DAF2-DA). F was measured before, during and after VNS and also during perfusion with NO donor, sodium nitroprusside (SNP, 100 μ M) and NO synthase inhibitor, N-nitro-L-arginine (LNA, 200 μ M).

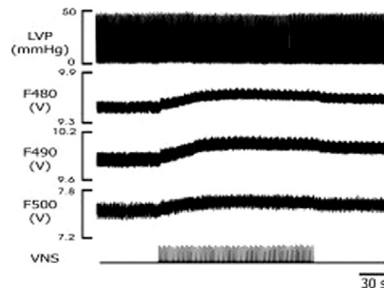
Results (mean±sem): VNS (9.4±0.6 Hz, 9.2±1.6V) decreased heart rate from 166.1±13.6 to 95.3±2.2 bpm. During constant pacing (200 bpm), VNS increased

F490 by 3.0±1.3% ($p<0.04$). SNP caused similar increase (3.0±0.5%, $p<0.005$) whilst LNA caused a decrease of 3.9±0.7% ($p<0.01$).

Mean data for F490 (V) during protocols

	Pre	During	Post
VNS	9.72±0.14	10.01±0.04 *	9.64±0.21
SNP	9.87±0.03	10.17±0.04 **	9.83±0.09
LNA	10.01±0.05	9.62±0.06 **	10.09±0.03

* $p<0.05$; ** $p<0.01$



Conclusions: These are the first data to demonstrate the increase in NO measured from vagus nerve stimulation in the isolated heart. Further work will allow the study of the NO synthase isoforms involved in NO release from vagus nerve stimulation.

GENETICS AND ATHEROSCLEROSIS

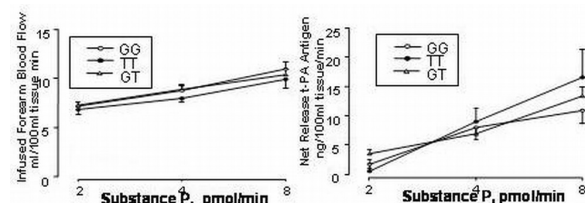
P828 Endothelial nitric oxide synthase polymorphism Glu298Asp does not influence forearm blood or acute t-PA release in patients with coronary heart disease

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Background A polymorphism (exon 7 Glu298Asp) within the endothelial nitric oxide synthase (eNOS) gene has been linked to an increased risk of coronary heart disease (CHD) as well as endothelial dysfunction. We investigated the effect of the Glu298Asp polymorphism on two complementary aspects of vascular function in patients with stable CHD.

Methods Plasma tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1) antigen concentrations and forearm blood flow (FBF) were measured in response to intra-brachial infusion of substance P in 91 patients with coronary heart disease. FBF was also measured during infusion of acetylcholine and sodium nitroprusside. Genotyping was undertaken using a PCR assay specifically designed to detect the Glu298Asp polymorphism.

Results The genotype distribution of Glu298Asp (GG 36.2%, GT 52.7%, TT 11.0%) was similar to that previously reported. Substance P caused a dose dependent increase in plasma t-PA ($P<0.01$) but not PAI-1 antigen concentrations. There was no effect of the Glu298Asp polymorphism on blood flow responses or net t-PA release ($P=ns$). Compared to nonsmokers, smokers exhibited impaired FBF responses ($P<0.01$) and decreased net release of t-PA antigen ($P=0.05$) and this smoking dependent impairment was not modified by Glu298Asp genotype.



Glu298Asp and endothelial function

Conclusions: Despite confirming previous findings that cigarette smoking is associated with impaired endogenous fibrinolysis, we have found no effect of the Glu298Asp eNOS polymorphism on these two complementary measures of endothelial function. The Glu298Asp polymorphism does not appear to be a major arbiter of endothelial dysfunction in patients with established coronary heart disease.

P829 Evaluation of eNOS polymorphisms and the risk of future cardiovascular events in the AtheroGene study



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Background: Genetic variations in the gene encoding endothelial nitric oxide synthase (eNOS) are discussed to constitute a risk factor for the development of atherosclerosis and coronary artery disease. We evaluated the relationship between eNOS polymorphisms (Glu298Asp, T-786C, G+11/in23T) and the risk of future cardiovascular events for patients with documented coronary artery disease (CAD) in the AtheroGene study.

Methods: Patients with documented CAD (n=1473) were genotyped for polymorphisms of the NOS3 gene by means of allele-specific oligonucleotide probes (ASO). Follow up was extended to a median period of 6.4 (maximum 7.7) years for a total of 1460 patients (99.1%) with 154 deaths from cardiovascular causes.

Results: Patients with or without fatal cardiovascular events do not differ in respect of the allele frequencies of T-788C and G+11/in23T polymorphisms. Homozygosity for the T allele of Glu298Asp was less frequent in patients with CV events compared to those without (7.6% vs. 11.1%; p = 0.20). After adjustment for age, sex and cardiovascular risk factors we found a trend towards more frequent future fatal CV events and the Glu298Asp polymorphism (Glu/Glu vs. Asp/Asp; p = 0.09). Additional adjustment for medication did not change the trend (p = 0.09) (Table 1).

Table 1

n = 144	NOS_298			P Value
	Glu/Glu/G	Glu/Asp/G/T	Asp/Asp/T/T	
Adjusted for age and sex (Model 1)				0.16
Hazard ratio	1	0.77	0.61	
95% CI	—	0.55 - 1.09	0.32 - 1.15	
P Value	—	0.14	0.13	
Adjusted for risk factors, medication (Model 2)*				0.11
Hazard ratio	1	0.76	0.58	
95% CI	—	0.53 - 1.07	0.31 - 1.08	
P Value	—	0.12	0.09	

* additional adjustment for BMI, diabetes, hypertension, smoking status, HDL-C, medication (ACE inhibitors, β -blockers, statins)

Summary: In the prospective AtheroGene study we found a trend in the correlation between the T allele of the eNOS Glu298Asp polymorphism and future fatal CV events in patients with documented cardiovascular disease.

P830 The functional -374T/A polymorphism of RAGE gene promoter predicts prognosis in patients with suspected coronary heart disease



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Background: The receptor for advanced glycation end products (RAGE) is a cell-surface molecule that could play a crucial role in the generation of a pro-inflammatory milieu in atherosclerotic vascular disease. The -374T/A polymorphism of RAGE gene promoter, linked to a reduced transcriptional activity, has been shown to exert a protective effect toward the development of coronary atherosclerosis both in diabetic and nondiabetic individuals. The aim of the present study was to investigate the prognostic effect of this common genetic variant on cardiovascular outcome in patients with suspected coronary heart disease.

Methods: A consecutive cohort of 800 nondiabetic patients with suspected coronary heart disease undergoing coronary angiography were prospectively followed up for 5.2 years (interquartile range: 2.1-8.2 years). The -374T/A RAGE polymorphism was genotyped by PCR-RFLPs. The study end point, a composite of cardiac death, non-fatal myocardial infarction and unstable angina, was evaluated in patients stratified according to the -374T/A RAGE genotypes (AA versus AT+TT).

Results: 561 patients had an angiographic confirmation of coronary vessel stenosis, while 239 subjects showed normal coronary angiograms. The frequencies of -374T/A genotypes did not deviate from Hardy-Weinberg equilibrium: 14.6% AA, 47.6% AT, and 37.8% TT. The 83 patients who developed an adverse event were less likely (7.5%) to be carriers of the homozygous AA genotype as compared with the 717 who did not (15.8%, p<0.05). In a univariate Cox proportional hazard analysis, the AA genotype was significantly related to a less frequent incidence of cardiac events (hazard ratio 0.49, 95% CI 0.22-0.73; p<0.5). After adjustment for most demographic, clinical and therapeutic confounders, the AA genotype remained significantly associated with a better cardiac prognosis (hazard ratio 0.51, 95% CI 0.27-0.75; p<0.5) in a multivariable Cox regression model.

Conclusions: In patients with suspected coronary heart disease, the carriage of the homozygous AA genotype is associated with a reduction of adverse cardiac events at follow-up. Determination of the -374T/A RAGE genotype might be use-

ful in risk stratification and in the evaluation of new therapies to improve cardiac prognosis in patients undergoing coronary angiography.

P831 Lp-PLA2 gene polymorphisms, plasma levels of Lp-PLA2 and risk of coronary heart disease. Results from a large case-control study



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Purpose: Lipoprotein-associated phospholipase A2 has been implicated as an emerging risk marker for coronary heart disease (CHD). It has also been demonstrated that genetic variants within the Lp-PLA2 gene might influence Lp-PLA2 plasma concentration. However, so far published data remain controversial and are scarce. We sought to determine various Lp-PLA2 single nucleotide polymorphisms (SNPs) within the Lp-PLA2 gene (PLA2G7) in a large case-control study. Furthermore, their association with stable CHD as well as the effect of PLA2G7 SNPs on Lp-PLA2 plasma concentration has also been assessed.

Methods: A large case-control study, comprising 312 patients with angiographically proven stable CHD and 477 age- and gender-matched healthy blood donors served as the study base. We investigated the distribution of various PLA2G7 SNPs in the coding region (Arg92His in Exon 4 (rs1805017); Ile198Thr in Exon 7 (rs1805018); Ala379Val in Exon 11, (rs1051931), as well as two SNPs in the promoter region at positions 2061 A/G (rs10948301), 3015 T/C (rs1421378) relative to AF027357. PLA2G7 genotypes were determined by RFLP-PCR. In addition, Lp-PLA2 plasma mass (diaDexus PLAC? test) and activity (as measured by 2 different assays: Hybrid Immuno Capture (HIC) and colorimetric activity method (CAM)) were assessed.

Results: We found no association between the various polymorphisms and increased risk for CHD after adjustment for age, gender, BMI, duration of school education, smoked pack years, alcohol consumption, history of hypertension and diabetes. Moreover, there was no consistent association between Lp-PLA2 gene variants and multivariate-adjusted mean values of Lp-PLA2 in plasma: only the common allele coding for Arg 92 showed a slight decrease in Lp-PLA2 mass (249.6 vs 269.3 vs 271.4 ng/mL for Arg/Arg, Arg/His and His/His respectively; p=0.04), with no association for Lp-PLA2 activity.

Conclusions: In this large case-control study, no consistent association between variants in the Lp-PLA2 gene and plasma levels of Lp-PLA2 mass and activity as well as the presence of CHD were found.

P832 The 1527 Ala/Gly polymorphism in the ATP-binding cassette transporter ABCA7 is associated with low HDL-Cholesterol and metabolic syndrome in women



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Introduction: ATP-binding cassette transporter A7 (ABCA7) is closely related to ABCA1 and promotes efflux of cellular phospholipids to apoA-I. Female ABCA7-Knockout mice show alterations in plasma lipids and body weight. ABCA7 has therefore been proposed as a potential candidate gene for determination of plasma HDL in humans. In the present study we tested the effect of two common single nucleotide polymorphisms on plasma lipids, glucose metabolism, body weight and blood pressure in a sample of the German general population.

Methods: The 1630 subjects originated from a gender- and age-stratified sample of all German residents of the Augsburg area (MONICA Augsburg survey 1994/1995). Genotyping was performed using the 5'prime exonuclease assay.

Results: Both polymorphisms were selected because they result in non-conserved amino-acid substitutions in conserved regions of the ABCA7-gene. The 463Arg/His polymorphism did not show any association with the tested variables. However, using a recessive model and adjusting for relevant covariates we found a statistically significant association of the 1527 Ala/Gly polymorphism with lower HDL (p=0.009), higher LDL- (p=0.027) and total Cholesterol (p=0.015) and higher HbA1c (p=0.013) in the entire population. Furthermore, for LDL-, total-Cholesterol, glucose, HbA1c and systolic blood pressure we also observed a significant interaction between the recessive genotype and gender. After stratification by gender we found that the effect of the 1527 Ala/Gly polymorphism on plasma-lipids, glucose, HbA1c and blood pressure was mainly attributable to female carriers of the rare allele. Women homozygous for the GG-allele of the 1527Ala/Gly polymorphism show significantly lower HDL-levels (p=0.024), higher LDL-levels (p=0.035), higher total cholesterol-levels (p=0.042), higher triglyceride levels (p=0.003), higher serum glucose levels (p=0.0004), higher HbA1c values (p=0.001) and higher systolic blood pressure (p=0.020) and diastolic blood pressure (p=0.019) readings. In summary these individuals display a distinct phenotype with typical features of the metabolic syndrome and could therefore carry an increased risk of cardiovascular disease.

Conclusions: In analogy to published in-vitro and in-vivo data from ABCA7/-mice our results suggest that genetic variation in ABCA7 contributes to the risk for dyslipidemia and metabolic syndrome in the German general population.

P833 Common genetic variation in platelet glycoprotein receptors for collagen, vWF and fibrinogen is not associated with the risk of MI and does not predict recurrent events during long-term follow-up



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Genetic predisposition has been shown to be associated with the risk of MI. Coronary thrombosis after plaque rupture is the central pathogenetic mechanism in MI. Genetic variation in key proteins of platelet surface adhesive receptors has been associated with an increased risk of MI in previous small study series. We aimed to study the importance of this genetic variation in a large series of consecutive hospitalised MI patients.

594 consecutive patients with acute myocardial infarction (STE-MI and NSTEMI) from a tertiary center were included in the study. The mean age of patients was 69.7 years. Follow-up was performed by phone calls, studying of patient charts and data from the national mortality records. Two major endpoints were recorded: the combined endpoint (recurrent UA/MI, ischemic stroke and death due to any cause) and all-cause mortality. Several platelet glycoprotein polymorphisms were determined by PCR-RFLP. Healthy blood donors were used as controls.

The alleged high-risk prothrombotic variants, the PIA2 allele of the GPIIIa polymorphism, the Met allele of the GPIb polymorphism and A1 allele of the GPIa polymorphism were found in 27.0%, 22.4% and 10.1% of our MI patients, respectively. These frequencies were not statistically different from those of our control population. Follow-up recurrent events and death were frequent in this real-life population of all-comers but could not be predicted by any of these genetic polymorphisms.

In conclusion, we have found that genetic variation in platelet glycoprotein receptors does not seem to influence the risk of MI in this hospital-based MI population of adequate size. In addition, this genetic variation was not associated with the long-term risk of recurrent events in our unselected contemporary study population.

P834 Association of transforming growth factor-beta 1 gene polymorphisms with myocardial infarction in patients with angiographically proven coronary heart disease



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Objective: Transforming growth factor-beta 1 (TGF-beta 1) is a multifunctional cytokine that exhibits vasculoprotective properties. Production and plasma levels of TGF-beta 1 are influenced by polymorphisms in the TGF-beta 1 gene (TGFB1). We investigated whether the -509C/T (rs1800469), 868T/C (rs1982073), 913G/C (rs1800471), and 11929C/T (rs1800472) polymorphisms of TGFB1 are associated with myocardial infarction.

Methods: The study population consisted of 3657 patients with myocardial infarction (885 women and 2772 men) and 1211 control individuals (598 women and 613 men) with angiographically normal coronary arteries and without signs or symptoms of myocardial infarction. Polymorphism-related genotypes were determined with TaqMan assays and haplotypes were estimated from the genotype data.

Results: The -509C/T polymorphism and -509C/868T/913G/11929C (CTGC) haplotype were associated with myocardial infarction in men, independently from the potentially confounding factors age, arterial hypertension, hypercholesterolemia, cigarette smoking, and diabetes mellitus. Lower risks of myocardial infarction were observed among the carriers of the -509CC genotype (adjusted OR 0.49, 95% CI 0.27-0.87; $P=0.014$) and homozygous carriers of the CTGC haplotype (adjusted OR 0.61, 95% CI 0.38-0.98; $P=0.042$) than among the noncarriers of this genotype or haplotype. None of the genotypes ($P\geq 0.37$) or haplotypes ($P\geq 0.35$) was associated with myocardial infarction in women.

Conclusions: Positive association findings in this study suggest that TGFB1 is a susceptibility locus for myocardial infarction.

P835 Exploring the effects of C-reactive protein (CRP) and interleukin-1B single nucleotide polymorphism on CRP concentration - a classification tree approach



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Background: C-reactive protein (CRP) is a novel predictor for future cardiovascular disease. Its serum level is affected by the polymorphisms on the genes coding for CRP and interleukins. The objective of this study was to illustrate the effects of these polymorphisms on serum CRP levels in a Taiwanese population with coronary heart disease (CHD).

Methods: A total of 390 patients (280 male and 110 female) with angiographically proven CHD was recruited and high-sensitivity CRP levels were measured. Six polymorphic alleles (CRP+1059, GT-repeat in the intron of the CRP gene, IL-1B+3954, IL-1B-511, IL-1B-31, and the identical tandem repeats on the intron

of the IL-1 receptor antagonist) were identified for each patient. A classification tree was applied to find the effects and interactions of the polymorphisms and non-genetic confounders on serum CRP levels.

Results: The data showed that the presence of hypertension was the most important factor that led to elevated CRP levels ($\geq 0.8\text{ mg/dL}$). In the hypertensive CHD patients, the presence of CRP+1059 G->C was associated with a lower risk for elevated CRP levels (OR=0.318, $p=0.001$). The coexistence of CRP+1059 and IL-1B-511 might result in changes in the CRP levels (OR = 0.241, $p=0.088$).

Conclusion: The results of the present study demonstrated the distribution of potential polymorphisms in the patients with CHD in the Taiwanese population. The application of the classification tree, a heuristic decision tool, may explain the complicated interaction among genetic and non-genetic factors.

P836 Association between SR-BI polymorphisms, composition, size and levels of HDL in mexican patients



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Background and Purpose: HDL include a heterogeneous group of lipoproteins of high density constituted by lipids and apolipoproteins in different quantitative and qualitative concentrations, resulting in various HDL subclasses. In this context, it has been suggested that concentration of HDL subclasses, determines their anti-atherogenic potential. The SR-BI component in the reverse cholesterol transport where it binds to HDL and is involved in the transfer of lipids from HDL-C and therefore the genetic variant of SR-BI may be an important determinant of abnormal lipoproteins and confer susceptibility to CHD. In the present study, we investigated the association between SR-BI polymorphisms, with composition, size and levels of HDL in Mexican patients.

Methods and Results: We studied 54 patients clinically healthy volunteers (non-CVD) recruited in the National Institute of Cardiology "Ignacio Chavez" in Mexico City. We measured the carotid artery intima-media thickness and total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C) and very low-density lipoproteins (LDL-C). After, we obtained HDL and then measure size and composition of HDL. Finally, we determine the SR-BI exon 8 variant CT. The subjects were divided to accord HDL-C levels on hypoalphalipoprotein (HA) ($\geq 40\text{ mg/dL}$, $n=13$), normoalphalipoprotein (NA) ($40-52\text{ mg/dL}$, $n=28$) and hyperalphalipoprotein (HEA) ($\leq 53\text{ mg/dL}$, $n=13$). We found increase in small HDL particles in subjects with HA vs NA (28.7 ± 6 and 24 ± 9.2 vs. 25.9 ± 8.6 and 20.5 ± 10.6 for HDL3b and HDL3c respectively), with respect to HDL chemical composition, also we found increase in free cholesterol, esterified cholesterol and phospholipids in this kind of subjects compared with NA subjects (2.4% vs 1.1% ; 27.3% vs 16.3% and 16% vs 10.5% respectively). With respect to SR-BI polymorphism we found 73.2% (CC), 23% (CT) and 3.8% (TT). TT subjects have increased TG and diminished HDL levels and more HDL3 subpopulation than HDL2 with respect to another polymorphisms.

Conclusion: Our results shown an association between HA subjects with increase in the proportion of HDL small size (HDL_{3b,3c}), and with TT genotype. Also, increase in free cholesterol and esterified cholesterol in HA subjects suggesting that it can be due to CETP activity deficiency or affinity SR-BI receptor reduction associate with this genotype.

P837 A functional variant in the CARD4 gene and risk of premature coronary heart disease



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Background: Infection and innate immunity have been suggested to be involved in the pathogenesis of atherosclerosis. The recently discovered Pattern-recognition receptors (PRRs) consists of molecules that initiate signaling after host-pathogen interactions. It has been shown that members of the PRRs, especially the Toll-like receptor 4 (TLR4), are involved in the development and progression of atherosclerosis. A newly discovered member of the PRRs is NOD1 (CARD4), which is a gene that seems to be associated with barrier function in chronic inflammatory disorders. Mutations in this gene predispose to a defective immune response to bacterial cell wall components.

We investigated whether allelic variation in the NOD1 gene was involved in disease onset.

Methods: 900 unrelated coronary heart disease (CHD) patients and 540 age- and gender-matched unrelated and healthy controls were genotyped. Study subjects were required to have coronary catheterization demonstrating significant CHD before the age of 55 years (mean age: 48 years).

We compared the frequencies of the major functional polymorphisms of the CARD4 gene, the indel mutation ND1+32656 and the two adjacent polymorphisms rs2075822 and rs2907748 in patients with CHD with those in controls.

Results: The genotyping data showed no evidence for a significant association of the CARD4 variants with CHD.

Conclusion: Our results suggest that the analyzed NOD1 (CARD4) mutations do not play a major role in the barrier dysfunction in CHD.

P838 Interleukin-8 gen promoter, a novel marker for recurrence in premature coronary syndromes

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Inflammation is crucial in premature acute coronary syndromes (ACS). Early complications impose an enormous challenge to long-term therapeutic and preventative strategies. Simple permanent markers are needed to detect patients at risk for extensive or aggressive disease and poorer outcome.

We analyzed the polymorphisms of three pleiotropic inflammatory mediators, interleukins IL-8 (-251 A/T), IL-6 (-174 C/G) and IL-1beta gene (+3953C/T) ±promoters with PCR-SSP techniques in 651 patients (P), with premature ACS (males under 50 and females under 60 y-o), and more than one year follow-up (average 10 years).

Results: Females were only 25%. Premature disease appeared 3 years earlier in smokers ($p<0.000$) and carriers of triglyceride/HDL index over 5 ($p<0.005$). Diabetes (36/27%; $p<0.032$), dyslipidemia (83/71%; $p<0.002$), metabolic syndrome (44/33%; $p<0.045$) were more frequent in multivessel disease and IL-8 TT among single vessel disease. Patients with recurrent ACS (37%) had higher prevalence of metabolic syndrome (42/33%; $p<0.045$) and multivessel disease (68/39%; $p<0.000$). Multivariate analysis adjusted by risk factors, gender, clinical features and genotypes, depicted multivessel disease ($p<0.000$; OR 2.45-6.66), smoking ($p<0.020$; OR 1.102-3.683), angina ($p<0.000$; OR 2.941-8.173) and variant IL-8 homozygous GG ($p<0.004$; OR 1.194-3.234; IC 95%) as the major markers of recurrence 70%.

Conclusions: Despite their youth our patients have high prevalence of classical risk factors and recurrence. IL-8 genotype is a simple, permanent and inexpensive (40€/case) marker that may contribute to characterize the profile of young patients at higher risk for further ACS.

P839 Interleukin 18 gene promoter polymorphisms in genetic predisposition to coronary artery disease in patients with type 2 diabetes mellitus

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Purpose: Aim of present study was to assess the role of interleukin 18 (IL-18) gene promoter polymorphisms in genetic predisposition to coronary artery disease (CAD) in patients with type 2 diabetes mellitus (DM).

Methods: Study was conducted in cohort of 584 patients after coronarography performed in our center. Studied population was selected at random from group of 4655 patients, who had this examination performed. Control group, to assess the distribution of studied alleles in population ($n=204$) consisted of apparently healthy, unrelated individuals. IL-18 gene promoter -607 C/A and -137 G/C polymorphisms of were evaluated in SSP-PCR, results were confirmed in DNA sequencing. Moreover, in 237 patients who underwent coronarography, randomly chosen from study group and in 40 patients from control group serum concentration of IL-18 was assessed.

Results: Serum concentration of IL-18 was the highest in subgroup of patients with unstable angina pectoris, comparing to population with stable angina and asymptomatic individuals ($p<0.04$), both in patients with DM and without metabolic disturbances. Patients with genotype -607AA had significantly higher serum concentration of IL-18 comparing to genotype -607 CC and -607 AC ($p<0.03$). Significant coronary atherosclerosis was more frequent in patients with haplotype -607AA/-137CC, comparing to other haplotypes. There was also a trend to higher frequency of genotype -607AA/-137CC prevalence along with growing number of significant lesions in coronarography (in patients with 2- and 3-vessel CAD).

Conclusions: 1. Significantly more frequent prevalence of IL-18 gene promoter -607AA/-137CC haplotype in patients with angina pectoris in comparison to asymptomatic individuals suggests the important role of IL-18 gene in determining the genetic predisposition to CAD in studied population.

2. Higher concentration of IL-18 in patients with symptoms of CAD as well as correlation between AA genotype in position -607 and higher concentrations of this cytokine seem to confirm the causal association of studied SNP with CAD.

3. Although any significant influence of studied IL-18 gene promoter polymorphisms on prevalence of coronary atherosclerosis in patients with diagnosed CAD hasn't been showed in the present study, observed trend towards higher frequency of -607AA and -137CC genotypes prevalence along with growing number of angiographically significant atherosclerotic lesions in coronarography implies the intentionality of further studies, conducted on the larger population of patients with coronary atherosclerosis.

P840 Mannose binding lectin genotype modulates the endothelial response to infection

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Background: Infection and inflammation are implicated in endothelial dysfunction (ED), a key event in early atherosclerosis. Variants in the mannose binding lectin (MBL, an integral component of innate immunity) gene predict circulating levels of this protein. Deficiency in MBL has been associated with increased susceptibility to and severity of infections in children and increased susceptibility to cardiovascular events in adults. We hypothesized that MBL genotype influences endothelial function during infection.

Methods: We studied 1719 children (aged 10yrs) drawn from the Avon Longitudinal Study of Parents and Children (ALSPAC): 414 with current or recent (<2 weeks) infection (INF), and 1305 healthy controls. Brachial artery flow mediated dilatation (FMD) was assessed using high-resolution ultrasound. Exon 1 and promoter polymorphisms in the MBL gene were determined by heteroduplexing procedures. The children were classified according to the MBL genotype in group 1: wild type, group 2: heterozygotes and group 3: homozygotes that have normal intermediate and low MBL levels respectively.

Results: Baseline characteristics of children were similar in groups 1-3. FMD was reduced in INF vs Control ($p<0.001$). Although MBL genotype was not associated with FMD in healthy children ($p=NS$), a relationship with the degree of impairment in FMD during INF was observed (9.7%, 9.6%, and 24.8% fall in FMD for groups 1-3 respectively, $p<0.05$). Additionally, group 3 was a predictor of an impaired FMD (lowest quartile) during INF (odds ratio [95%CI] 4.0 [1.35, 11.96] $p=0.01$). After multiple regression analysis adjusting for classical cardiovascular risk factors, homozygosity for MBL (group 3) remained the only independent predictor of reduced FMD with INF (2.6[1.04, 6.62] $p<0.05$).

Conclusions: Homozygosity for MBL variant allele, predictive of low MBL levels, is associated with greater impairment in endothelial function during infection, suggesting a gene-environment interaction that may be relevant to atherosclerotic disease.

ENDOTHELIAL FUNCTION IN DIABETES**P841 Effect of chronic sildenafil therapy on endothelial function in diabetic patients**

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Background: Phosphodiesterase-5 inhibitors (PDE5) improve erectile dysfunction and endothelial function. Diabetic patients with and without erectile dysfunction have lower response of the endothelium to PDE5 than the general patient population. Aim of this study was to evaluate the effects of chronic therapy with sildenafil (S) on endothelial function in patients with type II diabetes mellitus.

Methods: In a double-blind crossover design, 20 patients randomly received a loading dose of S (100 mg) for 3 days followed by either S 25 mg three times a day (tds) for 4 weeks or S 25 mg tds for four days followed by placebo tds for 3 weeks. Endothelial function was evaluated at baseline and at the end of each week of the study by flow mediated dilatation (FMD). Serum levels of NO, endothelin-1, CRP, IL-6, ICAM and VCAM were also measured.

Results: After one week FMD improved significantly (>50% compared to baseline) in patients allocated to both S arms 62% and 64% respectively. In patients allocated to chronic S a progressive increase in the number of responders was noted (78%, 86%, 94% at 2,3 and 4 weeks respectively) while a progressive decrease in the number of responders was found in the placebo group (45%, 18%, 6% at 2,3 and 4 weeks respectively). At the end of the study a significant improvement in FMD compared to baseline were noted in the chronic S group (FMD from 6.8 ± 0.5 to $12.5 \pm 0.7\%$, $p=0.01$ vs. baseline). A decrease in endothelin-1 levels and an increase in nitrite/nitrate levels were found in the chronic S group, (from 3.6 ± 0.5 to 2.8 ± 0.7 and from 39.1 ± 11.4 to 46.4 ± 7.3 , $p<0.05$, respectively, compared to baseline). In this group significant modifications in CRP, IL-6, ICAM and VCAM levels were also found (-22%, -29%, -18%, -32%, $p<0.05$, respectively compared to baseline). No changes were observed in the placebo group.

Conclusions: Our results demonstrate that in diabetic patients chronic S administration improves endothelial function and reduces the indices of vascular inflammation, chronic therapy also increases the number of patients responders to the treatment suggesting that in some patients with type II diabetes there is a marked derangement of endothelial function that may be improved with a long term stimulation.

P842 PPAR-gamma agonist rosiglitazone restores impaired in vivo reendothelialization capacity of endothelial progenitor cells in patients with diabetes: critical role of NAD(P)H oxidase and NO availability

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Background: Impaired in vitro function of endothelial progenitor cells (EPCs) has been shown in patients with diabetes, however, the implications for in vivo reendothelialization capacity remain to be determined. The aim of the present study was to compare in vivo reendothelialization capacity of EPCs from diabetics and age-matched healthy controls, and to evaluate the effect of two week rosiglitazone treatment on reendothelialization capacity, NAD(P)H oxidase-mediated superoxide and nitric oxide (NO) production of EPCs from diabetics.

Methods: EPC-mediated reendothelialization of diabetics and healthy subjects was determined by transplantation (Tx) of EPCs into nude mice using a carotid artery endothelial injury model. The reendothelialized area (REA) was measured 3 days post-Tx using computer-assisted morphometric analysis. Reendothelialization, NO and superoxide production of EPCs (assessed by electron spin resonance spectroscopy) were determined before and after siRNA knockdown of endothelial NO synthase (eNOS) and NAD(P)H oxidase subunit p47phox in EPCs. Diabetics were randomized to 2-week treatment with rosiglitazone (n=18) or placebo (n=12) and EPCs were characterized after therapy.

Results: Transplantation of EPCs from healthy subjects into nude mice markedly accelerated reendothelialization of carotid arteries compared to placebo (REA 37 ± 10 vs. $5 \pm 1\%$; $P < 0.05$). Importantly, reendothelialization capacity was markedly impaired in EPC of diabetics (REA $8 \pm 3\%$; $P < 0.05$ vs. healthy control). Superoxide production was increased and NO bioavailability was markedly reduced in EPCs from diabetics as compared to healthy controls. Treatment of diabetics with rosiglitazone reduced NAD(P)H oxidase-mediated superoxide production, increased NO bioavailability and restored reendothelialization capacity of EPCs (REA $38 \pm 4\%$; $P < 0.05$ vs. placebo). siRNA Knockout studies suggested a causal role of reduced NO availability of diabetic EPCs for impaired re-endothelialization capacity.

Conclusion: The present study suggests that EPC-mediated NO production and in vivo reendothelialization capacity is substantially impaired in diabetic patients as compared to healthy controls. Importantly, two week treatment of diabetics with rosiglitazone increased EPC mediated NO production and restored EPC in vivo reendothelialization capacity, at least in part by reducing NAD(P)H oxidase-mediated superoxide production and increasing EPC NO availability. These effects may importantly contribute to vasoprotective properties of rosiglitazone treatment.

P843 Uncoupling of the endothelial nitric oxide synthase in diabetes: implications for endothelial progenitor cells

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Endothelial progenitor cells (EPC) mobilized from bone marrow contribute to replacement of diseased endothelial cells, thereby limiting atherosclerotic plaque formation. Translocation of EPC to the circulation involves vascular endothelial growth factor (VEGF)/nitric oxide (NO) and matrix metalloproteinase-9 (MMP-9)-mediated pathways in bone marrow. In rats with streptozotocin-induced diabetes we investigated alterations of bone marrow molecular mobilising pathways which in part determine circulating EPC levels. In cultured EPC the effects of glucose on reactive oxygen species (ROS) formation were determined. Diabetes was associated with a marked reduction of circulating EPC to $39 \pm 5\%$ ($p < 0.05$) when compared to controls. Superoxide anion (O_2^-) production was substantially enhanced in diabetic bone marrow. Endothelial nitric oxide synthase (eNOS) protein expression was increased in bone marrow extracts of diabetic rats, but eNOS dimer/monomer ratio as well as eNOS and Akt phosphorylation were significantly reduced. NOS inhibition by NG-nitro-L-arginine (L-NNA) decreased O_2^- levels in bone marrow of diabetic rats indicating the involvement of eNOS in exaggerated O_2^- production. In addition, MMP-9 activity was depressed in bone marrow of diabetic animals compared to controls (86 ± 14 vs 162 ± 15 densitometric units/ μ g protein, $p < 0.01$). Treatment with the angiotensin receptor blocker telmisartan improved phosphorylation of eNOS in diabetic bone marrow and attenuated the reduction of EPC levels. Cultured EPC displayed increased ROS formation and impaired migratory and incorporation capacity after treatment with glucose (30mM). Addition of pegylated superoxide dismutase completely, and of the NOS inhibitor L-NNA in part, normalized the glucose-mediated detrimental effects on EPC. Our data support a fundamental role of eNOS uncoupling in diabetic bone marrow and glucose-treated EPC resulting in increased ROS formation. Subsequent reduction of EPC levels and impairment of cellular function are likely to contribute to the pathogenesis of vascular disease in diabetes mellitus.

P844 Insulin-like growth factor-1 axis exerts protective effects against inflammatory activation of human vascular endothelial cells

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The insulin-like growth factor(IGF)-1/IGF-1 receptor (IGF-1R) axis is a pleiotropic regulator of vascular function, but its role in atherosclerosis is controversial. Increasing evidence indicates that individuals with traditional cardiovascular risk factors, but normal or elevated IGF-1 may be protected against disease, while individuals with reduced IGF-1 levels are more exposed to the detrimental effects of vascular risk factors through unopposed endothelial dysfunction and apoptosis. Furthermore, plasma concentrations of IGF-1 have been shown to be positively associated with insulin sensitivity in subjects with different degrees of glucose tolerance and type 2 diabetes. We therefore investigated the effect of IGF-1 and its receptor on the expression of pro-atherogenic vascular cell adhesion molecule-1 (VCAM-1) in resting and cytokine-stimulated endothelial cells.

Methods: Human umbilical vein endothelial cells (HUVEC) were treated for 24 h with IGF-1 (1-100 ng/ml), $\pm$ lipopolysaccharide (LPS), tumor necrosis factor (TNF)-alpha or an IGF-1 receptor neutralizing antibody (0.1-10 ng/mL). Cell surface expression of VCAM-1 was measured by enzyme immunoassay (EIA).

Results: At concentrations ranging from those measured in physiological and pathophysiological conditions such as type 2 diabetes (1-100 ng/mL), IGF-1 did not increase VCAM-1 expression, while inhibition of IGF-1 signaling pathway through the blocking of IGF-1R, concentration-dependently increased VCAM-1 expression. At 10 and 100 nmol/l, IGF-1 concentration-dependently reduced the surface expression of VCAM-1 in HUVEC stimulated with LPS and TNF (see Table).

Treatment	VCAM-1
Untreated control	100 $\pm$ 4
anti IGF-R1 antibody, 1 ng/mL	143 $\pm$ 11*
anti IGF-R1 antibody, 10 ng/mL	246 $\pm$ 57*
TNF-alpha, 1 ng/mL	151 $\pm$ 20*
LPS, 50 ng/mL	207 $\pm$ 6*
TNF-alpha+ IGF-1, 100 ng/mL	105 $\pm$ 10**
LPS + IGF-1, 100 ng/mL	150 $\pm$ 6**

n=3, absorbance units as percent of untreated control; * $p < 0.05$ vs untreated control; ** $p < 0.05$ vs TNF or LPS

Conclusion: IGF-1 reduces the expression of VCAM-1 and therefore may have antiatherosclerotic effects.

P845 The PPAR-γ agonist pioglitazone prevents apoptosis of endothelial progenitor cells

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Background: In addition to insulin sensitizing, peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists (thiazolidinediones, TZDs) have been suggested to improve endothelial function. However, the underlying molecular mechanisms are incompletely understood. Bone marrow-derived endothelial progenitor cells (EPC) contribute to endothelial repair and neoangiogenesis.

Methods and Results: Treatment of C57/Bl6 mice with pioglitazone, 20 mg/kg/day, 10 days, increased circulating Sca-1/VEGFR-2 positive EPC to $235 \pm 60\%$ of vehicle-treated mice (n=24 per group). EPC in the bone marrow were upregulated to $166 \pm 30\%$. DiLDL/lectin positive EPC expanded from spleen-derived mononuclear cells were upregulated to $231 \pm 21\%$. Upregulation of EPC was persistent after 20 days of treatment. Treatment with TZD increased the SDF-1-induced migratory capacity per number of EPC by $246 \pm 73\%$ and upregulated expression of telomere repeat-binding factor (TRF2) to $320 \pm 50\%$. Pioglitazone increased in-vivo neoangiogenesis by 2-fold (disk assay, $214 \pm 42\%$, 20 d). Co-treatment with the NOS inhibitor L-NAME, 50 mg/kg did not alter the upregulation of EPC by TZD. EPC from TZD-treated animals were characterized by reduced apoptosis ($65 \pm 2.8\%$ of vehicle). To test these effects in humans, EPC were isolated from peripheral blood of healthy donors and cultured for 48h. Incubation of EPCs with H_2O_2 for 6 to 24 h resulted in a dose- and time-dependent increase of apoptosis. Pre-treatment with pioglitazone (10 μ M, 24h) prevented H_2O_2 -induced apoptosis ($20.6 \pm 7.7\%$ vs $46.4 \pm 11.3\%$ apoptotic cells, Annexin-V FACS). Similarly, quantification of EPC apoptosis by DAPI staining showed TZD-mediated protection ($19.3 \pm 10.4\%$ vs $68.7 \pm 17.2\%$ apoptotic cells). The inhibition of EPC apoptosis by TZD was abolished in the presence of the PI3K inhibitor LY294002 but not by LNMA.

Conclusion: The PPAR-γ agonist pioglitazone upregulates the number and functional capacity of endothelial progenitor cells. Pioglitazone prevents apoptosis of EPC in mice as well as in human EPC in a PI3K-dependent but NO-independent manner. Reduction of EPC apoptosis by TZD may be a potential beneficial mechanism for patients with vascular diseases.

P846 Hyperglycemia reduces endothelial progenitor cell adherence and differentiation in vitro



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Introduction: Hyperglycaemia is a major risk factor for the development of atherosclerosis. Reduced numbers of endothelial progenitor cells (EPCs) have been associated with an increased risk of coronary artery disease. In the present study we compared the effects of glucose alone, insulin alone and the combination of insulin + glucose on the ability of mononuclear cells to adhere and differentiate into EPCs in vitro.

Method & Results: Mononuclear cells (MNCs) were separated from peripheral blood of 15 healthy donors by Ficoll density gradient centrifugation. Isolated MNCs were suspended in endothelial basal medium supplemented with SingleQuots and 20% FCS and plated into fibronectin-coated 24-well plates. Cells were treated with either glucose (7, 12, or 22 mmol/L), insulin (0.01, 0.5, or 20 mg/ml) or glucose + insulin (12 mmol/L glucose plus either 0.001 or 0.01 mg/ml insulin) and incubated for 7 days. Control wells received no treatment. Non-adherent cells were removed by thorough washing with PBS on days 3, 6 and 7. Adherent cells were provided with fresh media (containing the relevant treatment) on days 3 and 6. Adherent cells were stained with 1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine-labeled acetylated LDL and FITC-labeled Ulex europaeus agglutinin I and Ulex Agglutinin on day 7. Dual stained cells were judged to represent EPCs and counted in 5 high-powered fields (hpf) per well. We found a significant reduction in EPC number (mean±SEM) with increasing doses of glucose (7 mmol/L: 47.2±11.3 cells/hpf, p=ns; 12mmol/L: 37.9±8.3 cells/hpf, p=0.0008; 22mmol/L: 27.4±5.3, p=0.0001) compared with control (54.2±12.6 cells/hpf). Increasing doses of insulin led to a significant increase in EPC number even at low doses (0.01 mg/ml: 44.8±4.4 cells/hpf, p=0.0001; 0.5mg/ml: 45.2±5.9 cells/hpf, p=0.0007; 20mg/ml: 51.72±5.9 cells/hpf, p=0.0012) compared to control (29.3±3.3 cells/hpf). The combination treatments showed no effect of insulin (0.001 mg/ml or 0.01 mg/ml) on the reduction in EPC numbers caused by 12mmol/L glucose (glucose alone 20.78±4.532 cells/hpf, plus 0.001 mg/ml 20.24±3.692 cells/hpf, plus 0.01 mg/ml 21.92±3.312 cells/hpf).

Conclusion: MNCs cultured in hyperglycaemic conditions exhibited impaired formation and adherence of EPCs. This effect was not reversed with the addition of insulin. Insulin treatment alone led to enhancement of EPC adherence and formation in vitro. Reduced formation and adherence of EPCs in vitro with hyperglycemia may reflect poor endothelial repair in vivo, which in turn could contribute to the increased risk of atherosclerosis seen in diabetes mellitus.

P847 Increased vascular expression of and enhanced platelet reactivity to fractalkine in type-II diabetic ZDF-rats



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Background: Diabetes is characterized by vascular inflammation and enhanced platelet reactivity. Both phenomena contribute to the exaggerated cardiovascular morbidity and mortality of diabetic patients. The chemokine fractalkine is expressed by inflamed endothelium, facilitates atherosclerotic lesion progression and induces platelet activation. We investigated whether type-II diabetic ZDF rats display enhanced vascular expression of fractalkine and whether their platelets show an exaggerated response to this chemokine.

Methods: We investigated 6-month-old male lean and obese ZDF-rats. Aortic fractalkine expression was determined by Western blotting. Platelet expression of the fractalkine receptor (CX3CR1) was assessed by flow cytometry. Surface expression of P-Selectin (CD62P) was measured after stimulation of platelets from lean and obese ZDF-rats with ADP (1µmol/L, 5µmol/L, 10µmol/L) and/or fractalkine (1µg/mL) for 10 minute.

Results: Aortic fractalkine expression was increased in obese vs. lean ZDF-rats. CX3CR1 expression on the platelet surface was significantly higher in platelets from obese vs. lean ZDF-rats. Stimulation of platelets from obese ZDF-rats with ADP resulted in significantly increased surface expression of P-Selectin compared to platelets from lean ZDF animals. Co-stimulation with fractalkine induced significantly higher P-Selectin expression in platelets from obese vs. lean ZDF animals.

Conclusion: We verified increased vascular fractalkine expression in obese ZDF rats. Platelets from obese ZDF rats showed significantly higher expression of CX3CR1 contributing to enhanced degranulation of diabetic platelets.

e-POSTER SESSION 1

P848 Repolarization variability identifies reduced-risk MADIT II patients with appropriate ICD therapy for ventricular tachycardia or fibrillation

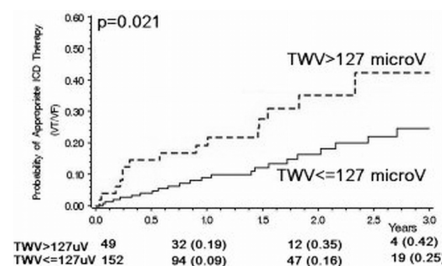


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QT variability has been reported to be associated with ventricular arrhythmias and sudden cardiac death. There is limited data regarding variability in T-wave morphology and its prognostic value. In this study, we present a novel approach for the measurement of T-wave variability (TWV) reflecting changes in T wave morphology and we investigate the prognostic significance of Holter-derived TWV in patients with and without ventricular arrhythmias requiring appropriate ICD therapy from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II).

Method: Study population consisted of 202 reduced-risk ICD patients after excluding patients with abnormal conduction or atrial fibrillation. TWV was measured based on amplitude variance of T-wave amplitude.

Results: During 2-year follow-up, 61 (22%) patients had appropriate ICD therapy for ventricular tachycardia or fibrillation. Patients with appropriate ICD therapy had higher levels of TWV measures than those without arrhythmic events. After adjustment for heart rate, ejection fraction and significant clinical predictors of arrhythmic events, a Cox proportional-hazards regression model revealed that dichotomized TWV values were predictive for ventricular tachyarrhythmias requiring appropriate ICD therapy (HR: 2.3, CI: 1.2-4.5, p=0.01). Based on the comprehensive testing TWV value above 127µV is predictive for arrhythmic events in MADIT II population (see Kaplan-Meier plots).



TWV in reduced-risk ICD MADIT II pts

Conclusion: Our newly designed method for the assessment of repolarization variability in ambulatory Holter recordings detected transient variability of T-wave morphology, which was predictive for ventricular tachyarrhythmias in the reduced-risk subset of MADIT II population.

P849 QT dispersion: what clinical implications in old patients?



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Background: In general population the dispersion of QT interval (dQT) is a predictive index for cardiovascular events and cardiac arrhythmias. In the elderly the clinical significance of dQT is not already clear. The aim of the study is to identify clinical and pharmacological factors related to a high dQT.

Methods: 750 subjects consequently recruited during ambulatory cardiogeriatric visits from september 1st, 2000 to March, 30th, 2005, were submitted to physiologic, clinical and pharmacologic history, including evaluation of comorbidity by means of Cumulative Illness Rating Scale (CIRS), antropometric evaluation, standard 12-leads ECG, and measurement of heart rate variability (HRV, index of autonomic nervous system activity). QT interval was measured in almost 9 leads from the 12-lead ECG (Archimed Instrument, 3.1 version, ESAOTE); dQT was defined as the difference between the longest and the shortest QT. 157 patients were excluded because of missing data; 593 subjects (mean age 75.4 ± 6.6 years, 42% males) were divided in two groups according to dQT value: dQT<80 msec, N=514 or dQT>80 msec, N=79 (80 msec is the 75° percentile).

Results: There were no differences between the two groups in terms of age, sex, and antropometric variables. Heart rate (76.6 ± 13.4 vs. 69.8 ± 13.1 bpm, p<0.001), systolic (160.4 ± 34.2 vs. 155.7 ± 23.4 mmHg, p=0.039) and diastolic blood pressure (92.1 ± 14.1 vs. 87.8 ± 13.1 mmHg, p=0.012) are higher in patients with dQT>80. HRV is lower in the group with dQT>80 (8.7 ± 5.4 vs. 10.9 ± 7.9 bpm, p=0.018), while comorbidity score is higher (CIRS score 8.4 ± 3.7 vs. 7.9 ± 3.6, p=0.007). Patients with high dQT took a lower number of ace-inhibitors (19.7% vs. 34.6%, p=0.009) and calcium channel blockers (21.9% vs. 34.2%, p=0.016). Multivariate analysis shows a significant association between dQT>80 and uncontrolled hypertension (p<0.0001), high comorbidity (p=0.023), above all in the presence of coronary heart disease (p=0.019), and reduced HRV (p=0.038), while ace-inhibitors (p=0.008) and calcium-channel blockers (p=0.012) display a protective effect.

Discussion: High dQT is associated with negative markers of health: uncontrolled hypertension, high comorbidity, reduced HRV, and low use of ace-inhibitors and calcium-channel blockers. This marker of "cardiac instability", that can be easily achieved, identifies an old population at risk of adverse events.

P850 New algorithm for arrhythmogenic focuses localization in patients with right ventricular outflow tract arrhythmias



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Premature ventricular contractions (PVCs) and ventricular tachycardia (VT) ECG morphology are proposed to localize the site of radiofrequency ablation (RFA) from the right ventricular outflow tract (RVOT). Aim. At the first step an ECG algorithm to localize the arrhythmogenic focus (Afo) in RVOT was designed. In the next step this algorithm was verified in prospective study.

Methods: Analysis of ECG morphology of PVCs and VT was performed in 30 pts (25 women), age 42.4 ± 10.5 , after RFA of Afo in RVOT. PVCs in 11 pts, VT in 5 pts, PVCs+VT in 14 pts were recorded. In the first step ECG data and fluoroscopic RVOT sites of RFA were combined to gain the characteristic QRS morphologies for exact sites of successful ablation (first 16 pts). Q, R and S waves < 0.5 mV in 12-lead ECG were coded as q,r,s and waves ≥ 0.5 mV as Q,R,S. This own algorithm was used to recognize Afo in following 14 pts by two independent cardiologists.

Results: First step: an algorithm is presented in table. Second step: Concordant ECG and RFA Afo locations were achieved: in all 14 pts in horizontal zones and in 13 pts in vertical zones. In overall 30 pts no Afo discordances were noted in horizontal zones. In vertical zones Afo location was concordant in 28 pts.

ECG leads	Vertical zones: 1,2,3		
	1	2	3
I	r/R	rs, rs', qr	qs/QS
V1-V6	superior transition from QS or r<s in V1 into r,R or R>s in V4	Horizontal zones: superior, intermediate, inferior intermediate R=S(r=s) in V4	inferior transition from r<s in V4 into r,R in V6

Conclusions: Our data shows that simple ECG algorithm based on PVCs morphology precisely localizes the Afo in RVOT. This analysis should be applied before RFA to shorten and simplify procedure.

P851 Analysis of high-frequency mid-QRS components is highly sensitive to myocardial ischemia caused by intra-coronary balloon occlusion

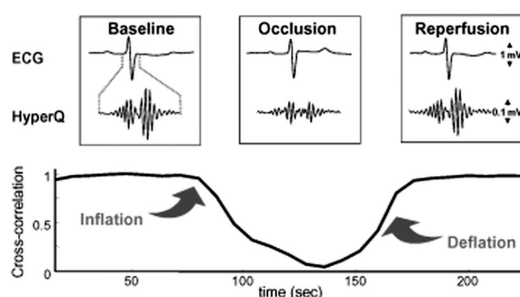


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Typical detection of myocardial ischemia focuses on changes in the repolarization phase of the ECG manifested in the ST-T segment. However, ischemia also induces changes to the depolarization phase, which can be quantified by analyzing the high-frequency content of the mid-QRS complex (HF-QRS). Our aim was to test this technique in detecting ischemia caused by short intra-coronary balloon occlusions and compare it to conventional ECG interpretation.

Methods: High resolution ECG was acquired and the HyperQ signal representing HF-QRS data derived using the HyperQ™ System (BSP, Israel) in 34 patients undergoing coronary angioplasty (16 LAD, 10 RCA, 8 LCX). Two epochs were defined for the first balloon occlusion: (i) 60 s baseline before inflation and (ii) immediately before deflation. Changes in the HyperQ signal and in the ST level were measured before deflation relative to baseline. Changes in the HyperQ signal were quantified by cross-correlation technique. HyperQ signal changes were considered significant if larger than three times the standard deviation of the signal during baseline.

Results: Occlusion duration was 68 ± 16 s. Typical HyperQ response to occlusion included marked changes in both the intensity and morphological features of the HyperQ signal, manifested in reduction of the correlation function (see fig-



HyperQ analysis during occlusion

ure). Significant HyperQ changes were found in 32 patients (94%). In contrast, significant ST changes were observed in 15 pts (44%, $p < 0.01$).

Conclusions: Intra-coronary balloon occlusion induced marked changes to the HyperQ signal. HyperQ-based ischemia detection scheme was found more sensitive than traditional ECG analysis. HyperQ analysis may allow improved diagnosis and monitoring of ischemia.

P852 Study of QT dispersion in children treated with anthracyclines for malignant hemopathies



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Purpose: To investigate the utility of electrocardiographic study of QT and QTc dispersion, in children with malignant hemopathies treated with anthracyclines, to correlate these with other cardiotoxicity signs of chemotherapy. Materials and methods. Patients: 40 patients, aged between 2-18 years, with malignant hemopathies, treated with anthracyclines. All patients have been clinically examined; we use Doppler echocardiography to evaluate left ventricle systolic and diastolic function, and surface electrocardiography to manually measure the QT interval, on three successive cardiac cycles, the values of QT dispersion (difference between the maximum and minimum QT interval) and corrected QT dispersion (Bazett's formula). Dispersion of QT and QTc interval in these patients was compared to similar values from 20 healthy children without cardiovascular history.

Results: The increase of QT and QTc dispersion in patients who received treatment with anthracyclines comparative to the control lot, was revealed in 73% cases, usually in those which had a cumulative anthracyclines doses over 400 mg/m², with medium values of QTD: 53.33 ± 10.18 msec and QTcD: 66.28 ± 12.8 msec. The increased dispersion of QT and QTc intervals was highlight most frequently in cases with echocardiographical signs of anthracyclines cardiotoxicity, even in cases with only diastolic dysfunction of left ventricle.

Conclusions: The significant incidence of increasing the QT and QTc dispersion in patients who received treatment with anthracyclines and the correlation with cumulative anthracyclines doses and echocardiographical modifications, especially in diastolic dysfunction, recommend currently investigation of QT dispersion as an earlier marker for cardiotoxicity of anthracyclines.

P853 Electrical and morphological atrial adaptations in hypertensives with paroxysmal atrial fibrillation



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Purpose: Essential hypertension and atrial fibrillation quite often coexist and due to their increased risk for cardiovascular events, they both constitute major targets for primary intervention. In this endeavour to clarify the entangled pathophysiological pathways, the present study was conducted to reveal any plausible interrelationships of the atrial electrical and morphological properties of the hypertensive heart in the setting of paroxysmal atrial fibrillation (PAF).

Methods: We studied 46 consecutive essential hypertensive subjects (aged 64 years, 22 men, office blood pressure (BP) $144/86$ mmHg) with a history of paroxysmal atrial fibrillation and no other evident comorbidity and 49 consecutive essential hypertensives without any evidence of PAF, matched for age, sex and BP. Standard 12-lead electrocardiograms (ECG) were recorded from all included subjects while on sinus rhythm. Simultaneously, a complete conventional and tissue doppler imaging (TDI) echocardiographic study was performed. Left Ventricular (LV) diastolic function was estimated by TDI, averaging the diastolic mitral annular velocities measurements.

Results: The two groups were similar regarding demographics but compared to those without PAF had a longer duration of hypertension (5 ± 1 vs 2 ± 1 years, $p < 0.05$), and showed significantly increased relative wall thickness (0.46 vs 0.44 , $p < 0.05$), left atrial volume indexed for body surface area (LAV index) (23.63 ± 7.9 vs 19.68 ± 3.7 ml/m², $p < 0.05$) and lower Em (7.5 ± 1.6 vs 8.4 ± 1.4 cm, $p < 0.05$) and Em/Am values (0.8 ± 0.11 vs 0.9 ± 0.38 , $p < 0.05$). Concerning their ECG findings hypertensives with PAF did not differ except from the significantly longer duration of P wave and PR interval (124 ± 18 vs 111 ± 11 ms, and 177 ± 22 vs 155 ± 21 ms, both $p < 0.001$).

Conclusions: Hypertensive subjects with a history of PAF have in parallel significantly higher LAV index values, worse TDI-detected LV diastolic dysfunction and significantly elongated duration of P wave and PR interval. Although the underlying pathophysiological mechanisms of this vicious circle are partially understood, this association merit further investigation through interventional prospective studies.

P854 Spectral and nonlinear dynamics of heart rate variability after repair of Tetralogy of Fallot



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It is known that patients (pts) after Tetralogy of Fallot (TOF) repair may have an increased risk of arrhythmic events. The aim of the study was to evaluate the effects of TOF repair on spectral and nonlinear dynamics measures of heart rate variability (HRV).

Methods: Nineteen pts with TOF repair (mean age 8.8 ± 3.5 years) and 21 pts with repair of ventricular septal defect (VSD, mean age 8.3 ± 2.7 years) entered study. In the TOF group 15 pts underwent repair with transannular patch, 4 pts - right ventricular outflow patch and pulmonary regurgitation was found in 8 pts. All pts underwent 24-hour Holter monitoring before and 4-6 days after repair with assessment of time-domain (SDNN, SDANN), frequency-domain (ULF, VLF, LF, HF and TP) and nonlinear (Poincare plot - SD12 ratio) measures of HRV.

Results: Spectral and nonlinear measures of HRV reduced after repair in TOF pts ($p=0.0001$ for all), while VSD pts had reduction of SDNN and SDANN ($p=0.0001$ for both), VLF, LF and HF ($p=0.001$), SD12 ratio ($p=0.0001$) and increase in LH/HF ratio ($p=0.02$). Comparison of both groups after repair showed differences in measures of overall and long-term variability between pts with TOF and VSD ($p=0.0001$ for SDNN and SDANN, $p=0.01$ for TP and $p=0.002$ for VLF).

HRV measures				
	TF	VSD	P	
SDNN, ms	before	123.8 $\pm$ 27.0	119.9 $\pm$ 20.8	ns
	after	53.7 $\pm$ 19.8***	75.5 $\pm$ 12.6***	0.0001
SDANN, ms	before	105.8 $\pm$ 25.2	101.6 $\pm$ 7.5	ns
	after	42.2 $\pm$ 20.4***	67.2 $\pm$ 13.2***	0.0001
ULF, ms2	before	343.3 $\pm$ 325.9	1313.7 $\pm$ 1826.2	0.02
	after	350.4 $\pm$ 256.3	1006.0 $\pm$ 1890.9	ns
VLF, ms2	before	1945.6 $\pm$ 1306.9	2118.2 $\pm$ 1157.3	ns
	after	470.7 $\pm$ 305.7***	1012.1 $\pm$ 643.0**	0.002
LF, ms2	before	723.5 $\pm$ 514.8	803.9 $\pm$ 646.5	ns
	after	209.2 $\pm$ 156.9***	261.1 $\pm$ 202.9**	ns
HF, ms2	before	659.3 $\pm$ 461.8	518.1 $\pm$ 415.8	ns
	after	100.2 $\pm$ 63.3***	135.4 $\pm$ 142.6**	ns
TP, ms2	before	3163.9 $\pm$ 2014.4	2055.0 $\pm$ 1315.5	ns
	after	1127.4 $\pm$ 613.6**	2243.1 $\pm$ 740.8	0.01
LF/HF ratio	before	2.5 $\pm$ 2.9	1.7 $\pm$ 0.8	ns
	after	2.4 $\pm$ 2.8	3.8 $\pm$ 3.9*	ns
SD12	before	0.27 $\pm$ 0.04	0.31 $\pm$ 0.08	ns
	after	0.19 $\pm$ 0.04***	0.22 $\pm$ 0.07***	ns

*** - $p=0.0001$, ** - $p=0.001$, * $p=0.02$ for intragroup differences before and after operation

Conclusion: HRV reduced significantly soon after repair of TOF and VSD. Whether low overall and long-term HRV in TOF pts is related to structural, hemodynamic features of the defect, repair technique and thus contributes for risk of arrhythmia further studies should be addressed.

P855 Long-term outcomes of left bundle branch block in high-risk survivors of acute myocardial infarction: the VALIANT experience



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Purpose: In survivors of acute myocardial infarction (MI), left bundle branch block (LBBB) is associated with adverse outcomes including risk of death at 1 year. To determine whether LBBB is an independent predictor of long-term fatal and non-fatal outcomes in acute MI patients, we reviewed data from the VALSartan in Acute myocardial infarction (VALIANT) trial.

Methods: In VALIANT, 14,703 patients with left ventricular dysfunction, heart failure (HF), or both were randomized to valsartan, captopril, or their combination a mean of 4.9 days after MI. Baseline electrocardiogram (ECG) data were available from 14,259 patients. We assessed the predictive value of LBBB for death and major cardiovascular outcomes using a Cox proportional hazards model, adjusting for 37 baseline covariates including ejection fraction.

Results: Patients with LBBB ($n=608$; 4.2%) were older and had more comorbidities compared with patients without LBBB ($n=13,651$; 95.8%). At 3 years of follow-up, patients with LBBB had increased adjusted risk of death (hazard ratio [HR] 1.3; 95% confidence interval [CI], 1.1-1.5), cardiovascular death (HR 1.4; 95% CI, 1.2-1.7), HF (HR 1.3; 95% CI, 1.1-1.6), MI (HR 1.5; 95% CI, 1.2-1.9), and composite of death, HF, or MI (HR 1.4; 95% CI, 1.2-1.6).

Conclusions: In patients surviving acute MI, the presence of LBBB at baseline was an independent predictor of all major adverse cardiovascular outcomes during the 3 year follow-up period even after adjusting for age, ejection fraction, comorbidities, and other infarct characteristics. This suggests a need for more aggressive treatment strategies and closer follow-up in these high-risk patients.

P856 Prospective randomized multicenter comparison of a simplified ICD homemonitoring follow-up compared to a conventional regimen in MADIT II patients (REFORM trial)



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Background: The number of patients with ICD implantation for primary prevention is increasing. A conventional 3 monthly follow-up regimen may exceed health-care resources. The REFORM trial is a prospective, randomized multicenter study comparing a simplified homemonitoring ICD follow-up against a conventional regimen in MADIT II patients.

Methods: 126 patients (90% men, 10% women; 62 ± 10 Jahre) with coronary artery disease (previous myocardial infarction > 1 month) and an EF < 30% received ICD implantation for primary prevention (116 single chamber ICDs, 10 dual chamber ICDs). All ICDs were equipped with homemonitoring technology. 3 months after implantation the patients were randomized towards a simplified homemonitoring based follow-up (12M = one consultation in the ICD clinic per year only) or a conventional follow-up (3M = one consultation in the ICD clinic per 3 months). The primary endpoint analyzed the number of additional unplanned consultations in the ICD clinic in each group. The secondary endpoints studied total follow-up costs, patients' quality of life (SF-36) and total mortality.

Results: The average follow-up time measured 372 days (92-702 days). Left ventricular ejection fraction was $25 \pm 6\%$. Distribution between NYHA class I to IV was as followed: NYHA I = 6%; NYHA II = 52%; NYHA III = 42%; NYHA IV = 0%. During the study period 93 additional unplanned consultations in the ICD clinic occurred. Of those 40 (43%) occurred in the 3M group and 53 (57%) in the 12M group ($p=0.092$). Of the 93 unplanned consultations 12 (13%) were initiated by the patient and 81 (83%) by the supervising physician ($p=0.001$). Of the 12 patient initiated additional follow-up visits 2 (17%) occurred in the 3M group and 10 (83%) in the 12M group ($p=0.04$). Of the 81 physician initiated additional follow up visits 38 (46%) occurred in the 3M group and 43 (54%) in the 12M group ($p=0.125$).

Conclusions: A simplified 12 monthly homemonitoring based ICD follow-up does not create a significantly higher number of additional unplanned consultations in the ICD clinic than a conventional 3 monthly follow-up regimen. However, patient initiated additional consultations occurred significantly more frequent in the 12 months follow-up regimen.

P857 Treatment related electrocardiographical changes in patients with chronic thromboembolic pulmonary hypertension undergoing thromboendarterectomy



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Background: Electrocardiographic (ECG) changes during acute phase of pulmonary embolism are well described, contrasting with only a few data about ECG pattern following successful treatment of chronic thromboembolic pulmonary hypertension (CTEPH). The aim of our study was to compare ECG before and after pulmonary thromboendarterectomy (PTE). Moreover correlations between the resolution of echocardiographical signs of pulmonary hypertension with ECG were assessed.

Methods: Fourty three CTEPH patients (33 male and 10 female, mean age 51 ± 12.9 years, functional class WHO II/III/IV: $n=2/27/14$, with mean pulmonary artery pressure MPAP 49.3 ± 9 mmHg before PTE were observed. We assessed 12 standard leads ECG and transthoracic echocardiography before PTE, 0-6 months, 6-16 months and more than 24 months after PTE. Ten different ECG signs of right ventricle overload and hypertrophy were assessed.

Results: All the patients had electrocardiographic abnormalities. The most common ones before PTE were: right axis deviation (69%), T wave inversion in precordial leads V1-V4 (64%), negative T wave in II,III,aVF (51.2%), signs of right ventricle hypertrophy RVH (48.7%), S₁Q₃T₃ (46.1%), clockwise rotation of the heart (43%) and nRBBB (39%). After operation MPAP decreased to 27.9 ± 8 mmHg, echocardiographic signs of pulmonary hypertension decreased and remind low. Negative T V1-V4 in post-operative period disappeared, in contrast the most ECG signs persisted, consisting of negative T waves II,III,aVF (51.2%), nRBBB (43.2%), S₁Q₃T₃ (35%). At long term follow-up after PTE both nRBBB (48%) and S₁Q₃T₃ (46.1%) were still very common. Presence of signs of right ventricle hypertrophy in ECG was related to right ventricle dimension in echocardiography ($p=0.03$). P pulmonale was related to right ventricle dimension ($p=0.03$) and acceleration time of RV ejection on Doppler-echocardiography ($p=0.02$). There was no relation between degree of pulmonary pressure assessed from tricuspid jet velocity and ECG signs of right ventricle overload.

Conclusions: All the patients with severe CTEPH have electrocardiographical abnormalities and consist of right axis deviation, negative T wave in precordial leads V1-V4 and negative T wave in II,III,aVF. An nRBBB and S₁Q₃T₃ are the most common abnormalities persisting despite successful PTE during long term observation while negative T in V1-V4 virtually disappear. Right ventricular di-

astolic dimension may be the main parameter determining ECG pattern among patients with CTEPH.

P858 Cardiac remote telemetry for syncope: how long should we monitorize our patients?

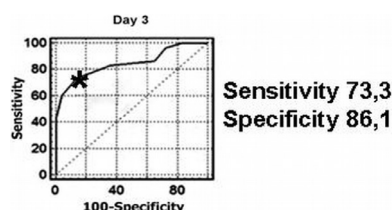


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Background: Diagnosing arrhythmias as cause of syncope is often difficult and telemetry (TL) may benefit hospitalized patients (PP). We describe the outcomes of PP admitted to a TL unit with the diagnosis of syncope and analyze how long TL should be maintained and when safely withheld.

Methods: We analyzed prospectively 102 PP, 52% men, 73±14 years-old. TL was controlled by trained nurses. Arrhythmias with clinical significance (guided therapy or use of diagnostic test), transfers to intensive care unit (ICU) and mortality were documented. Arrhythmias considered: atrial fibrillation/flutter of new diagnosis, ventricular fibrillation/tachycardia, sick sinus syndrome, extreme bradycardia, asystole >3 seconds, second and third-degree AV-block. Descriptive statistics and ROC curve analysis was performed to determine the moment of higher diagnostic accuracy.

Results: Mean stay on TL was 4,8±2,7 days. 30 PP (29,4%) presented events. The mean time to event was 2,3±1,8 days. All the events occurred in the first 7 days and those that conditioned ICU transfer occurred in the first 4 days, it occurred in 15 PP (14,7%) principally related with extreme bradycardia and third-degree AV-block. TL was diagnostic in 18 PP (17,6%) in which arrhythmias coincided with symptoms. No death was documented. ROC curve analysis showed that the third day had the best diagnostic accuracy with sensitivity 0,73 and specificity 0,86 (area under ROC curve 0,76) - see figure.



Conclusion: TL utility for syncope is not defined. In our study, 29% of the PP presented events, 17% were diagnosed of cardiac syncope and near 15% were transferred to ICU. These prospective results show that TL is useful and maybe lifesaving. Our findings also show that events related to ICU transfers occurred soon and maybe at least 3 days of TL are needed to retire it safely.

P859 Perfusion ratio: a new tool to objectively assess microcirculation perfusion after primary Percutaneous Coronary Intervention



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Introduction: TIMI III coronary flow after primary Percutaneous Coronary Intervention (PCI) in acute myocardial infarction (AMI) does not always correlate with adequate myocardial perfusion. Myocardial Blush Grade (MBG) is a subjective index to assess microcirculation integrity which correlates with patient prognosis.

Method: We have developed a new method to perform an automatic analysis of angiographical sequences. It provides a graphical representation of the myocardial dyeing pattern represented by a scatter-plot (fig.1) that has an 'U'-shape with two prominent arms (A and B). They represent, respectively, epicardial artery (A) and microcirculation dyeing (B). The ratio between the maximum value of A and B (Amax/Bmax), Perfusion Ratio (PR), reflects myocardial perfusion. We argue that changes in PR before and after PCI correlates with MBG. We have determined PR pre and post PCI in 12 patients with AMI in which TIMI III flow was achieved and with MBG 0, 1, 2 and 3.

Results: Fig. 2 shows the correlation between PR and MBG in those patients.

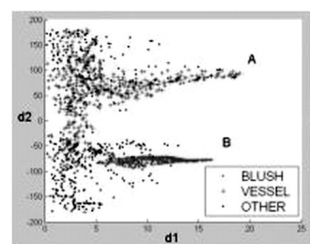


Fig1: Myocardial dyeing pattern.

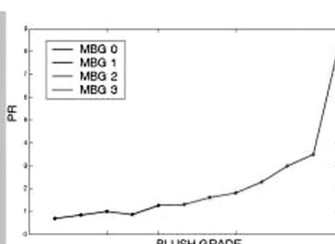


Fig2: Correlation between PR and MBG.

Conclusion: PR is an objective and automatic measure of myocardial perfusion in patients with AMI who after primary PCI achieve TIMI III flow pattern. PR could be a useful tool to determine microcirculation integrity in those patients.

P860 Noninvasive assessment of the transtricuspid pressure difference (TTPD) in humans



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Background: In the absence of a valvular stenosis, the Bernoulli equation is not suitable for calculation of transvalvular pressure gradients. We have recently developed and validated a new method for estimating intracardiac pressure differences by digital post-processing of color Doppler M-mode (CDMM) recordings. The aim of this study is to describe the normal values of TTPD in healthy subjects and assess the effect of pharmacological interventions on this measurement.

Methods: CDMM images of transtricuspid flow were obtained in 20 healthy volunteers (age 28±5 years old, 55% female) at baseline and during infusion of esmolol, nitroglycerin, acute volume overload and atropine. Images were post-processed using custom-built software that decodes flow velocity, solves Euler's equation, and overlays pressure gradient fields on the greyscale M-mode. TTPDs are obtained by spatial integration between the right atrium and right ventricle in these images. Four to 7 beats were analyzed in each hemodynamic phase. All images were acquired using a modified apical 4 chamber view during end-expiratory apnea.

Results: Images suitable for analysis were impossible to obtain in one subject. Mean ± SD values of baseline TTPD were 2.3±0.9 mmHg, ranging from 1.2 to 5.2 mmHg. Compared to baseline values, TTPD decreased significantly with esmolol and nitroglycerin infusion and increased with volume and atropine (see Table).

	Difference (95% C.I.) mmHg	p
Esmolol-Baseline	-0.4 (-0.6 to -0.17)	<0.05
Ntg-Baseline	-0.5 (-0.7 to -0.3)	<0.05
Volume-Baseline	0.2 (0.0 to 0.4)	<0.05
Atropine-Baseline	0.2 (0.1 to 0.4)	ns

Table. 95% C.I. and p values obtained for the true within subject difference by linear mixed-effects model analysis

Conclusions: This study provides the first values of the physiologic TTPD in humans. The effects of changes in heart rate, preload and relaxation on the TTPD can be characterized using this method. Therefore, color-processing of CDMM provides a method for understanding RV filling dynamics and can be readily used in the clinical setting.

P861 Intravascular ultrasound tissue characterization using radio frequency signals



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Objective: The main goal of this work is to assess the accuracy of three different techniques for tissue classification. A texture-based IVUS image technique is compared with two non-normalized radio frequency (RF) signals analysis techniques.

Method: Regarding the image classification based on texture, the features used are the co-occurrence matrix measures and the local binary patterns. Additionally, we experimented with RF signal, from which we obtained its power spectrum using Auto Regressive (AR) models. The first RF technique consists of using directly the data estimated by the AR model. The second one is based on extracting some descriptive features of the AR model such as maximum power, mean power, maximum slope among others. The classification technique used is Adaboost with 50 decision stumps.

The datasets consist of 30 regions of interest of each type of tissue from 5 different patients, selected with the physician's supervision. In both methods given a patient the IVUS image and its correspondent RF signal has been analyzed.

The classification was repeated 50 times in which the training and test data were randomly chosen. We used 90% of the samples for training and the rest for testing purposes.

Result: The preliminary results for the methods are: Firstly, for the texture based image classification, 79% of calcified tissue, 81% of soft tissue, and 81% percent of fibrosis are correctly detected. Secondly, using directly the estimation provided by the AR model the results show that 83% of calcified tissue, 90% of the soft tissue and 90% of fibrosis are detected. Thirdly, with the AR descriptors an 86% of calcified tissue, 90% percent of the soft tissue and 92% percent of fibrosis are well detected.

Conclusion We can conclude that the RF signal classification is more accurate than the texture-based image classification technique. However, we think that

these techniques can be used together to improve the tissue classification due to their statistical independence.

P862 Analysis of the changes in angiography local grey-level values to determine myocardial perfusion



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Introduction: Angiography has limitations to objectively determine coronary microcirculation. We present an image processing tool to assess it.

Method: We analyse the local variations in image grey values during the angiographic sequence. The signal obtained is the contribution of several phenomena: breathing, heart beating and dyeing. Each phenomenon has a distinctive repetition pattern (frequency), which range is determined by a statistical analysis. The lowest range yields the myocardial dyeing pattern (fig.1) for each image pixel.

For each graphic (fig.1) we obtain the maximum dyeing intensity (d1) and its time (d2) and we represent those measures as points in the x-y plane (fig.2).

Results: We have analysed 7 healthy right coronary arteries (RCA). The scatter-plots (fig.2) obtained have an 'U'-shape with two prominent arms (A and B) that represent, respectively, epicardial artery dyeing (A) and microcirculation dyeing (B). In these healthy RCA, both arms have the same length.

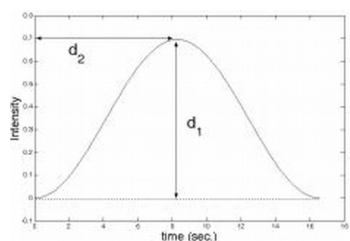


Fig1: Dyeing intensity.

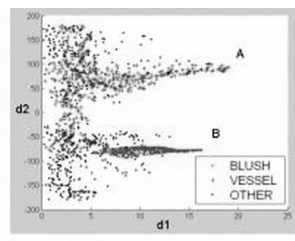


Fig2: Myocardial dyeing pattern.

Conclusion: The method proposed allows an objective assessment of the myocardial dyeing and thus a quantification of the coronary microcirculation in healthy RCA. Consequently, this tool could serve in a future to extract a quantitative measure of the myocardial perfusion grade.

P863 Integration of risk scores and B-type natriuretic peptide levels in the expert system for acute coronary syndromes



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Aim: to develop and evaluate the expert system (ES) for risk stratification and therapeutic decision making in acute coronary syndromes (ACS). Material and methods: ES was developed and was integrated with the database. Knowledge base contains rules according to the current guidelines. ES consists of: a) risk voting system which votes on risk according to 4 risk scores (SIMPLE, TIMI, GRACE, ZWOLLE) and on B-type natriuretic peptide levels (BNP); b) module suggesting the type of therapy (invasive vs. conservative); c) module which chooses pharmacotherapy. The system was evaluated on medical data of 149 consecutive patients.

Results: BNP showed strong predicting value for 30-day mortality - area under ROC curve was 0,892 (95% confidence interval [CI]: 0,831 - 0,937). BNP at level of 334 pg/ml had 90,0% sensitivity and 88,5% specificity. In multivariate analysis BNP levels had independent prognostic value. Areas under ROC curves for risk scores were for: SIMPLE - 0,859 (95%CI: 0,793 - 0,911), TIMI STEMI - 0,869 (95%CI: 0,804 - 0,918), GRACE - 0,819 (95%CI: 0,748 - 0,877), ZWOLLE - 0,9 (95%CI: 0,84 - 0,943). There was no good agreement between BNP levels and risk scores in risk stratification. In multivariate analysis incorporating BNP and each risk score separately, BNP remained independent risk factor for 30-day mortality. The addition of BNP into the model increased ROC. Classification error for risk scores and BNP were: for SIMPLE - 8,05%; TIMI - 4,70%; GRACE - 6,71%; ZWOLLE - 6,04%; BNP - 11,41%. Developed majority voting system had the lowest classification error - 4,03%. Changes in cut-off number of votes on high risk resulted in sensitivity (from 50% to 90%) and specificity (from 93% to 100%) changes. Full agreement was seen between physician-expert and ES in decision for the need of reperfusion therapy; good agreement in decision for the type of reperfusion therapy (kappa=0,65), good for angiotensin converting enzyme inhibitors (kappa=0,69), beta-adrenolitics (kappa=0,705), nitroglycerin (kappa=0,69), furosemide (kappa=0,72), very good agreement for aspirin (kappa=0,889) and full (kappa=1) for heparin.

Conclusions: 1) addition of BNP levels into popular risk scores improves risk stratification in patients with acute ACS; 2) developed voting system significantly decreased classification error to risk groups, changes in cut-off for votes on high

risk improved sensitivity or specificity for risk classification dependently on the reference level of cardiologic centre; 3) good and very good agreement was observed between ES and physician-expert in type of therapy (reperfusion, pharmacotherapy) choice.

P864 Concomitant use of statins and CYP3A4 inhibitor drugs: data from 380 000 statin users



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Background: Drug-drug interactions are estimated to represent 3-5% of all in-hospital medication errors¹ and are an important cause of patient visits to emergency departments². Atorvastatin (ATV), lovastatin (LOV), simvastatin (SMV) and SMV/ezetimibe (EZE) (but not fluvastatin [FLU], pravastatin [PRA] or rosuvastatin [RSV]) are significantly metabolized via cytochrome P450 3A4 (CYP3A4). CYP3A4 enzyme inhibitors may raise statin plasma concentrations, potentially increasing risk of adverse drug reactions.

Objective: To determine the number of patients in a US administrative claims database who had overlapping dispensed prescriptions for statins and CYP3A4 inhibitors.

Methods: Pharmacy dispensing information from the PharMetrics Patient-Centric database (an integrated set of fully adjudicated medical and pharmaceutical claims for all covered services) was used to identify medications dispensed to patients (aged ≥ 18 y) between January 2004-March 2005 to capture exposure status for the 12-month period of April 2004-March 2005. All available statins and known CYP3A4 inhibitors were assessed as well as CYP3A4 inhibitors listed in the Precautions sections of the US product labels for statins (eg, antifungal agents [itraconazole, ketoconazole], antibiotics [erythromycin, clarithromycin], anti-HIV agents [all protease inhibitors], calcium-channel blockers [verapamil], amiodarone, and cyclosporine).

Results: Of the 4 849 504 individuals ≥ 18 y in the database, 382 818 were dispensed statin prescriptions between April 2004-March 2005 based on the date of prescription fill and the number of days supply dispensed. Of these, overlapping prescription fills were recorded for 32% of statin users for any CYP3A4 inhibitor, and for 9.1% for CYP3A4 inhibitors listed in US statin labels. Among patients dispensed statins metabolized via CYP3A4, 8.9% had overlapping prescription fills for listed CYP3A4 inhibitors (8.7% ATV, 8.8% LOV, 8.8% SMV, 11.0% SMV/EZE). Among patients dispensed non-CYP3A4 metabolized statins, 10.1% had overlapping prescription fills for listed CYP3A4 inhibitors (10.7% FLU, 10.1% PRA, 9.7% RSV).

Conclusions: Based on this analysis, 1 in 3 statin users were concomitantly dispensed prescriptions for any of the CYP3A4 inhibitors, and 1 in 11 CYP3A4-metabolized statin users were concomitantly dispensed CYP3A4 inhibitors listed in US statin labels. Healthcare professionals should recognize the potential for drug-drug interactions resulting in adverse events.

1. Leape et al. JAMA 1995;274:35-43; 2. Raschetti et al. Eur J Clin Pharmacol 1999;54:959-963.

P865 Risk factor profile and outcomes of myocardial infarction patients registered in the Coronary Heart Attack Ireland Register (CHAIR)



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Aim: The aim of this study was to compare the risk factor profile and outcomes of patients with a discharge diagnosis of ST elevation myocardial infarction (STEMI) with that of patients with a discharge diagnosis of non-ST elevation myocardial infarction (non-STEMI) in the Coronary Heart Attack Ireland Register (CHAIR) cohort.

Methods: CHAIR is a prospective registry of all patients admitted with a confirmed or suspected acute coronary syndrome (ACS) to eight hospitals in the counties of Cork and Kerry. ACS comprises STEMI, non-STEMI and unstable angina. Information is extracted from hospital notes by dedicated registration officers and stored in an electronic database. CHAIR has been operating as a pilot in all 8 hospitals since mid 2003 and has recorded details on over 12,000 admissions comprising around 10,000 patients.

Results: Data are available on over 3,000 patients with a discharge diagnosis of myocardial infarction - 34% with STEMI and 66% with non-STEMI.

Among the non-STEMI patients, 65% are male, 29% are current smokers, 46% have a history of coronary heart disease, 50% have hypertension, 19% have diabetes and 32% have a family history of heart disease. The average age of non-STEMI patients is 71 years.

Among the STEMI patients, 69% are male, 41% are current smokers, 25% have a history of coronary heart disease, 35% have hypertension, 13% have diabetes and 33% have a family history of hypertension. The average age of STEMI patients is 66 years.

For non-STEMI patients, in hospital mortality was 10%, 70% of patients were discharged home (with 19% scheduled for coronary intervention) and 14% were transferred to another hospital.

For STEMI patients, in hospital mortality was 11%, 66% of patients were discharged home (with 22% scheduled for coronary intervention) and 17% were transferred to another hospital.

Conclusions: – Of patients admitted with a suspected ACS only 40% have an ACS discharge diagnosis.

– Of all ACS diagnosed patients only 25% have STEMI.

– STEMI patients are younger, have a higher prevalence of current smoking and a lower prevalence of diabetes and hypertension than non-STEMI patients.

– A similar proportion of STEMI and non-STEMI patients die during their hospital admission.

P866 Determinants of positive T-wave alternans after acute MI and early PCI



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T-wave alternans (TWA) has been proposed as a marker of susceptibility to ventricular tachycardia/fibrillation after acute MI. However, TWA value in the era of early primary coronary intervention (PCI) has not been clearly defined. The presence of TWA, as well as other established and proposed risk factors in the prospectively enrolled consecutive patients with first, only anterior wall MI undergoing PCI<12 hours from symptoms onset with TIMI 3 flow in LAD after procedure, treated according to current guidelines were assessed. Demographics, troponin I (Tn I), CKMB, ECG, arrhythmias, HRV, SAECHG, ECHO and treatment data were collected. At 30-day follow-up ECHO for ejection fraction recovery >5% (EF+) and TWA test were performed.

Results: We enrolled 96 pts (aged 58±11 years, 23 female/73 male) with mean EF 40.9±7.6% and time from symptom onset to reperfusion 303±193 minutes. At 30 day EF was 48.8±15.2%. Alternans was present in 22 pts (TWA+), absent in 62 (TWA-) and in 12 pts it was undetermined or not performed (due to AF or disability). There were no differences in gender, age, comorbidities, treatment, time from symptoms onset to reperfusion, intrahospital delay and extent of coronary lesions in both groups. TWA+ pts had higher maximum 6-24 hours levels of Tn I (44±8 vs. 30±19 ng/ml, p<0.05) and CKMB (398±147 vs. 264±182 UI, p<0.05), worse wall motion score index (1.57±0.17 vs. 1.37±0.15; p<0.05) and perfusion index (1.40±0.23 vs. 1.79±0.22; p<0.001) assessed by real-time myocardial contrast ECHO than TWA- pts, but not standard EF measures at baseline ECHO. All 30-day ECHO indices were significantly worse in TWA+ pts. EF+ was more frequently present in TWA- pts (p<0.05).

Conclusions: Presence of TWA could be predicted by perfusion and contractility indices and extent of myocardial necrosis but neither with ECG nor standard ECHO parameters.

P867 Surface electrocardiographic characteristics of counterclockwise typical atrial flutter in right precordial leads



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Introduction: Counterclockwise-isthmus dependent atrial flutter (CCWID-AFL) exhibit a typical morphology on the surface ECG. However, F wave morphology in right precordial leads has never been described.

Aim: To analyze the morphology of CCWID-AFL in right precordial leads.

Methods: Surface ECG recordings of right precordial leads (V3R to V6R) were obtained during atrial flutter (AFL). Assessment of all right precordial leads showed the highest F wave amplitude in lead V3R which was used for the analysis. The following data were analyzed: F wave polarity and F wave amplitude. In addition F wave activation time in V3R related to F wave in leads DIII and V1 was measured as follows (figure): Time from nadir of F wave in DIII to the positive maximum value in V3R (DIII-V3R) and time from the maximum positive value in V1 to the maximum positive value in V3R (V1-V3R).

Results: Nineteen patients with CCWID-AFL were included (18 males, age 66±14). In all patients entrainment mapping demonstrated the presence of a CCWID-AFL cycle length of 255±38 ms. All patients had AFL termination during ablation at the cavo-tricuspid isthmus. The F wave polarity in lead V3R showed two different patterns: a flat-positive morphology in 11 patients (58%) and a small initial negative with dominant terminal positive wave in 7 patients (42%). The

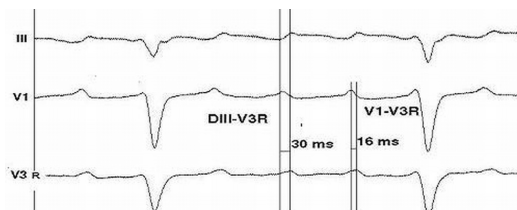


Fig. 1. Example

mean amplitude of the positive component in V3R was 0.16 mV (0.04 to 0.25 mV). The DIII-V3R and V1-V3R intervals were 44±18 ms and 14±10 ms respectively, being the predominant positive component of the F wave in V3R clearly delayed related to nadir of F wave in DIII and the maximum positive value in V1 in all patients.

Conclusions: F waves in surface ECG in CCWID-AFL have a predominant positive morphology in lead V3R and show a delayed activation time related to DIII and V1.

P868 Ambulatory ECG indications still actual



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Aims: The purpose of the study was the evaluation of how the ambulatory ECG indications were made in our Cardiology Department daily practice and how this investigation affects the patient treatment.

Methods: Six hundred and nine patients (58% male, age 16-91 years, medium age 60.7 years) perform an ambulatory ECG examination in our Cardiology Department between 01.08.2004 and 01.01.2006. The device used for 24 hours ECG monitoring was MT-100 and the software used for ECG analysis was MT-200 (Schiller AG, Switzerland). The referring physician indications were classified according to ACC/AHA Guidelines for Ambulatory Electrocardiography (Circulation 1999; 100: 886-893). Changes of the patients treatment after the examination imposed by results (permanent pacemaker implantation or changes in medical treatment) were noted. Primary source data were analyzed by Epiinfo 2000 statistical software, version 3.3.2.

Results: The most frequent indications in our study group were class IIb (60%). Of them, only 5% were followed by permanent pacemaker implantation and 7.5% changes in medical treatment compared to 23% and 10.5% respectively for class I indications. Presence of a syncope represents 46% of class I indications. In patients with a syncope classified as class I indication, univariate analysis showed a relative risk for pacemaker implantation of 3.6 (p<0.001) when a 2nd degree Mobitz II AV block was present, 1.5 (p=ns) for the association with an intraventricular conduction abnormality and 1.6 (p=ns) when sinus bradycardia or sinoatrial block was noted on the 12 leads ECG. Permanent cardiac pacing was indicated only for 14.8% of patients with a syncope classified as class IIb, compared to 24.5% if the syncope was judged as a class I indication (p=ns). Arrhythmia detection represents half of class IIb indications, but only 5% of evaluations were done for patients with heart failure and 1% for patients with acute myocardial infarction. Three percent of evaluations were made for evaluation of a permanent pacemaker activity.

Conclusions: Ambulatory ECG is an effective selection tool for patients who have permanent pace-maker implantation indication, results being as better as the ambulatory ECG indication is in a higher class. In daily practice, most of indications are in class IIb, situation which should also be discussed concerning the cost-effective relationship.

P869 Parameters of time domain analysis of high-resolution signal averaged ECG in patients with ankylosing spondylitis effectively treated with whole-body cryotherapy



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Ventricular late potentials (VLP) are low-amplitude, high-frequency (>25MHz) signals, which are caused by slow or delayed conduction of in the heart. VLP are recorded from the body surface with SAECHG (parameters: uQRS, RMS40, LAS40). Ankylosing spondylitis (AS) is a chronic rheumatic inflammatory disease primarily affecting the axial skeleton and para-articular structures. Extraspinal manifestations of the disease include aortic valve distortion, aortic valve regurgitation, aortitis, carditis. Anti-inflammatory effect was observed after sessions of cryotherapy. The aim of this study was to assess the preservation of parameters of high-resolution signal averaged ECG and ventricular late potentials in patients with ankylosing spondylitis effectively treated with whole-body cryotherapy. We assessed 7 male patients age ranging 42.5 (±5.4) suffering with ankylosing spondylitis for 17.3 (±6) years. Our trial was carried out on patients exposed to 10 cycles of two minute-lasting sessions of treatment. First the patients were re-

Table 1

	CRP		Sero-mucoid		IgA		IgG		IgM		uQRS		RMS40		LAS40	
	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
M.K. *	6.84	<6.00	1.20	1.09	260	250	876	837	58	60	121.0	122.0	18.24	23.43	42.01	40.00
P.J.	9.06	<6.00	1.15	1.10	330	222	1030	714	248	169	94.0	99.0	101.23	105.50	19.00	20.00
P.K.	7.92	<6.00	0.97	0.73	323	294	813	908	120	161	112.0	114.0	77.98	87.89	23.00	24.00
S.A.	<6.00	<6.00	0.85	0.79	313	288	939	948	66	81	115.0	115.0	81.98	100.73	25.00	24.00
D.Z.	>6.00	<6.00	1.18	1.16	222	205	946	768	39	38	126.0	125.0	83.11	111.46	29.00	28.00
N.R.	6.91	<6.00	1.07	0.82	198	262	1250	1110	89	69	115.0	112.0	55.36	70.44	24.00	22.00
F.J. *	8.10	5.00	1.24	0.76	—	—	—	—	—	—	119.0	122.0	23.05	23.49	40.00	37.00
p =	0.0009		0.0137		0.0006		0.001		NS		NS		NS		NS	

The level of inflammatory indicators, Ig, and parameters of high-resolution signal averaged ECG (before and after cryotherapy). 1. Before cryotherapy. 2. After cryotherapy. NS - statistically insignificant difference, *presence of ventricular late potentials.

cruited their full medical history was taken, they were physically examined and had SAECG, immunology test performed. The level of CRP, seromucoid was also measured. All examinations were done the day before and after therapy.

Results: see Table 1. A statistically significant decrease of inflammatory indicators earlier described in literature and confirmed in our study seems to be a marker of the efficacy of cryotherapy.

P870 Glue (toluene) abuse: electrocardiographic changes, increased QT dispersion and their relation with symptoms



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Purpose: Exposure to toluene, one of the major components of glue, can lead to cardiac arrhythmias and sudden sniffing death syndrome. QT dispersion is a useful risk marker for cardiac arrhythmias and sudden cardiac death. Aim of this study is to investigate the effects of glue abuse on ECG, QT interval and QT dispersion.

Methods: The present study included 39 patients with inhalant abuse and 34 healthy controls. Patients were divided into three groups: Group I, symptomatic glue abusers (n:20); group II, asymptomatic glue abusers (n:19); group III, healthy control subjects (n:34). PR, QRS and QT intervals, QT dispersion and corrected QT dispersion values were measured.

Results: PR interval were slightly longer in both symptomatic and asymptomatic toluene abusers than control group but it did not reach statistical significance. QT and QTc duration were greater in group I than in group II and greater in group II than in group III. QRS duration in group I was greater than group II and III. (93.5±6 ms, 90±8 ms and 85.6±7ms, respectively). The difference between group I and III reached statistical significance (p<0.0001). QT and QTc dispersion in both group I and II were significantly greater than group III (p<0.001) and also QT and QTc dispersion in group I was greater in group II. P<0.011 and p<0.022).

Table 1

Parameters	Group I	Group II	Group III	p
Age (Years)	21,3±0.9	21,4±0.5	22,7±1	NS
BMI(kg/m ²)	22,3± 3	23,8±4	24,6±4	NS
Systolic BP (mmhg)	124±6	126± 5	121±4	NS
PR ms	144,3±15	145,5±15	142,2±16	NS
QRS ms	93,5±6,3	90,2±8,7	85,6±7,3	0.02
QT Duration ms	386,1±13,5	375,8±13	366,4±13,1	0.0001
QTc Duration ms	483,1±17	466,5±21	456,6±17,2	0.0001
QT Dispersion ms	52,5 ±6,4	47,4±6,5	42±4,1	0.0001
QTc Dispersionms	60,4±7,4	54,5±7,5	48,4±4,7	0.0001

Values are n or mean, P values for global variance analysis. BMI, body mass index; BP, blood pressure

Conclusions: The findings demonstrate that increased QRS interval, QT and QTc dispersion in patients with either symptomatic or asymptomatic toluene abuser. The QT and QTc dispersion were also longer in symptomatic group than those with asymptomatic group.

P871 T-wave amplitude - QT duration correlation: a new tool for validation of TWA?



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Background: In 1999 Pastore et al. have shown that not every T-wave alternans (TWA) indicates the risk of SCD - concordant TWA (TWA-C) is benign, while discordant TWA (TWA-D) is a sign of an arrhythmic malignancy. Methods of differentiation between TWA-C and TWA-D in non-experimental settings have not yet been established.

Patients and methods: 88 pts with coronary artery disease and implanted ICD were studied. TWA occurrence and QT interval duration (defined as time from Q wave to the point of maximal amplitude of T-wave) were assessed.

Results: Positive TWA was found in 18 pts. In all these pts mean correlation of 0.7 between TWA amplitude and QT was found. In TWA-negative patients the relationship between QT and TWA was random. Out of TWA-positive patients, major events (ICD interventions or death) during follow-up (mean 10 months) occurred in 8. Mean correlation TWA-QT in these pts was as high as 0.8 while for TWA-positive and event-free pts correlation was only 0.6 (p<0.01).

Conclusions: 1. Differences in repolarisation pattern between event-positive and event-free pts with positive TWA were found. 2. Our preliminary results suggest that TWA amplitude-QT correlation analysis in TWA-positive pts may be helpful for differentiation between TWA-C and TWA-D.

P872 Automatic detection of atrial fibrillation and telemedical ECG transmission via a loop recorder



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Purpose: Various complications may be caused by atrial fibrillation, particularly thromboembolisms. The problem lies in detecting atrial fibrillation with certainty as a number of studies have shown approximately 70% of all episodes of atrial fibrillation to be asymptomatic.

Methods: A recently developed loop recorder (3100 BT, Vitaphone, Mannheim, Germany) with a new algorithm for automatically detecting atrial fibrillation (Search Atrial Fibrillation Algorithm) was tested clinically for the first time. The automatically recorded ECGs are transmitted using bluetooth technology to a cell-phone and from this cellphone to a telemedical service center (autotransfer) with no effort on the part of the patient.

The clinical tests included 25 consecutive patients with permanent atrial fibrillation and 25 patients with stable sinus rhythm and no evidence of atrial fibrillation. As a reference method, a Holter ECG monitor (Getemed, Teltow, Germany) was used to concurrently make recordings over 24 h.

Results: In all 25 patients with permanent atrial fibrillation, the atrial fibrillation was recognized immediately after placement of the loop recorder. The new method for automatically detecting atrial fibrillation and using telemedical ECG transmission could detect atrial fibrillation with a sensitivity of 100%. In the 25 patients with stable sinus rhythm, 98 false-positive ECGs were transmitted (3.9 per patient). The false-positive findings were caused mainly by large numbers of supraventricular extrasystoles (77.6%).

Conclusions: The new method allows atrial fibrillation to be detected even in asymptomatic patients. The use of telemedical transmission allows the patient to be mobile.

P873 Time to treatment is reduced by diversion of STEMI patients for primary percutaneous coronary intervention based on wireless prehospital ECG transmission directly to a cardiologists handheld device



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Purpose: Primary percutaneous coronary intervention (pPCI) is the preferred reperfusion method for patients with acute myocardial infarction. However, valuable time is lost transferring patients from a primary receiving hospital to a pPCI center. This study tests the hypothesis that time to pPCI can be reduced by wireless transmission of prehospital electrocardiograms (ECGs) directly to a cardiologist's hand-held digital device in patients with symptoms suggesting acute coronary syndrome.

Method: During a 2-year period all patients in the Copenhagen area with acute, non-traumatic chest pain had a prehospital ECG recorded in the ambulance, and transmitted via wireless technology directly to a cardiologist's hand-held device in a pPCI center. The function of the technology was evaluated, and transmission failures documented. Times of symptom onset, emergency call, ECG recording, hospital arrival and pPCI were obtained. All time intervals are presented as median values, and compared to historic controls from the Danish multicenter study, DANAMI-2.

Results: 606 patients had a prehospital ECG transmitted, and evaluated by a cardiologist, and 170 patients were redirected for pPCI based on ST-segment elevation. Additionally, 14 patients were rerouted for pPCI after admission to a primary hospital. Transmission was successful in approximately 90% of patients. Time from symptom onset to emergency call was 1 hour and 23 minutes (range 1 - 764 min), and ambulance response time was 6 minutes. Time from ECG recording to hospital arrival was 26 minutes, allowing the catheterization personnel to prepare for the pPCI procedure. Hospital arrival to pPCI was 27 minutes compared to 94 minutes in the DANAMI-2 historic control group (p<0.01).

Conclusion: Transmission of prehospital ECGs for evaluation by a cardiologist is an efficient technology for optimizing patient care by saving valuable time in patients with an acute myocardial infarction redirected for pPCI.

P874 Management of dyslipidemia: general practitioners compliance with clinical reminders and the synergism with cardiologist consultation. Lesson from the computerized community cholesterol control (4C)



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Background: Despite the existence of widely accepted guidelines for management of dyslipidemia and effective pharmacotherapy, there is a wide "treatment gap" as only a small proportion of patients with clinical atherosclerosis reach the secondary prevention LDL-C target levels.

Methods: Our study is a descriptive analysis of an intervention program. In the

setting of 4C intervention project, patient-tailored clinical reminders (CRs) were generated by a computerized clinical decision support system (CDSS) regarding patients with clinical atherosclerosis related diagnoses. 1656 patients were recruited upon discharge from "SorokaMedicalCenter" between 9/2002-5/2003. CRs recommending lipid panel screening or statins prescription were mailed to their general practitioners (GPs) in 40 "Clalit Health Services" primary care clinics. The intervention was aimed at improving GPs' adherence to lipid management guidelines. We analyzed compliance patterns with the CRs, as well as patients' clinical outcomes after one year follow up.

Results: Overall compliance with the CRs was 40.9%. Higher compliance rate was associated with lipid panel screening reminders compared to other recommendations (62.2% vs. 18.6%, $p < 0.001$). Among patients requiring pharmacotherapy initiation or up-titration, linear association was found between initial patients' LDL-C levels and compliance with the recommendation ($p = 0.011$). Adjusted to various patient-related factors, patient's visit at a cardiology clinic was found to be an important predictor of compliance with reminders regarding drug therapy (Adjusted Odds Ratio [AOR] = 2.42; 95% Confidence Interval: 1.34 - 4.40). One year follow up showed correlation between GPs' rate of compliance and the percent of their patients that reached LDL-C target levels ($R = 0.35$, $p = 0.003$).

Conclusions: The initial GPs' adherence to lipid management guidelines was poor and moderately improved by the computerized intervention program. The synergism between lipid level monitoring improvement by the 4C intervention and collaboration with cardiologists, shown to improve proper titration of drug therapy, can further enhance adherence to dyslipidemia treatment guidelines.

P875 Assessment of the benefit of pervasive self-care ECG recording in arrhythmogenic patients



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Introduction: The early detection of arrhythmic events is one of the coming challenges of telemedicine to decrease the risk of cardiac sudden death. To reach this objective, the European EPI-MEDICS project developed a personal ECG monitor (PEM) of professional quality which can be easily used by the patients themselves at home or anywhere.

Purpose: We present here the results of the medical evaluation of the use of 20 PEM prototypes which has been performed during several months in the Rhône-Alpes area.

Methods: A set of 116 patients gave their informed consent to take part in this evaluation. The recruitment was performed at their discharge from the arrhythmia department or from the intensive care unit of the cardiology hospital of Lyon, or following a consultation in rhythmology at the hospital. A PEM device was delivered to the enrolled patients with the advice to record themselves a PEM ECG each time they do not feel well, and to send back the PEM within 4 weeks. An oral explanation and a user manual were provided to the patients, and at the same time a technician recorded on each patient a PEM ECG and a standard digital 12-lead reference ECG. The recorded PEM-ECGs were retrieved from the PEM data cards when the PEM were returned to the hospital, and analyzed by two experienced cardiologists.

Results: In addition to very positive self-care procedures and PEM ECGs data quality assessment results, the main finding was the detection in 40% of the patients of the occurrence of 421 arrhythmia events (paroxysmal supraventricular tachycardia, atrial flutter, atrioventricular block, atrial bigeminy, atrial fibrillation and Wolf-Parkinson-White syndrome) that have been recorded at home by the patients themselves. Moreover, for 22% of these patients, despite several investigations (Holter recordings, ...), these events were never diagnosed before.

Conclusion: Thanks to the use of the PEM device at home, in situations where the patients suspected a cardiac problem, new ECG findings could be detected and managed. Our evaluation results show the benefit of setting-up new concepts of personalized eHealth in the hands of the patients themselves for improving their medical follow-up.

P876 Home management of old patients with chronic heart diseases: role of telecardiology and tele consultancy



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Background: Acute cardiovascular mortality has been significantly reduced thanks to scientific and technological advancements. This has lead simultaneously to a higher average age and an increase in the number of old people with chronic cardiovascular diseases. Such major health, social and economic consequences call for new management strategies. Health assistance in the elderly mainly regards chronic heart failure, untreatable chronic heart ischemia and arrhythmias. A new management model aims to improve patient home care by involving family doctors in assisting chronic cardiovascular diseases in elderly, especially for housebound patient. It is better to integrate cardiology department and family medicine with hospital promoted two-way counselling: a best fit hospital admittance and specialist examinations.

Materials and Methods: Pieve di Coriano (Mantua, Italy) Hospital's tele-electrocardiography and consultancy service at present follow 43.000 people of

whom 12.000 over 65 years, 3.070 over 75 years and about 1.000 over 90. About 40% of this population is affected by chronic cardiovascular diseases and heart failure is the main reason for hospitalization. Since February 2004 eighteen family doctors in the catchment area were supplied with 12 lead portable electrocardiographs connected by phone line to the terminal service in the cardiology department.

Results: 388 telecardiology EKG and teleconsultancies were carried out between February 2004 and December 2005 in patients over 65 years, 220 females (56.7%) and 168 males (43.3%), average age 82 ± 5 years. Reason for the demands may be divided into two groups:

1 - Follow-up of chronic heart failure with/without atrial fibrillation (199 patients; 51.2%)

2 - Recurrent assessment of chronic heart diseases: chest pain, near-syncope, non-specific symptoms (189 patients; 48.8%)

In the first group of 199 patients, 134 (67.3%) were found to be stable and ongoing therapy was confirmed, in 32 (16.1%) treatment was modified on-line and only 33 (16.6%) required further hospital investigation.

In the second group of 189 patients, only 58 (30.6%) required emergency hospital treatment, 23 (12.3%) required further non-urgent tests and in 158 patients (57.1%) no cardiac emergency was detected.

Conclusions: Preliminary results of this model of management for dealing with heart diseases confirm the validity of tele-cardiology in home managing chronically old sick patients and could reduce the need for further investigations and/or hospitalization.

P877 Experiences performing ward rounds with a mobile computer connected to a multimedia medical information system



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Background: The ward round is the central confluence point for all streams of information regarding the patients medical care within a hospital stay. We developed and evaluated an information system that facilitates the presentation of clinical documents, medical images, films and laboratory results on a mobile computer on rounds. What is the impact of such a system on daily rounds?

Methods: The project system called "Mobile Multimedia Medical Information System" (M³IS) accepts documents through DICOM and HL7 interfaces and provides a web-based client interface that allows for a quick and easy access to the system through a web browser. Access with mobile computers is made possible by using a wireless local area network (WLAN). To allow faster access to catheterization and echo films, the sequences were transcoded from the original DICOM format to the compressed MPEG-4 format defined by the Motion Picture Expert Group. In order to comply with data protection requirements, the system implements a powerful access control scheme.

Results: Prior to the implementation of the M³IS system the time spent on ward rounds was composed as follows: 41 minutes (min) information uptake, 30 min information processing, 8 min internal information transfer and 47 min of talking to the twelve patients on the ward. Additionally to the 126 min spent on rounds another 93 min per day were taken for preparing the round with collecting laboratory results and medical images. After the M³IS system has been installed, the total round time remains about the same (116 min). Significant time savings were observed in gathering information and preparing the round (66 min). During the round, time was saved for the information uptake (33 min) that could be spent with medical discussion, which is a vital aspect of information processing (35 min) and patient conversation (51 min).

Conclusion: Ward rounds with the M³IS system significantly improve the clinical information level by making most of the relevant information available via mobile computers. The greatest advantage is the availability of all films and images from the catheterization and the echocardiography laboratory as well as endoscopic images. These images give all ward physicians the primary examiner's detailed information and provides them with profound knowledge prior to advising the patient. Using the web browser to access the system, physicians from other departments or hospitals and general practitioners can share this information.

P878 Acute myocardial infarction home diagnosis in a region wide telecardiology network for public emergency health care service: an experience from Italy



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Background: We report data coming out from the first, the largest and the longest Italian region wide experience of telecardiology applied to public emergency health care. The network involved 154 crews of "118" emergency number that were equipped with CardioVox-P12 devices for 12 leads ECG recording and telephone transmission. Logistic support was furnished by Cardio-on-line Europe S.r.l. thanks to a grant by PfizerTM.

Methods: 15475 patients from all over Apulia (19.362 Km², 4 millions inhabitants) referred since October 2004 until November 2005 to "118" and underwent ECG

according to a previously fixed inclusion protocol. Data recorded were transmitted with mobile telephone to a call-center with a consultant cardiologist. Hospitalization or further cardiologic examination were disposed by emergency physicians on basis of ECG diagnosis and consultation.

Results Mean age was 65 ± 18 years; 73% of patients referred chest or epigastric pain, 10% loss of consciousness, 4% breathlessness, 3% palpitations. Acute myocardial infarction (AMI) was diagnosed in 2.2%. Peak in incidence of AMI was observed in autumn. Among patients with chest or epigastric pain, in 2.4% of cases ECG showed STEMI; patients with AMI referred chest pain in 76.5% of cases, breathlessness in 5.2%, palpitations in 1.16%, loss of consciousness in 7%, other symptoms in 5.2%. 5% of subjects referred to "118" <30 minutes after onset of symptoms, 35% between 30 m' and 3 hours, 52% 3-6 hours, 1% 6-12 hours, 6% >12 hours; out of 11.000 patients with chest or epigastric pain, thus 1.48% of patients was theoretically eligible for fibrinolysis or primary PCI. In this subset of patients telecardiology diagnosis consistently shortened delay to treatment. More than 35% of subjects with STEMI was more than 75 years old. 49.8% received "118" assistance in towns without coronary care unit (CCU); 46% of patients with STEMI was from small towns without CCU, thus benefiting from immediate diagnosis. Among these patients from small towns, 47% called "118" within 30 m' after onset of chest pain, 38% within 3 hours, thus further benefiting from a very early diagnosis of STEMI because of time to reach CCU or cathlab; similar time delay was recorded in bigger towns with CCU (43.3%+41.7%).

Conclusions: This first region wide leading experience showed feasibility and reliability of telecardiology applied to a public emergency health care. Lower number of improper hospitalizations and shorter delay in diagnosis process point out advantages yieldable applying telemedicine protocols also to large public emergency health care networks.

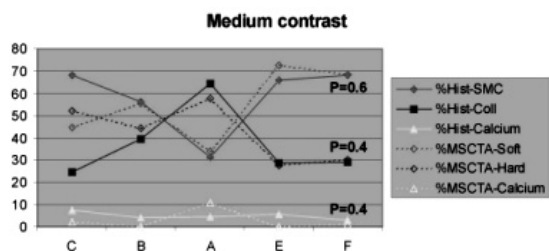
P879 A new automated method for quantitative coronary plaque compositional imaging applying non-invasive multi-slice computed tomography: an ex-vivo feasibility study

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Background: Multi-slice computed tomography coronary angiography (MSCT-CA) is making rapid progress into clinical practice. Although only recently introduced it seems to become one of the standard imaging tools for diagnosing patients with suspected cardiovascular diseases. The big advantage over coronary angiography is that MSCT-CA is capable of showing the coronary plaque too. However, would it be possible to quantify, besides measuring plaque dimensions, plaque composition by MSCT-CA as well?

Material and methods: An explanted human LAD was imaged with both MSCT-CA (Sensation 16, Siemens, Germany) with different concentrations of contrast and saline and optical coherence tomography (OCT). The high resolution of the OCT imaging technique, almost similar to that of histology and being approximately 7 μ m, was used to synchronize the MSCT data to the histology results. Histology was then performed at 5 different sub-segments of 15 histology slices each, making a total of 65 slices.

Results: The individual results of each sub-segment were averaged for both MSCT-CA and histology and are presented in figure 1. There were no statistically significant differences between both techniques. The measurements with saline instead of medium contrast concentration (HU=300) showed similar results. Only sub-segment C showed a deviation between the results caused by the limited amount of plaque present there, in this case difficult to image with MSCT-CA.



Conclusion: This ex-vivo non-invasive feasibility study of quantitative plaque compositional imaging by MSCT-CA showed promising results, it encourages further in-depth research in this field.

e-POSTER SESSION 2

P880 Non-invasive evaluation of coronary artery stent patency and in-stent restenosis with 64-slice CT coronary angiography: comparison with conventional angiography

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Purpose: Coronary stent implantation is a frequently applied treatment for coronary artery diseases. But in-stent restenosis can compromise the success of angioplasty, therefore coronary stent patency should be effectively monitored. A reliable non-invasive evaluation of coronary stents may be very helpful to eliminate repeated invasive procedures. The purpose of our study is to assess the role of multislice CT in the evaluation of coronary stent patency and in-stent restenosis.

Materials and Methods: 43 patients with 51 coronary stents, suspected for in-stent restenosis and scheduled for conventional angiography, were included in the study group. The CT examinations were done with a 64-slice CT scanner (Sensation Cardiac 64, Siemens, Germany). The imaging parameters were as follows: Slice collimation 64x0.6mm, rotation time 0.33sec, kV 120, mAs 900, pitch 0.2. 80 ml of non-ionic contrast material was injected with a rate of 5.5ml/sec followed by a 40ml saline chaser bolus. Automatic bolus tracking method was used to optimize the timing of the start of the acquisition. Scan time was approximately 10sec. Simultaneous recording of ECG permitted the retrospective reconstruction of axial images at different data acquisition windows. The evaluations were done by two radiologists blinded to the results of coronary angiography. Luminal low density filling defects were evaluated as intimal hyperplasia and narrowing more than 50% of diameter was considered as significant stenosis. Consensus reading was compared with coronary angiography as the standard of reference.

Results: In all patients, the image quality was eligible for the evaluation of stent patency. In 43 stents, conventional angiography demonstrated 11 occlusions and 14 in-stent stenosis. The rest 18 stents were normal. With CT angiography, all of the occluded stents and 12 of the in-stent restenosis were correctly demonstrated. 1 normal stent was misdiagnosed. According to these results, sensitivity, specificity, accuracy, positive and negative predictive values were 92%, 94%, 93%, 96% and 89% respectively.

Conclusion: Multislice CT angiography is an efficient and feasible non-invasive method to assess coronary stent patency and in-stent restenosis having high correlation with conventional angiography. Therefore, can be considered as an alternative especially for follow-up purposes.

P881 In vivo imaging of macrophage infiltration with N1177-enhanced computed tomography in atherosclerotic plaques of hypercholesterolemic rabbits

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Introduction: Vulnerable atherosclerotic plaques are characterized by their high density in macrophages. N1177 (Nanoscan Imaging) is a new computed tomography (CT) contrast agent formed of insoluble iodine molecules suspended in micelles, which are taken up by macrophages. The aim of this study was to image macrophage infiltration in vivo in atherosclerotic plaques of hypercholesterolemic rabbits with N1177-enhanced CT.

Methods: Atherosclerotic plaques were induced in the aorta of 4 New-Zealand White rabbits by double balloon injury (4 weeks apart) and 4 months of hypercholesterolemic diet. Two non-injured rabbits fed a chow diet were used as controls. A 64-slice CT of the aorta (n=6) was acquired before and 2 hours after intravenous injection of N1177 or the conventional iodinated contrast agent (iopamidol). Changes in signal densities in aortic wall after injection of contrast agents were compared to macrophage infiltration studied by immunohistochemistry (anti-RAM-11 antibody).

Results: A high density signal (Figure) was found on axial CT views in the aortic wall of all (4/4) atherosclerotic rabbits (increase of 11.2 ± 6.3 Hounsfield units; $p = 0.05$ vs. baseline), but in none (2/2) of control rabbits, 2 hours after N1177 injection. No detectable change in aortic parietal signal density was observed

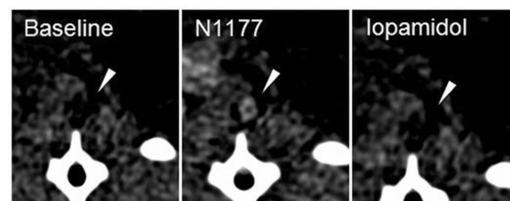


Fig. 1. Axial views of the aorta on CT

after injection of iopamidol, neither in atherosclerotic nor in control rabbits (6/6). An intense macrophage infiltration (RAM-11-positive) was found on aortic cross-sections corresponding to atherosclerotic plaques showing a high density signal on CT after N1177 injection.

Conclusion: Macrophage-rich atherosclerotic plaques can be detected in vivo in hypercholesterolemic rabbits with N1177-enhanced CT.

P882 Predictive value of coronary calcifications for future cardiac events in asymptomatic patients with diabetes mellitus: a prospective study over 8 years in 300 patients



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A reliable risk stratification is crucial for the efficient prophylaxis of coronary artery disease. The following prospective study determined the predictive value of coronary calcifications for future cardiovascular events in asymptomatic patients with diabetes mellitus.

We included 308 patients suffering from diabetes mellitus (176 men, 132 women, age 58.7 ± 13.3 years) in this study. On study entry all patients were asymptomatic regarding coronary artery disease and showed no signs of coronary artery disease in ECG, stress ECG or echocardiography. Coronary calcifications were determined with the Imatron C 150 XP electron beam computed tomograph. For quantification of coronary calcifications we calculated the Agatston score. Over a mean observation period of 8.2 ± 1.3 years we registered the event rate for cardiac death (CD) and myocardial infarction (MI).

During the observation period 30 patients suffered from MI, 13 patients died from acute CD. Thereby the Agatston score in patients that suffered from MI (593 ± 263) or died from CD (628 ± 293) was significantly higher compared to those without cardiac events (217 ± 185 , $p < 0.01$). An Agatston score above the 75. percentile was associated with an significantly higher annualised event rate for MI (3.7% versus 1.5%, $p < 0.05$) and for CD (2.3% versus 0.8%, $p < 0.05$) compared to patients with scores below the 75. percentile. No cardiac events were observed in patients with exclusion of coronary calcifications. The relative risk of future MI showed a high correlation to the initially determined Agatston score with a correlation coefficient of 0.91.

By determination of coronary calcifications patients at risk for future MI and CD could be identified within an asymptomatic population of patients with diabetes mellitus. On the other hand future events could be excluded in patients without coronary calcifications.

P883 Cardiovascular screening with multidetector computed tomography in type 2 diabetics



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Background: Eighty percent of type 2 diabetics (2D) die from cardiovascular disease and 75% of these, die from coronary artery disease (CAD). Non-invasive coronary angiography (N-ICA) with contrast-enhanced multidetector computed tomography (MDCT) permits direct visualization of the coronary artery tree. The aim of this study was to investigate the potential of MDCT for the evaluation of CAD among asymptomatic 2D (A2D).

Methods: A total of 45 patients (pts) (31 men, 14 women, aged 55.6 ± 7.5) with A2D underwent cardiac evaluation with exercise test and MDCT. MDCT included coronary calcium score (CCS), coronary calcium volumen (CCV) and N-ICA. In pts with significant findings a subsequent myocardial perfusion stress test was performed to consider coronary angiogram.

Results: Risk factors (RF) included: smoking in 19 pts (42%), hypertension in 28 pts (62%), hypercholesterolemia in 30 pts (67%), hypertriglyceridemia in 19 pts (42%) and mean body mass index was $29 (\pm 7.4) \text{ kg/m}^2$. Exercise test revealed ischemic ST changes in 4 pts (8%). Mean values for CCS were $134 (\pm 293)$, for CCV $104 (\pm 231)$ and for age and sex percentile (P) $48 (\pm 29\%)$. CCS > 80 was found in 14 pts (31%). P $> 75\%$ was present in 11 pts (24%). N-ICA revealed CAD in 27 pts (63%). Significant coronary lesions were noted in 7 pts (15%). Coronary angiography was indicated in all of them after a positive perfusion test. In 6 pts coronary revascularization was performed (13%). No correlation was found between others RF and MDCT findings.

Conclusions: Independently from others RF, CAD is highly prevalent among A2D

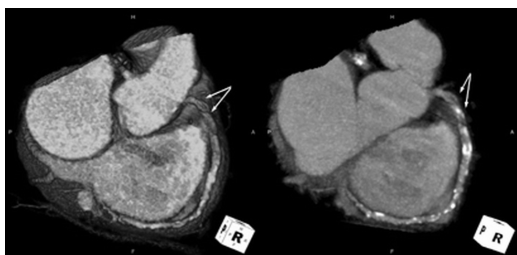


Fig. 1. Severe lesion at proximal RCA with MDCT

pts. A considerable number of A2D required coronary intervention. MDCT is a useful non-invasive tool for the screening of these high risk pts.

P884 Results of a validation study for a quantitative coronary CT angiography (QCCTA) analysis system



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Background: The high spatial and temporal resolution of 64-slice coronary CT angiography allows for the detection of coronary stenoses with high sensitivity and specificity. However, the analysis of coronary CT angiography studies is currently based on the visual estimation of the degree of lumen narrowing. An automated quantitative analysis package may offer more consistent and reproducible assessments of the coronary lumen than the variable visual assessment. Furthermore, the noninvasive quantification of total plaque burden may add prognostic information to a coronary CT study beyond the traditional assessment of coronary calcifications.

Methods: We developed a quantitative coronary CT angiography (QCCTA) analysis system which was implemented as follows: in a first step, a segmentation of the target vessel along an automatically defined vessel centerline was performed. Then, an automated contour detection of the lumen and vessel boundaries based on adaptive thresholds was implemented. Finally, a regional quantification of morphological parameters of the vessel such as luminal and wall areas was provided based on reformatted cross-sectional images. In a first in-vitro validation study we investigated the accuracy in lumen and vessel wall detection with the use of a vessel phantom. Using different plexiglass tubes, this phantom provided different vessel diameters (lumen diameter 2.7-4.7mm) and the vessel wall imitated the attenuation of predominantly fibrotic plaque tissue with approximately 90-100 HU. The tubes were filled with different contrast dye concentrations to mimic different clinical settings (range: 200-700HU). Data was acquired with a 64-slice CT system using different clinical acquisition protocols (tube voltage: 100kV and 120kV).

Results: The overall accuracy values (defined as difference between measured and true dimensions) were 0.3 mm^2 and 1.3 mm^2 for lumen and vessel areas, respectively. These accuracy values were independent of tube currents and contrast agent concentrations and corresponded to a 2.7% and 4.9% overestimation of the true lumen and vessel wall dimensions. The overall precision values (standard deviation of the differences) were 1.0 mm^2 and 2.1 mm^2 for the lumen and vessel areas, respectively. The interobserver variability was $0.1 \pm 0.1 \text{ mm}^2$ and $0.2 \pm 0.3 \text{ mm}^2$ for lumen and vessel area measurements, respectively.

Conclusion: We developed a QCCTA system which allows the accurate and reproducible extraction of quantitative parameters of CT angiography data sets in vessel phantoms. Further validation studies will demonstrate its accuracy in a clinical setting.

P885 Early characterization of atherosclerotic coronary plaques with multidetector computed tomography in patients with acute coronary syndrome. A comparative study with intravascular ultrasound



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Objectives: Non invasive coronary imaging with multislice computed tomography (MSCT) has been assessed in stable condition and with carefully selected exams to determine plaque composition, plaque burden and vascular remodelling. Accordingly, we sought to compare MSCT with intravascular ultrasound (IVUS) examination for the non invasive detection and characterization of atherosclerotic lesions in the early phase of acute coronary syndrome (ACS).

Methods: Twenty consecutive patients were prospectively studied with both 16-slice CT and 40 MHz catheter based IVUS, less than 48 hours after onset of symptoms. Coronary plaque density was compared with echogenicity assessed during three-vessel examination. Minimum lumen area (MLA) and cross-sectional vessel area (CVA) were manually traced for all significant lesions using multiplanar reconstructions that were orientated perpendicular to the longitudinal axis of the artery. Remodelling was calculated by dividing the CVA at the site of maximum luminal narrowing by the CVA in the reference segment.

Results: One hundred sixty nine coronary segments were analyzed and 84 plaques were visualized by both techniques with good image quality. MSCT detected 19/20 culprit lesions (95%). Ten culprit lesions (50%) were localised in proximal segments. Eight were hypochoic (40%), 5 were hyperechoic (25%), and 7 lesions were mixed (35%). IVUS was able to visualize plaque rupture in 5 culprit lesions (20%) but also in remote arteries for 4 patients (15%). These ruptures were not detected by MSCT. CT-derived density measurements within all coronary lesions revealed different values for hypochoic ($38 \pm 33 \text{ HU}$), hyperechoic ($94 \pm 44 \text{ HU}$), and calcified plaques ($561 \pm 216 \text{ HU}$), ($p < 0.0001$, by Kruskal-Wallis analysis). MSCT measurements correlated significantly with IVUS; for MLA and CVA, $r^2 = 0.70$ and 0.81 , respectively ($p < 0.001$), however MSCT tended to overestimate the vessel dimensions. Agreement between both techniques for remodelling analysis was relatively good (Kappa = 0.54, $n=84$, $p < 0.001$).

Conclusions: CT was able to detect with good accuracy the lesion responsible for the ACS and to characterize atheroma in remote coronary lesions. However, spatial resolution of the 16-slice CTA remains a major drawback to quantitatively assess the severity of lesions in these unstable patients.

P886 Use of automatic exposure control in multislice computed tomography of the coronaries: comparison of 16-row and 64-row scanner data with conventional coronary angiography

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Aims: The rapid growth in Multislice computed tomography (MSCT) of the coronaries (CTA) has resulted in considerable emphasis to adjust technique factors in order to reduce radiation dose exposure. In our study we evaluated the radiation dose reduction potential of automatic exposure control (AEC) in 16-slice and 64-slice MSCT of the coronaries in patients.

Methods and results: A retrospective data analysis of 154 patients was performed who had undergone MSCT-coronary angiography using different MSCT scanners and different protocols. Group 1 (56 patients) underwent 16-slice MSCT (ECG-triggered tube current modulation [ECG-TTCM], no AEC) as well as an invasive coronary angiography (ICA). In group 2 (51 patients) the 16-slice MSCT CTA was performed with the additional application of AEC. Group 3 (47 patients) was investigated with a 64-slice scanner (AEC, no ECG-TTCM). The results are shown in the table below. The use of AEC resulted in a 40,3% dose reduction. Effective dose for CXA in group 1 was 2.6 ± 1.27 mSv. In comparison to CXA data MSCT CTA without AEC shows a 3.8 fold and CTA with AEC a 1.9 fold higher radiation dose. In all investigations the image quality allowed to evaluate all coronary segments.

Patients and results			
	Group 1	Group 2	Group 3
Heart rate (beats per min.)	64.07 $\pm$ 11.35 (n= 56)	60.94 $\pm$ 7.40 (n= 51)	55.00 $\pm$ 5.80 (n= 470)
Body surface area (m ²)	1.96 $\pm$ 0.18 (n1 = 51)	2.01 $\pm$ 0.16 (n2 = 51)	1.85 $\pm$ 0.18 (n3 = 47)
Effective dose of Calciumscore (mSV)	2.72 $\pm$ 0.35 (n1 = 45)	1.26 $\pm$ 0.28 (n2 = 36)	1.83 $\pm$ 0.50 (n3 = 36)
Effective dose CTA without Calciumscore (mSV)	9.76 $\pm$ 1.84 (n2 = 56)	5.83 $\pm$ 1.73 (n2 = 51)	13.58 $\pm$ 2.80 (n3 = 47)

The legend shows the patient characteristics (with regard to radiation dose influencing factors like heart rate and body surface area) and the values of radiation dose for each group for Calciumscore and CTA

Conclusion: This is the first study to show the significant dose reduction potential (40,3%) of AEC in MSCT CTA in patients. In order to comply with an "as low as reasonably achievable radiation dose" while maintaining satisfactory image quality this relatively new technique can be used to optimize both the scanning protocols and the radiation dose levels in MSCT CTA.

P887 Is new generation cardiac multi-detector computed tomography a reliable tool for diagnosing coronary artery disease in women?

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Background: Coronary artery disease (CAD) is under-diagnosed in women and accuracy of non-invasive diagnostic testing is sub-optimal. Usefulness and reliability of new generation multidetector cardiac CT (MDCT) has not been examined specifically in women.

Methods: MDCT (40-slice, Philips) was performed in 111 unselected pts (21 women, 90 men) scheduled for invasive coronary angiography (ICA). We examined accuracy of MDCT for detecting >50% diameter stenosis in 1,297 coronary segments (AHA model) (quantitative analysis of ICA, visual inspection of MDCT) and compared findings in men and women.

Results: Women were older (67 ± 12 vs 58 ± 10 yr, $p=0.002$), but had similar duration of CAD (4.6 ± 6.8 vs 3.6 ± 5.7 yr, ns). Extent of CAD on MDCT was similar to men (15.1% vs 16.2% segments, ns). MDCT was non-assessable in more segments in women (24.8% vs 11.2% segments $p<0.001$) due to more calcification (13.5% vs 4.6% segments, $p<0.0001$) and motion artifact (7.1% vs 0.8% segments, $p<0.0001$). Female gender independently predicted non-assessable segments ($p<0.001$) as did older age and duration of CAD (both $p<0.001$). Positive

Accuracy of MDCT in women and in men

	Pts with non-assessable MDCT	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Predictive accuracy (%)
Women (N=21)	4 (19.0%)	72.2	94.6	66.7	95.4	86.6
Men (N=90)	5 (5.6%) ¹	72.0	94.2	71.7	94.7	91.0

¹p=0.04

PPV=positive predictive value; NPV=negative predictive value

predictive value (PPV) and predictive accuracy were marginally lower in women (Table).

Conclusions: 1. Predictive accuracy of MDCT for diagnosing CAD was lower in women, and 2. Prevalence of non-assessable segments (age-adjusted) was higher. 3. MDCT was none-the-less a useful new diagnostic modality for diagnosis of CAD in women.

P888 Diagnostic accuracy of coronary in-stent restenosis using 64-slice computed tomography: comparison with invasive coronary angiography

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Purpose: The purpose of this study was to assess the diagnostic value of 64-slice computed tomography (64-MSCT) to detect coronary in-stent restenosis (ISR).

Methods: Using 64-MSCT (SOMATOM Sensation cardiac 64), we performed coronary angiography (CTA) in 80 patients who had previously undergone coronary stent implantation (mean age 68, 62 male), and 128 images of stented segments (165 stents) were obtained. The mean heart rate during scan was 69.9/min, scan time 13.2 seconds and the total amount of contrast media was 73.6 mL. Multiplanar reconstructed images generated with both smooth (B20f) and sharp (B46f) kernels were estimated in their long and short axes. ISR for each segment was diagnosed according to luminal contrast attenuation inside the stent. Invasive coronary angiography (ICA) was performed at the same period, and > 50% diameter stenosis (%DS) on quantitative coronary angiography was defined as ISR. Diagnostic accuracy of 64-MSCT to detect ISR was evaluated.

Results: Fifteen lesions (12%) were not assessable by CTA mainly because of motion artifact and calcification. On ICA, ISR was observed overall in 23 segments, and in 22 segments of the CTA assessable images. Sensitivity, specificity, positive and negative predictive value (PPV and NPV) of CTA compared to ICA were 96%, 90%, 70% and 99%, respectively. There was only one false negative ISR diagnose. Concerning patient-based analysis, the sensitivity, specificity, PPV and NPV were 89%, 87%, 71% and 96%, respectively.

Validation of ISR on CTA compared to ICA

	ISR (+) on CTA	ISR (-) on CTA	Total
ISR (+) on ICA	21 (TP)	1 (FN)	22
ISR (-) on ICA	9 (FP)	82 (TN)	91
Total	30	83	113

TP = true positive, TN = true negative, FP = false positive and FN = false negative.

Conclusion: 64-MSCT allows the detection of ISR with high diagnostic PPV compared to ICA. The high rate of false positive diagnose reflect an overestimation of the degree of ISR by CTA.

P889 Computed tomographic angiography for the grading of coronary collaterals in Total Occlusions

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The number of total occlusions (TO) in the general population is difficult to estimate. PCI in these cases reveals only low success rate due to the often complex lesion morphology and the concealed course of the occluded coronary artery. The factors influencing the decision to reopen the coronary artery comprise location and morphology of the TO, presence of viable myocardium in the dependent region, degree of collateralization and the presence of potential reversible ischemia. The commonly used and most sensitive tool to diagnose total occlusions is coronary angiography. Advances in MDCT technology with sub-millimeter slice collimation and high temporal resolution permit contrast-enhanced imaging of coronary arteries and even visualization of the occluded parts of the coronary arteries making MDCT an interesting option for pre-procedural imaging. The aim of our study was therefore, to determine the visibility of collaterals, the determination of lesion length and the grade of collateralization by MDCT in patients with total occlusions and to compare it to coronary angiography as present reference standard.

Methods: 22 Patients with total occlusions by angiography (TIMI grade 0) in one of the major coronary arteries were eligible for this analysis if beneath angiography a MDCT had been performed within three weeks. In addition to lesion length and lesion calcification the analyzed parameters comprised also the presence and degree of collateralization as assessed by MDCT (0= no collaterals visible; 1= collaterals visible but not over the entire length; 2= collaterals visible over the entire length but not adequate in size; 3= collaterals present and adequate in size) and angiography (Rentrop Grade 0-3).

Results: TO's were located in RCA (n=13), LAD (n=4) and LCx (n=5). In 19/22 patients collateralization (≥ 1 Rentrop) was present. A total of 30 collaterals (mean 1.36 ± 0.8) per patient were present by angiography and 24 (mean 1.1 ± 0.8)

collaterals by MDCT. MDCT identified. The degree of collateralization as assessed by MDCT and angiography revealed a close correlation ($r=0.889$ p Ren-trop 1 were correctly identified).

Conclusion: MDCT is able to reliably detect collateral circulation in patients with total occlusions. A close correlation between the MDCT and angiography based grading was observed.

P890 16-slice multidetector row computed tomography could assess noninvasively the coronary reperfusion after thrombolytic therapy in patients with ST elevation myocardial infarction

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Background: The objective of this study was to assess the efficacy of the 16-slice multidetector row computed tomography (MDCT) in estimating residual stenosis and successful reperfusion after thrombolytic therapy in patients with ST elevation myocardial infarction (STEMI).

Methods: From December 2004 to October 2005, 37 patients with STEMI received thrombolytic agents for initial coronary reperfusion therapy. Out of these patients, total 31 patients underwent MDCT scan performed within 6 hours (mean 4.6 ± 1.1 hours) after thrombolysis. The results of the MDCT were compared to conventional coronary angiography (CCA) performed within 24 hours (mean 12.1 ± 5.6 hours) after the MDCT scan. Significant residual stenosis and distal flow of the infarct-related artery (IRA) was compared between the two modalities. Successful reperfusion was defined as Thrombolysis In Myocardial Infarction (TIMI) 2 or 3 distal flow by CCA and full contrast enhancement in distal artery landmarks by MDCT.

Results: A final analysis was performed on 24 patients (312 segments). The MDCT correctly assessed 33 of 46 significant stenotic segments detected by CCA. There were 13 missed (false negative) and 12 overestimated lesions (false positive) by MDCT. Thus, MDCT had a positive predictive value of 73.3% and a negative predictive value of 95.1%. CCA identified 7 patients (29.2%) with a TIMI 3 flow and 11 patients (45.8%) with a TIMI 2 flow, who were considered as patients with successful reperfusion of the IRA. However, there were 6 patients who failed coronary reperfusion; 1 patient (4.2%) with a TIMI 1 flow and 5 patients (20.8%) with a TIMI 0 flow. MDCT accurately estimated 17 of 18 patients with successful reperfusion and 5 of 6 with reperfusion failure on the basis of comparison with CCA. Therefore, MDCT had a positive predictive value of 94.5% and a negative predictive value of 83.3% in estimating reperfusion in the IRA.

Conclusions: The MDCT demonstrated high accuracy not only for the detection of residual stenosis, but also for the assessment of successful reperfusion after thrombolytic therapy in patients with STEMI.

P891 Determination of cardiac allograft vasculopathy in heart transplant patients with 64-slice Multislice CT

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Cardiac allograft vasculopathy (CAV) is the major obstacle to long-term survival after heart transplantation. Because of the silent nature of CAV routine conventional angiography remains the gold standard for diagnosis. The aim of the present study was to assess the efficacy of 64-slice Multislice Computed Tomography (MSCT) for the detection and exclusion of significant (>50%) focal stenosis in heart transplant patients. 34 consecutive male patients (age 53 ± 12 y), 6 ± 5 y after heart transplantation underwent 64-slice MSCT (Sensation 64, Siemens Medical Solutions, Forchheim) angiography within 24 hours after the annual routine angiography. To obtain a resting heart rate < 70 beats/min. all patients received oral beta-blockers (100mg metoprolol) 1 h before MSCT. All vessels (AHA 15 segment model) were analyzed and MSCT lesions were analyzed quantitatively and compared to quantitative coronary angiography (QCA). Four patients have to be excluded from further MSCT evaluation due to severe renal insufficiency and in four patients image quality was non diagnostic after the MSCT scan (motion artifacts $n = 4$, heart rate = 86 ± 7 beats/min.). In the remaining 26 patients a comparison of 375/390 segments (96%) between MSCT and QCA was possible. Consensus in classifying the degree of stenosis with both methods was achieved in 7/8 angiographically stenotic segments and in 352/367 of disease free segments. 15 segments without evidence of atherosclerosis on OCA were graded stenotic on 64-slice CT and in two segments a present lesion was overestimated. Sensitivity for the detection of significant stenosis was 88%, specificity = 96% (negative predictive value = 99%). The diagnostic accuracy was calculated as 96%. On a patient basis 64-slice MSCT correctly ruled out significant CAV as compared to conventional angiography in 20/22 (90%) patients. 64-slice computed tomography can be applied with an excellent diagnostic accuracy in the routine follow-up of heart transplant patients for determination and exclusion of significant CAV. Nevertheless the application is restricted to subjects without extensive renal insufficiency and requires lower heart rates to achieve diagnostic image quality.

P892 Interobserver variability of 64-slice computed tomography in the quantification of non-calcified coronary atherosclerotic plaques

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Purpose: While the assessment and quantification of calcified plaques in the coronary arteries using multi-detector CT (MDCT) is well established, only very limited information exists concerning the accuracy of MDCT to evaluate non-calcified plaques. We therefore evaluated the interobserver variability for measuring non-calcified plaque volumes using 64-slice computed tomography.

Methods: In 34 patients with detectable non-calcified plaque in 64-slice CT (Sensation 64, Siemens, Germany, 330 ms rotation, 0.6 mm collimation, 60 ml contrast agent i.v. at 5 ml/s), two separate investigators independently measured plaque volumes in the left main and proximal left anterior descending coronary artery (ostium to 1st diagonal branch) by manually tracing plaque areas in contiguous cross-sectional reconstructions (1 mm thickness) rendered along the vessel centerline in 0.5 mm increments. Interobserver differences concerning non-calcified plaque volumes were determined and the influence of heart rate, plaque volume and image quality (1 = excellent without artifacts, 2 = evaluable with slight artifacts, 3 = artifacts impair evaluability) on the extent of the interobserver difference was evaluated.

Results: The mean volume of non-calcified plaque in all 34 patients was 140 ± 135 mm³. The mean absolute difference in plaque volume between the two observers was 32 ± 64 mm³, which corresponds to a mean interobserver variability of $19 \pm 16\%$. There was a significant correlation between interobserver variability and the extent of the plaque volume itself ($r=0.88$, $p=0.01$). Interobserver variability was also dependent on image quality with an average interobserver difference of 8 ± 6 mm³ for the image quality group 1, of 17 ± 7 mm³ for group 2 and 116 ± 122 mm³ for group 3 ($p < 0.001$). Finally, the interobserver difference showed a weak but significant correlation with heart rate ($r=0.38$, $p=0.05$, mean heart rate of all examinations: 58 ± 4 bpm).

Conclusions: Interobserver variability for quantification of non-calcified plaque volume in 64-slice MDCT is substantial. Variability is strongly influenced by image quality and, similar to coronary calcium, is influenced by heart rate and the magnitude of plaque volume itself.

P893 How useful is cardiac multi-detector computed tomography for evaluating coronary disease in patients who have undergone previous coronary bypass/interventional revascularization procedures?

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Background: Many coronary pts require re-assessment following myocardial revascularization procedures. Although multidetector cardiac CT (MDCT) can demonstrate graft patency after bypass surgery, diagnostic accuracy for examining anastomotic sites, distal segments and patency of coronary stents after PCI is uncertain.

Methods: Cardiac MDCT (40-slice, Brilliance 40, Philips) was performed in 111 unselected pts (90, 81% men), of whom 47 (42.3%) had undergone prior revascularization (18 CABG, 37 PCI) and were referred for repeat invasive coronary angiography (ICA). Exclusion criteria were renal failure and irregular heart rhythm. Vessels ≤ 1.5 mm diameter were not assessed. We examined accuracy of MDCT for detecting $\geq 50\%$ diameter stenosis on a segmental basis (AHA model) with additional segments for each bypass graft (quantitative analysis of ICA, visual inspection of MDCT).

Results: Sensitivity and positive predictive value (PPV) of MDCT were higher in pts with prior revascularization. Proportion of non-assessable coronary segments was increased (Table).

Accuracy of MDCT

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Non-assessable segments (%)
Prior revasc.	76	95	80	94	19
No prior revasc.	67	95	62	96	10 ¹

PPV=positive predictive value; NPV=negative predictive value. ¹ $p < 0.001$

Conclusions: MDCT was useful for detecting obstructive coronary lesions after CABG/PCI, but almost 20% of coronary segments were non-assessable by MDCT in these pts.

P894 Coronary sinus in 64-slice CT - preliminary study

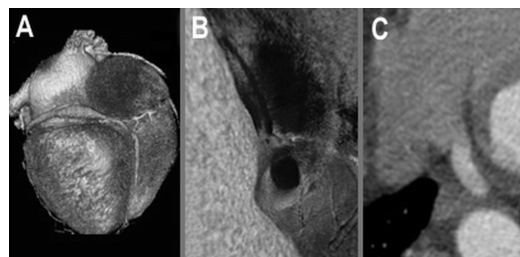
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Cardiac Resynchronization Therapy (CRT) is a new method of treatment for heart failure. Visualization of the coronary sinus (CS) and the venous system of the heart in patients prepared for implantation of CRT devices

is very helpful for implanting doctors. THE PURPOSE OF THIS STUDY was to evaluate possibility of visualization of the CS in multi-slice CT.

Methods: In 38 patients 64-slice CT (Toshiba Aquilion 64) were performed to visualize CS. Modified protocols for scanning and for contrast application were used in 18%, the standard protocol in the rest of patients. 79% images were reconstructed at 40% or 50% R-R wave interval. All analyses were done both in 2D MPR and 3D VR reconstructions.

Results: In 37 patients we were able to visualize CS (97%). Good or very good quality of images of CS was get in 88% cases. Coronary arteries (CA) were also estimated in 100% cases, however modified protocol in 4 cases worsen image quality of CA. It was especially marked on RCA, and Cx. All patients tolerated the examination well. On the picture below we present an example of the results (segment: 780 ms; layer: 0.5mm; 120 ml Ultravist 370). A - 3D reconstruction of the heart including CS and veins (posterior view); B - Ostium of CS (3D view from inside of RA); C - 2D MPR. View of ostium of CS from inside of RA we were able reconstruct in 56% cases.



Coronary Sinus

Conclusions: 64-slice CT is a good alternative for visualization of the CS and its branches before the implantation of CRT. A modified protocol for visualization of CS and the veins of the heart in some cases can worsen the quality of the picture of CA, especially RCA. 3. Additional research is necessary to work out an optimal scheme of visualization of CS in multi-slice CT as a compromise between the quality of coronary arteries, CS and quantity of contrast.

P895 Accuracy of 16-row multi-detector computed tomography for the assessment of coronary artery stenosis: a multicenter trial



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Background: Multi-detector computer tomography (MDCT) has been proposed as a non-invasive method to evaluate coronary anatomy. We performed a prospective multicenter study to determine the diagnostic accuracy of 16-row cardiac MDCT for the detection of obstructive coronary disease.

Methods: Eleven participating sites enrolled 238 patients who were clinically referred for non-emergent coronary angiography. Following a low-dose MDCT scan to evaluate calcium, 187 patients with an Agatston score <600 underwent contrast-enhanced MDCT. Conventional angiography was performed 1-14 days after MDCT. Data sets were quantitatively analyzed by independent MDCT and Angiographic Core Laboratories.

Results: Of 1613 segments >2 mm in diameter, 71% were evaluable on MDCT. The sensitivity, specificity, positive and negative predictive values for detecting >50% luminal stenoses were 85%, 91%, 36% and 99%. In a patient-based analysis, after exclusion of 46 (24.6%) non-evaluable studies, the sensitivity, specificity, positive and negative predictive values for detecting subjects with at least one segment with >50% stenosis were 98%, 70%, 60% and 99%. By implementing the results of this study, a negative evaluable MDCT may have avoided unnecessary conventional angiography in 57 of 223 patients (26%) while missing only 1 patient with single vessel obstruction (0.4%).

Conclusions: Although limited by a non-evaluable rate of nearly 24%, 16-row MDCT reliably excludes obstructive coronary disease in a significant group of patients at intermediate to high risk. Thus, with appropriate clinical implementation, MDCT may reduce the performance of unnecessary conventional diagnostic angiography.

P896 A negative or low coronary artery calcium score by multislice computed tomography does not rule out significant coronary artery stenosis



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Background: Coronary calcifications are specific markers for coronary atherosclerosis. The extent of coronary artery calcification has been reported to be predictive of the significance of coronary artery disease (CAD). The high

negative predictive value of the technique has prompted its use in ruling out this condition in asymptomatic subjects.

Purpose: To evaluate the presence and extent of coronary artery calcium in patients with unrecognized CAD as detected by the presence of at least one significant stenosis in a multislice computed tomography (MSCT) study.

Material and methods: From a total of 1000 MSCT exams performed on an Aquilion Toshiba (16- or 64-slice systems), 116 were retrospectively analyzed as they corresponded to patients either asymptomatic or with atypical chest pain, and with at least one coronary artery stenosis (>50%). In these patients, the presence of coronary artery calcium and its extent, as evaluated by the Agatston score, were determined.

Results: From the total population of 116 patients, 96 (83%) were males. Ages ranged from 33-89 (mean: 65; SD: 9.8). The distribution of patients according to the Agatston score is shown on the table. Although there was a wide distribution among the different levels of score severity, up to 28% showed a score <100 including 4% who showed complete absence of coronary calcium (0 score).

Agatston score	Number of patients (%)
0	5 (4%)
1-100	28 (24%)
101-400	32 (28%)
401-1000	26 (22%)
>1000	25 (22%)

Conclusion: A significant proportion of patients with unrecognized coronary artery stenosis (>50%) present with an MSCT Agatston calcium score on the low level of severity. This may lead to consider performing a noninvasive MSCT coronary angiography in addition to a coronary calcium study to effectively rule out CAD.

P897 Accuracy of multislice computed tomography for the noninvasive detection of calcified plaques in chronic total occlusions: comparison with 3D-IVUS



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Objectives: Successful recanalization of a chronic total occlusion (CTO) is last frontier of percutaneous coronary intervention (PCI). Previous studies demonstrated that calcification of target lesion detected by both angiography and multislice computed tomography (MSCT) was significant predictor for PCI of CTO. We aimed to evaluate the accuracy of MSCT for the noninvasive detection of calcified plaque of CTO and compared it with 3D-intravascular ultrasound (IVUS).

Methods: Fifteen angiographic CTO (5 in LAD, 3 in LCX and 7 in RCA) in 14 patients (mean age 68±5 years, 11 males) were included. All patients had undergone 16-slice CT (Mx8000IDT, Phillips Medical Systems) prior to PCI. The presence and location of calcified plaque within the CTO were systematically assessed by MSCT. Quantitative analysis of the IVUS (40-MHz IVUS catheter, Atlantis, Boston Scientific; motorized pullback at 0.5 mm/s) images was performed after dilation of a 1.5-mm balloon. The length of the calcified plaque was measured. MSCT measurements were verified by IVUS.

Results: All CTO segments were visualized. Procedural success was obtained in all. Calcified plaques were detected in 30 lesions of 13 CTO segments, but were not detected in the other 2 by MSCT. Location of calcified plaque was proximal, mid and distal site of CTO in 2 segments, both proximal and distal in 3, both proximal and mid in 2, both mid and distal in 2, mid in 2 and distal in 2. For the detection of calcified plaque by MSCT, sensitivity and specificity were 88.9% and 100% for proximal site of CTO, 29.4% and 100% for mid site, respectively, and 100% and 100% for distal site, respectively. For mid site, the length of detected calcified plaque in MSCT was significant higher than that of undetected calcified plaque (6.7 ± 2.3 mm vs. 2.7 ± 1.2 mm, $p < 0.0001$).

Conclusions: MSCT permits an accurate identification of calcified plaques for both proximal and distal site of CTO segment. However further improvements in image quality will be necessary to achieve reliable assessment, for mid site within CTO, especially of small calcified plaque.

P898 Significance of CT-low-dense coronary artery plaques: study by intravascular ultrasound and coronary angiography



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Background: Although CT-low-dense plaques defined by multislice computed tomography (MSCT) correspond to soft plaques defined by intravascular ultrasound (IVUS), whether or not they represent vulnerable plaques is unknown.

Methods: MSCT was performed in 34 patients with coronary artery disease using an Aquilion 16 with collimation of 0.5mm and gantry rotation of 0.4s/rotation. Plaque CT densities were measured in at least 4 randomly selected regions of interest within the plaque and the minimum CT density was determined. Based

on IVUS, plaques were classified into soft, fibrous and hard plaques. The minimum CT plaque density was compared to the IVUS-derived plaque texture. The plaques were also evaluated by coronary angiography and divided into white and yellow plaques according to the 4-point scoring system (0=white, 1=light yellow, 2=yellow, 3=intensive yellow). Plaques with color grade 0-1 were defined as white plaques and plaques with color grade 2-3 were defined as yellow plaques.

Results: The CT densities in soft, fibrous and hard plaques were 47 ± 22 Hounsfield units (HU), 101 ± 29 HU, and 573 ± 203 HU, respectively. When plaques with CT density < 50 HU were defined as soft plaques, the sensitivity and specificity of CT to detect IVUS-defined soft plaques were 100% and 94%, respectively, whereas, the sensitivity and specificity to detect angiographically defined yellow plaques were 75% and 56%.

Conclusions: MSCT may permit accurate assessment of coronary artery soft plaques, but it is insensitive to detect yellow plaques which are sensitive markers of vulnerable plaques. The significance of CT-low-dense plaques awaits further prospective clinical observations.

P899 Time Series of Volumetric Measurement of Porcine Three Dimensional Segmented Myocardial Perfusion by Selective Contrast Injection Using 256 Slice Cone Beam Computed Tomography



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Purpose: To measure time series of volume of segmented myocardial perfusion by selective contrast injection in 4D films, we used a new prototype 256-slice cone beam CT (Athena, Sony Toshiba) at one rotation per second and a section thickness of 0.5 mm.

Materials and Methods: Six domestic pigs (20 kg each) were anesthetized with isoflurane. Distal tips of catheters were positioned in the left anterior descending branch (LAD) of the coronary artery (pigs 1,2), and left circumflex branch (LCx) (pig 3). Scan conditions for the 256-slice cone beam CT were: 120kV, 200mA, 1.0second gantry rotation time and 256×0.5 mm slice collimation. Volumetric scanning and contrast injection (10ml iodinated contrast material (300mg/ml) diluted in 40 ml of saline, 3ml/second) were started simultaneously and continued for 20 seconds, and images were reconstructed at one-second intervals.

Results: In pigs 1, and 2, 4D filming revealed coronary arterial trees, followed by selective 3D images of the anterior, apical and IVS portions of the LV supplied by the LAD in pigs 1 and 2, and the lateral and posterior portions of the LV supplied by the LCx in pig 3. Furthermore coronary sinus trees could be observed. Time series of volume of segmented myocardial perfusion revealed 4.5 (2 sec), 12.3 (3 sec), 18.3 (4 sec), 24.4 (5 sec), 25.4 (6 sec), 26.3 (7 sec), 28.4 (8 sec), 30.2 (9 sec), 30.8 (10 sec), 29.8 (11 sec), 30.3 (12 sec) 30.5 (13 sec), 30.7 (14 sec), 30.6 (15 sec), 30.2 (16 sec), 30.1 (17 sec), 29.7 (18 sec), 29.2 (19 sec) and 29.6mm³ (20 sec after contrast injection) for myocardium supplied exclusively by the LAD in pig 1 and 2.9 (2 sec), 8.3 (3 sec), 14.3 (4 sec), 19.4 (5 sec), 22.4 (6 sec), 23.9 (7 sec), 21.9 (8 sec), 27.9 (9 sec), 27.2 (10 sec), 26.3 (11 sec), 27.3 (12 sec) 27.5 (13 sec), 27.3 (14 sec), 27.4 (15 sec), 27.2 (16 sec), 27.2 (17 sec), 26.9 (18 sec), 26.2 (19 sec) and 26.6mm³ (20 sec after contrast injection) for myocardium supplied exclusively by the LCx in pig 3.

Conclusions: Using 256-slice CT with selective contrast injection, time series of volume of segmented myocardial perfusion was obtained in 4D. Time series of segmented volume may improve strategies of percutaneous coronary intervention or coronary bypass.

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P900 Evaluation of patients with previous stent implantation using 64-slice multi-slice computed tomography



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Purpose: With previous generations of multi-slice computed tomography (MSCT), assessment of in-stent restenosis was still problematic. The purpose of this study therefore was to evaluate the accuracy of 64-slice MSCT in the detection of in-stent restenosis.

Methods: In 30 patients with previously implanted stents, Multi-Slice Computed Tomography (MSCT) was performed. For each stent, assessability was determined and related to stent type and diameter. Subsequently, the presence of significant restenosis was determined in the evaluable stents. In addition, peri-stent lumina (5.00mm proximal and distal to the stent) were also evaluated. Conventional angiography in combination with quantitative coronary angiography (QCA) served as the standard of reference. MSCT was performed successfully in all patients.

Results: Of 40 stents, 34 (85%) were determined assessable. No relation was observed between uninterpretability and either stent diameter or strut thickness. In 4 patients, stents were placed partially overlapping resulting in 35 stented segments, of which 31 (89%) were evaluable. In these stented segments, all 3 in-stent

restenoses were detected and the absence of restenosis was correctly identified in the 28 remaining stented segments without restenosis. Sensitivity and specificity for the detection of peri-stent stenosis were 100% and 97%, respectively. In addition, the presence of non-significant in-stent restenosis was correctly identified in 22 of 28 (79%) stented segments.

Conclusion: The present study suggests that evaluation of coronary stents has improved substantially using 64-slice MSCT. In patients with previous stent implantation, 64-slice MSCT may be useful for non-invasive exclusion of in-stent or peri-stent restenosis and avoid invasive imaging in a considerable number of patients.

P901 Influence of age and cardiovascular risk factors on the volume of calcified and non-calcified coronary atherosclerotic plaque: assessment by 64-slice computed tomography



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64-slice multi-detector CT (MDCT) permits visualization of the coronary arteries. Good image quality is achieved especially in proximal vessel segments. Several studies have demonstrated that calcified and non-calcified coronary atherosclerotic plaque can be detected and quantified by MDCT. We studied the effect of age and cardiovascular risk factors on the volumes of calcified and non-calcified atherosclerotic plaque in the left main and proximal left anterior descending coronary artery.

100 consecutive patients (65 male, 35 female, mean age 59 ± 12 y) referred for rule out of coronary artery stenoses were studied (Sensation 64, 330 ms rotation, 120 kV). Volumes of calcified and non-calcified plaque in the left main and proximal left anterior descending coronary artery were assessed by manual tracing of plaque dimensions in serial multiplanar reconstructions (1 mm thickness, 0.5 mm increment). Analysis was performed blinded to age, gender, and risk factor status of the patients.

Plaque was detectable in 66 patients. Mean volume of calcified plaque was 35 ± 69 mm³ and of non-calcified plaque was 28 ± 39 mm³. Age was significantly correlated to the volume of calcified plaque ($r=0.34$, $p=0.001$) and to that of non-calcified plaque ($r=0.25$, $p=0.011$) with regression coefficients of 1.89 (95% CI 0.84 - 2.94) and 0.79 (95% CI 0.18 - 1.41) respectively. In univariate analyses, age, sex, and lipostats use were associated with calcified plaque, whereas age, sex, hypertension, and smoking were associated with non-calcified plaque. Using logistic regression there was an increase in the odds of having slight to extensive calcified plaque by 4 times with every unit increase in age group (OR=4.08, 95% CI 1.94-8.59, $p>0.001$), and males showed a 7 times increase in odds compared to females (OR=7.18, 95% CI 2.41-21.34, $p>0.001$), while the non-calcified plaque also showed an increasing OR for every unit increase in age-group (OR=2.24, 95% CI 1.23-4.09, $p=0.008$), a 6 times increase in males compared to females (OR=5.99, 95% CI 2.15-16.67, $p=0.001$), a 3 times increase when comparing hypertensive to normotensive (OR=3.20, 95% CI 1.09-9.36, $p=0.034$), and nearly a 4 times increase in the odds of having slight to extensive non-calcified plaque when comparing smokers to non-smokers (OR=3.85, 95% CI 1.35- 10.98, $p=0.012$).

In conclusion, measurement of plaque volumes is feasible in 64-slice CT. Significant effect of age and cardiovascular risk factors on the amount of plaque and the relationship between calcified and non-calcified plaque was observed.

P902 Are non-calcifying coronary plaques as detected with multislice computed tomography correlated with acute cardiac events?



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Purpose: to evaluate whether different coronary plaque types as assessed with 16-multislice computed tomography (16-MSCT) are correlated to acute cardiac events (ACE).

Methods: 63 patients who underwent 16-MSCT coronary angiography (Sensation 16®, Siemens, Germany) (16×0.75 mm, 0.42 s, 120 kV, 500 mAs, eff.sl. 1 mm, inc. 0.5, retrospective ECG-gating, 100 ml Iodixanol (Visipaque®), flow 3-4.5 ml/s) were retrospectively analysed. Coronary plaques were defined as type 1=calcifying (C); type 2=mixed (C>non-calcifying (N)); type 3=mixed (N>C); type 4=non-calcifying. All patients underwent cardiac catheterization (CAG). 17 patients had intracoronary ultrasound (ICUS). Acute cardiac events (ACE) were defined as Acute Coronary Syndrome (ACS) (Troponin T elevation, NSTEMI- ECG abnormalities, chest pain) or STEMI within < 17 days prior to 16-MSCT examination. All patients underwent catheterized coronary angiography. 17 patients underwent intracoronary ultrasonography (ICUS).

Results: A total of 58 patients had coronary plaques as detected with 16-MSCT (predominant plaque type 1:n=12; type 2:n=10; type 3:n=16; type 4:n=14). The presence of a non-calcifying plaque component (type 2-4)(40/63) was strongly correlated with an ACE (n=17) ($p<0.0001$; Fisher-exact-test). Mixed plaque type 3 was significantly correlated with ACE ($p=0.01$). Mixed plaque type 2 ($p=1$) and

plaque type 4 ($p=0.09$) were not related to ACE. 16-MSCT correctly classified plaque types in 15 of 17 patients when compared with ICUS. 45 of 63 patients had at least one coronary stenosis $>50\%$ on CAG (Sensitivity of 16-MSCT: 98% (43/45); specificity 90%; NPV 97%; PPV 97%). 15 of 17 patients with ACE had CAD ($n=1$:coronary anomaly; $n=1$:acute myocarditis).

Conclusion: Mixed, predominantly non-calcifying coronary plaques as detected with MSCT are correlated with acute cardiac events suggesting higher plaque vulnerability. MSCT may have the potential to identify high-risk patients who should be treated more aggressively.

P903 Simultaneous automated assessment of atrial and ventricular volumes and left ventricular mass by Multi-Detector Computed Tomography using a novel algorithm

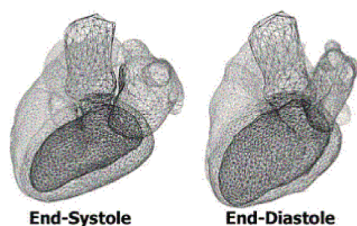


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Background: While cardiac magnetic resonance is the gold standard for quantification of cardiac mass and chamber volumes, it is limited by lack of convenience and widespread availability. Multi-detector computed tomography (MDCT) is an expanding modality which has the potential for rapid and accurate acquisition of similar data in patients with cardiac disease.

Methods: A prototype post-processing software program was used to analyze 12 patients (mean age 41, range 36-71, 9 males) undergoing MDCT in a 64-slice scanner using an adaptive learning algorithm which enables automatic segmentation based on count density and shape variability of imaged cardiac anatomical structures including chambers, valve planes, and great vessels. Multiphase off-line reconstruction was performed at 10% RR-interval increments with calculation of right atrial (RA), left atrial (LA), right ventricular (RV), and left ventricular (LV) volumes, and LV mass.

Results: Full volumetric data sets were easily obtained in all 12 patients, allowing calculation of stroke volume, cardiac output, and ejection fraction. The figure shows a representative segmentation of atrial and ventricular volumes and LV myocardial mass created by the prototype software.



Conclusions: We describe a novel four-dimensional MDCT technique to simultaneously assess volumes from all four cardiac chambers. This technology may have a role in the evaluation of ventricular and atrial size and function in various disease states or in response to medical or device-based therapy over time, and warrants further validation.

P904 Multislice spiral computed tomography for the evaluation of stent patency after left main coronary artery stenting: a comparison with conventional coronary angiography and intravascular ultrasound



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Background: Surveillance conventional coronary angiography (CCA) is generally recommended 3 to 6 months after stent-supported left main coronary artery (LMCA) percutaneous coronary intervention due to the unpredictable occurrence of in-stent restenosis (ISR), with its attendant risks. Multislice computed tomography (MSCT) is a promising technique for noninvasive coronary evaluation.

Methods and Results: Seventy-four patients were prospectively identified from a consecutive patient population scheduled for follow-up CCA after LMCA stenting and underwent MSCT before CCA. Until August 2004 a 16-slice MSCT ($n=27$), and since then a 64-slice MSCT ($n=43$), was used. Among patients with tech-

Table 1

	All patients	Simple stenting	Complex bifurcation stenting
Total number	70	46	24
Sensitivity, %	100 (72-100)	100 (61-100)	100 (51-100)
Specificity, %	91 (82-96)	97 (87-99)	80 (58-92)
Positive predictive value, %	67 (42-85)	86 (49-97)	50 (22-78)
Negative predictive value, %	100 (93-100)	100 (91-100)	100 (81-100)

"Simple stenting group" includes patients who underwent stenting of the left main stem only or stenting of the distal left main extending into a single major side branch. The "complex bifurcation stenting group" comprises patients in whom the left main stem and both the LAD and CX were stented. Values in parentheses are 95 percent confidence intervals.

nically adequate scans ($n=70$), MSCT correctly identified all patients with ISR (10/70), but misclassified 5 patients without ISR (false positives). Overall the accuracy of MSCT for detection of angiographic ISR was 93%. The sensitivity and specificity was 100% and 91%, respectively. When analysis was restricted to patients with stenting of the LMCA with or without extension of the stent into a single major side branch, accuracy was 98%. When both branches of the LMCA bifurcation were stented, accuracy was 83%.

Conclusions: Current MSCT technology, in combination with optimal heart rate control, allows reliable noninvasive evaluation of selected patients after LMCA stenting. A negative MSCT scan virtually rules out the presence of left main ISR. MSCT may therefore be an acceptable first-line alternative to CCA.

P905 Comparison of 4, 16 and 64 row multi-slice computed tomography to evaluate in stent restenosis and MLD



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Background: Multi-slice computed tomography (MSCT) is currently used to perform non-invasive evaluation with suspected coronary artery disease. Its actual accuracy to evaluate the late results of patients with coronary stents is still uncertain. Some authors have suggested that this would not be a limitation in the new generation 64 row scanners.

Objective: The goal of this study was to evaluate the accuracy of 64 row scanner to evaluate the presence of in stent restenosis (ISR) and the minimal lumen diameter (MLD), comparing its results to those obtained in a 4 and in a 16 row scanners.

Patients: We selected 90 patients that were completing their 9 month follow-up after the implantation of bare metal stents.

Methods: We studied 30 patients in the 4 row scanner (group I), 30 in the 16 row scanner (group II) and 30 in the 64 row scanner (group III). We used beta blockers in all patients with heart rate >70 bpm and injected 100 ml of non ionic, low osmolality contrast media at 4 ml/sec intravenously in all patients. Images were reviewed by a single operator, who identified ISR and measured the in-stent MLD. Cardiac catheterisation was performed 2 to 4 days after the MSCT and its results were compared to those of the latter, by an independent observer.

Results: The MLD comparison between MSCT and the invasive evaluation are in the table.

	Group I	Group II	Group III
MSCT MLD	2.14 ± 1.2 mm	2.48 ± 0.85 mm	2.76 ± 0.78 mm
Angiography MLD	2.63 ± 0.8 mm	2.73 ± 0.5 mm	2.93 ± 0.83 mm
p	0.003	0.006	0.02

There were 2 ISR in Group I, and the 4 row MSCT did not identify one. In Group II there was one restenosis, that was identified by MSCT and in Group III there were 3 restenosis, all identified by MSCT.

Conclusion: Despite the fact that 64 row MSCT has better results than 4 and 16 row scanners, it still is limited in evaluating in stent MLD. There is need of further technological developments before MSCT can be routinely used to the non-invasive assessment of coronary stents

P906 The normal values of electron beam computed tomography (EBCT) cannot necessarily be extrapolated to multi-slice computed tomography (MSCT)



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The assessment of coronary risk according to the coronary calcium (ca) score attained by computer tomography (CT) is being used more often due to the increasingly positive status of data. The determination of the "Agatston-Score" is recommended for patients (pat.) at "medium risk" according to traditional risk factor scoring. All prognostic data related to ca-scoring were evaluated 10 years ago with EBCT. Today, multislice computer tomography (MSCT) has almost replaced EBCT. However, the question remains whether the "normal values" (limits of percentile distribution) attained by EBCT can be extrapolated to modern MSCT. The objective of the study is to determine the ca-score for pat. without known coronary artery disease (CAD) using the MSCT and compare these values with the percentiles attained via EBCT.

2000 consecutive pat. were investigated (74% male), mean age males (56 years), females (59 years). The percentage of pat. with diabetes (male/female) was 6%/5%, smokers 20%/17%, hyperlipidemia 52%/54% and arterial hypertension 41%/44%. Pat. with known CAD, history of possible angina or other arterial diseases were excluded. See Table 1.

It was scientifically shown that the assessment of coronary risk according to EBCT percentiles is independent of traditional risk factor scoring. But, since the ca-scores determined with the new MSCT were in the mean 60% lower than the EBCT-determined The percentile limits of EBCT cannot simply be transferred to

Table 1

Age group	30-39	40-44	45-49	50-54	55-59	60-64	65-69
75th percentile							
MSCT	0	1	9	59	156	291	502
EBCT	2	11	44	101	187	434	569
90th percentile							
MSCT	4	16	95	221	390	748	1056
EBCT	21	64	176	320	502	804	1178

MSCT. One possible explanation is the smaller slice thickness in MSCT (3.0 vs. 1.5 mm), resulting in lower "partial volume effects" with low ca-scores. The difference between EBCT and MSCT is especially prominent in pat. with lower ca-scores. Therefore, for the identification of pat. at high coronary risk with MSCT, a new database with a new definition of percentiles must be established to avoid an underestimation of coronary risk.

P907 Feasibility of multislice cardiac computed tomography in assessing stents in proximal coronary segments after percutaneous coronary intervention

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Purpose: We assessed the feasibility of Multislice cardiac CT (MSCT) to evaluate the patency of coronary stents of the major coronary arteries after percutaneous coronary intervention (PCI).

Methods: The study included 61 patients (11 females; age 44 - 81 years) with 95 stents in one or more of the major coronary arteries, and typical complaints of angina. All underwent a MSCT (Siemens Sensation, 16-slice, or GE 64-slice VCT, 20 of the 95 stents) and conventional coronary angiography (CA). Metoprolol was administered if the heart rate was above 70 beats per minute. The major coronary arteries were divided in to 9 segments (left main (LM), proximal, mid- and distal segments), and stented segments were assessed for in-stent restenosis (significant or non significant lumen obstruction by hypo dense zones), edge-effect (significant or non significant stenosis at stent edges) and distal run off (normal, limited or no contrast opacification). The image analysis was performed with multiplanar reformatting, maximum intensity projection, and volume rendering. The sensitivity and specificity data includes segments deemed assessable as well as non-assessable (due to blooming artefacts).

Results: There were no stents in the LM, with 46 and 34 stents respectively in the left anterior descendens (LAD) and right coronary artery (RCA) mainly proximal and mid-segments, and 15 in the circumflex artery (CX). Angiographically there were 29 non patent stents, 15 of which were correctly identified by MSCT, and those mainly for the proximal segments. For all stented segments the specificity varied between 87% to 100%, and the sensitivity between 43 and 100%. For 31 proximal segments with stents (LAD, CX and RCA) there was 91% agreement between CT angiography and CA (kappa = 0.81). The sensitivity and specificity for these proximal segments were respectively 80% and 95%. For the mid- and distal segments with stents, the concordance between CT angiography and CA was only moderate, with sensitivities ranging between 43 - 87%, and specificity between 87 to 100%.

Conclusions: Non invasive assessment of stents in proximal coronary segments is feasible with MSCT, and shows very good concordance with CA. The newer generation MSCT scanners show improved assessment of mid- and distal coronary segments with stents.

P908 Accuracy of multidetector computed tomography (MDCT) in detecting significant coronary stenosis in patients with different pretest likelihood of coronary artery disease (CAD)

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Background: MDCT has recently been introduced as a promising method for non-invasive imaging of CAD. Previous studies have shown high feasibility (Fe) and sensitivity (Se), good specificity (Sp) associated with global negative (NPV) and positive predictive values (PPV) of 95-98% and 80% respectively in selected populations, generally with high prevalence of CAD. Few data are available concerning patients (pts) with lower prevalence of CAD.

Aim: The aim of this study was to test the accuracy of MDCT to detect CAD as compared to invasive coronary angiography (CA) in population with different pretest likelihood of CAD.

Methods: we studied 120 consecutive pts (82 males, age 62 ± 10 years) with history of chest pain, scheduled for conventional coronary angiography. At admission, pretest likelihood of CAD was determined according to AHA/ACC guidelines for the management of chronic stable angina defining two types of chest pain: atypical angina (Group 1) and typical angina (Group 2). All pts underwent to MDCT (GE Medical System Light Speed Pro 16) before CA. A single intravenous dose of metoprolol was administered 15 minutes before the scan if the heart rate was >65 beats/min. The MDCT data sets were analyzed by three expert readers blinded to clinical history and tested versus CA in detection significant

stenoses (≥50% diameter reduction) in both groups analyzing any differences among groups.

Results: 37 out of 120 pts (31%) received intra-venous dose of metoprolol (average dose: 4.8 ± 1.2 mg). Four patients were excluded because heart rate was above of 70 beats/min despite b-blockade treatment. The average heart rate was 61 ± 9 beats/min. The global Fe of MDCT was 92% for all vessels excluding small vessels (diameter ≤ 1.5 mm). Group 2-pts were older than Group 1-pts (66 ± 9 vs 60 ± 10 years respectively, p<0.05) and the prevalence of CAD was lower in Group 1 vs Group 2 (41% vs 77% respectively, p<0.01). In comparison to CA the sensitivity, specificity, positive and negative predictive value were: Group 1 (Se: 100%, Sp: 89%, PPV: 88%, NPV: 100%); Group 2 (Se: 100%, Sp: 75%, PPV: 93%, NPV: 100%). Chi-Squared test between the two groups showed a significant reduction of Sp in the Group 2 (p<0.05).

Conclusions: Our data confirmed the high accuracy of MDCT in ruling-out coronary lesions independently of pretest likelihood of CAD. However MDCT is more useful in pts with lower prevalence of CAD because of more higher Sp, suggesting an important clinical role particularly in the evaluation of pts with atypical angina avoiding unnecessary invasive procedures.

P909 Role of pre-operative multidetector computed tomography in biventricular devices implantation

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Background: biventricular ventricular pacing has been shown to improve hemodynamic and clinical status of patients with advanced congestive heart failure (HF). Placement of the lead in a coronary sinus (CS) tributary requires accurate knowledge of CS anatomy and of its veins. Aim of this study was to compare success rate and procedural times in pts underwent ICD implantation in whom CS anatomy study was performed during implant by retrograde venography (RV) or by pre-operative ECG-triggered multidetector computed tomography (MDCT).

Methods: 20 pts (mean age 60.6±6.8 years) were enrolled. In 10 pts (Group 1), a MDCT was performed before implantation (16-slices Lightspeed, General Electric, USA); 10 pts (Group 2), during implantation underwent a conventional RV. Success rate, total procedural times, time to CS cannulation and time to insert the left lead into a CS major vein were compared in the two groups.

Results: in pts of Group 1, success in insertion of left ventricular lead was higher than in Group 2 (95 vs 85%). In Group 1 a significant reduction of total procedural times was noted (127±26 vs 187±38 minutes of Group 2, p<0.03); similarly, time to CS cannulation and time to place the lead in the target vein were lower in Group 1 (11±5 vs 18±4 minutes, p<0.04 and 22±14 vs 44±16 minutes, p<0.03, respectively).

Conclusions: pre-operative visualization by MDCT of position of CS ostium and of location, diameter and angulation of CS tributaries improves success rate of biventricular implantation; non-invasive identification of left target vein allows a more accurate choice of guide-catheter, guidewires, and of shape of left ventricular lead.

P910 Effect of statins on non-calcifying coronary plaque: Noninvasive monitoring with Multislice Computed Tomography

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Purpose: Statins may influence coronary plaque composition. The aim of this study was to assess the effects of a lipid-lowering therapy on non-calcifying coronary artery plaque with multislice computed tomography (MSCT) after 6 months and 1 year treatment with statins.

Methods: 43 coronary plaque (in 11 patients) were assessed with 16-multislice computed tomography (MSCT) angiography (Sensation 16™, Siemens) (16 x 0.75 mm; rot. 0.42; TF= 6.5 mm/s; 500 mAs; 120 kV; eff. slice 1 mm; inc. 0.6; B10f; retrospective ECG gating; 100 ml Iodixanol (Visipaque® 320, Amersham); flow rate 3-4 ml/s) baseline and after 6 months or 1 year treatment with statins (20 mg atorvastatin/day or 20 mg simvastatin/day). Plaque area (PA), lumen area (LA) and mean CT-densities of non-calcifying plaque expressed as Hounsfield Units (HU) were measured with dedicated software. Exclusively non-calcifying plaques at proximal coronary segments were taken for the analysis.

Results: After 1 year treatment with statins (coronary plaque:n = 20), a significant regression of plaque area (0.10 cm² vs. 0.05 cm²; p < 0.001) and a significant increase in mean CT-densities from 63 HU to 90 HU (p < 0.05) suggesting an increase in fibrotic and a reduction of lipidic plaque component was observed. After 6 months (coronary plaque:n=24), a moderate but yet significant decrease in PA (0.17 cm² vs. 0.14 cm²; p=0.02) was observed. The difference in luminal area was not significant after 6 months (0.06 cm² vs. 0.07 cm²) and 1 year (0.12 cm² vs. 0.14 cm²) treatment. The mean difference in the intraluminal contrast attenuation was ±4.6 HU (0.6 - 14.4 HU).

Conclusion: MSCT provides a non-invasive imaging modality for serial monitoring of non-calcifying coronary artery plaque in patients who receive statin ther-

apy. Statins may induce regression and may lead to stabilization of non-calcifying coronary plaque.

P911 Feasibility and diagnostic accuracy of multidetector computed tomography coronary angiography in patients with dilated cardiomyopathy



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Introduction: The prevalence of coronary artery disease (CAD) in patients with dilated cardiomyopathy (DCM) of unknown etiology is approximately 50% and therefore coronary angiography is mandatory. Recent studies with multidetector computed tomography (MDCT) showed very high level of sensibility in detecting CAD and MDCT may be proposed as a non-invasive screening test. Aim of the study: To evaluate the feasibility and accuracy of coronary imaging by MDCT in a population with DCM of unknown etiology vs conventional coronary angiography. Materials and methods: 61 patients (47 males, 14 females; age 62 ± 12 years) affected by DCM (ejection fraction: $33 \pm 8\%$, end diastolic volume: 199 ± 89 ml) in stable clinical conditions underwent to coronary angiography and coronary MDCT. MDCT images has been acquired by means of CT 16 layers (Light speed General Electric) and evaluated with multiple approach including volume rendering and vessel analysis. The degree of stenosis was estimated in 15 segments of coronary arteries: left main (LM), proximal, medium and distal left anterior descending (LAD), first and second diagonal branch (D1 and D2), proximal, medium and distal left circumflex (LCX), first and second marginal branch (M1 and M2), proximal, medium and distal right coronary artery (RCA) and posterior descending (PD).

Results: MDCT overall feasibility of coronary artery visualisation was 97.2% (863 of 888 segments). Major cause of artifact is interference of hypertrophic cardiac venous system (10 artifacts, 40%). At conventional coronary angiography 44 of cases had normal coronary arteries. All cases with normal (44) or pathological (17) coronary arteries were detected by MDCT, even though in 1 case a disparity in term of severity of stenosis was observed. In comparison to conventional angiography, sensitivity, specificity and positive and negative predictive value to identify > 50% obstructed branches was 99%, 96.2%, 81.2% and 99.8% respectively. Sensitivity was 100% for all segments with the exception of M2. Specificity value in the different segments was included between 92% (distal LAD) and 100% (distal LCX and PD).

Conclusions: our results suggest that feasibility of evaluation of the entire coronary tree in the DCM is very high (97.2%). The almost absolute absence of false negative in the detection of the degree of stenosis (sensitivity 99%, VPN 99.8%) could allow MDCT as screening test for detection of CAD in dilated cardiomyopathy.

YOUNG INVESTIGATORS' AWARD SESSION BASIC SCIENCE

913 Thrombospondin-2 acts as a soldier against age-related cardiomyopathy



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Background: The progressive shift from young age to senescence is characterized by structural and functional changes in the cardiac extracellular matrix (ECM). Recently our group revealed a yet unknown protective role of thrombospondin-2 (TSP2) against pressure-overload induced heart failure by reinforcing matrix integrity. The current study investigated whether TSP2 may protect against age-related cardiomyopathy.

Methods and Results: TSP2 wild type (WT) (n=24) and TSP2 deficient (KO) (n=20) mice were followed for up to 55 weeks. Survival with aging was significantly decreased in the TSP2 KO mice compared with TSP2 WT mice: only 11 out of 20 TSP2 KO-mainly female-mice survived at 55 weeks, whereas all TSP2 WT mice survived. Echocardiographic analysis revealed increased cardiac dilatation and decreased systolic function in TSP2 KO vs. WT mice (end-diastolic diameter, mm; 3.05 ± 0.29 in KO vs. 2.6 ± 0.14 in WT, $P < 0.05$; % fractional shortening: 35 ± 2.0 in KO vs. 46 ± 2.7 in WT mice, $P < 0.05$). Concordantly, load-independent performance at pressure-volume loop analysis was significantly decreased in TSP2 KO mice at 55 weeks (Ees, 5.9 ± 2 in KO vs. 9.6 ± 2.5 in WT mice, $P < 0.01$). At 24 weeks systolic function was decreased in TSP2 KO mice (% fractional shortening: 26.1 ± 9.6 in KO vs. 37.9 ± 9.8 in WT mice, $P < 0.05$). In addition, end-diastolic pressure-volume relationship, a parameter for diastolic function was significantly decreased in female KO mice (0.12 ± 0.03 in KO vs. 0.20 ± 0.03 in WT), whereas stroke work and pressure corrected contractility were significantly decreased in male KO mice at 24 weeks. Histological analysis revealed severe myocyte necrosis and increased cardiac collagen content in TSP2 KO compared with WT mice at 55 weeks (% Sirius red/total area: 6.5 ± 3.2 in KO vs. 0.8 ± 0.4 in WT, $P < 0.05$). Accelerated myocardial aging and myocyte suffering in TSP2 KO mice was

further demonstrated by increased immunoreactivity of p16 (aging), ubiquitin (aging and injury), desmin (injury) and annexin (apoptosis) in myocytes of TSP2 KO compared with WT hearts.

Conclusion: In conclusion, TSP2 is essential to protect against age-related dilated cardiomyopathy and heart failure.

914 Human epicardium-derived cells: a novel source of autologous cells for myocardial repair



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Background: During embryonic development ingrowth of epicardium-derived cells (EPDCs) into the premature myocardium is essential for the proper development of compact myocardium, the coronary vessels and the Purkinje network. We hypothesised that after transplantation of adult human EPDCs (hEPDCs) in ischemic myocardium the embryonic program can be recapitulated and thus can improve cardiac performance after myocardial infarction (MI).

Methods: hEPDCs were isolated from human atrial tissue and characterised by immunohistochemistry, FACS and RT-PCR. MI was created in immune-compromised NOD/scid mice by ligation of the LAD, followed immediately by intramyocardial injection of 4×10^5 hEPDCs labelled with eGFP in culture medium (n=17) or culture medium only (n=14). After induction of MI, infarct size (after 2 days) and left ventricular function (after 2 and 14 days) were assessed using a 9.4 T animal-MRI. Subsequently, mice were sacrificed and processed for immunohistochemistry. Data were analysed using 'Mass for Mice' software.

Results: hEPDCs were positive for GATA-4, Mef2c and cTnT. All functional parameters were corrected for infarct size assessed on day 2. Ejection fraction (EF) on day 2 did not differ between groups (hEPDC: $29.2 \pm 1.5\%$ vs. control: $27.7 \pm 1.7\%$, p=n.s.). In the hEPDC-injected group EF on day 14 was significantly higher than in the medium-injected group (hEPDC: $25.9 \pm 1.3\%$ vs. control $12.7 \pm 1.4\%$, $p < 0.001$). End-systolic volume (ESV) and end-diastolic volume (EDV) on day 14 were significantly smaller in the hEPDC-injected group as compared to the medium-injected group (hEPDC: $87.1 \pm 5.8 \mu\text{l}$ vs. control: $122.8 \pm 6.4 \mu\text{l}$, $p = 0.001$ and hEPDC: $116.5 \pm 5.6 \mu\text{l}$ vs. control: $140.1 \pm 6.2 \mu\text{l}$, $p < 0.05$, respectively). Immunohistochemistry at day 15 showed massive engraftment and survival of the injected hEPDCs, which appeared as elongated cells incorporated in the ischemic border zone and the free wall of the left ventricle.

Conclusions: Intramyocardial injection of adult hEPDCs resulted in engraftment of the transplanted cells, preserved left ventricular function and reduced left ventricular remodelling two weeks after MI. These results suggest that hEPDCs isolated from autologous atrial tissue might be a novel cell type to be used in clinical cardiac cell therapy.

915 Novel injectable alginate scaffold attenuates progressive infarct expansion and preserves left ventricular systolic and diastolic function late after myocardial infarction



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Background: Cessation or reversal of progressive left ventricular (LV) dysfunction is a major aim of heart failure therapy. We developed a cross-linked concentrated alginate solution, which upon solidification in tissue becomes a hydrogel. The aim of the present study was to test the hypothesis that an injection of this novel alginate solution mimicking the extracellular matrix (ECM) into an old scar tissue, late after myocardial infarction (MI), will provide physical and biological scaffolding, promote tissue rejuvenation and will prevent progressive LV dysfunction.

Methods and results: Rats (n=40) were subjected to extensive anterior myocardial infarction (MI). Two months later, the survivors were randomized to injection of alginate solution (n=15) or PBS (control, n=12) into myocardial scar. Four months after MI and two months after injection, postmortem morphometric analysis and histological examination of the hearts revealed that alginate solution injection increased scar thickness (2.79 ± 0.27 cm vs. 1.63 ± 0.31 cm; $p = 0.01$) and significantly reduced expansion index (0.56 ± 0.08 vs. 1.05 ± 0.26 ; $p < 0.0001$), as compared with controls. Serial echocardiography studies showed that alginate solution injection attenuated the progressive deterioration in LV fractional shortening, as compared with control ($12 \pm 6\%$ vs. $37 \pm 9\%$; $p < 0.05$). Anterior wall diastolic and systolic thickness were markedly increased in alginate-treated hearts ($25 \pm 4.5\%$ vs. $7 \pm 6.7\%$; $p = 0.03$, and $31 \pm 6.2\%$ vs. $3 \pm 6.8\%$; $p = 0.006$, respectively). Furthermore, while control animals developed restrictive LV filling pattern, as assessed by Doppler echocardiogram, diastolic function improved in alginate-treated hearts (E/A wave ratio of 1.73 ± 0.09 for alginate vs. 3.34 ± 0.5 for control; $p < 0.0001$).

Conclusions: Our work shows, for the first time, that injection of in situ gelling solution of cross-linked alginate into an old scar tissue provides physical and biological scaffolding, and preserves LV systolic and diastolic function. Our work enables a minimally invasive, catheter-based, acellular option to repair old scar tissue and to prevent heart failure.

916 The sarcolemmal calcium pump: a novel mediator of cellular signalling and contractile function in the heart

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Calcium transport within the cardiomyocyte and across the sarcolemma regulates two essential processes in the heart, contraction and signalling. However, the mechanisms by which the myocardial cell distinguishes between these two functions of calcium remain unclear. The sarcolemmal calcium pump (or PMCA: plasma membrane calcium/calmodulin-dependent ATPase) has been regarded as a calcium transporter that is not directly involved in the excitation-contraction cycle. However, we have previously shown in an in vitro system (HEK293 cells) that the isoform 4 of PMCA regulates nNOS, an important determinant of cardiac contractility. Here, we analyse whether PMCA4 regulates cardiac contractile function in vivo by mediating nNOS activity. We have generated mice deficient in PMCA4 (PMCA4^{-/-}), mice overexpressing PMCA4 specifically in the heart, and mice overexpressing mutant form of PMCA4 ct120. PMCA4 ct120 is a constitutively active mutant form of the pump which does not interact with nNOS. We employed an integrated approach incorporating in vivo haemodynamics studies, as well as cellular and molecular analyses to study the role of PMCA4 in the regulation of cardiac contractility. Ca²⁺ was extruded normally from PMCA4^{-/-} cardiomyocytes, however, both contractility and speed of relaxation were significantly elevated in PMCA4^{-/-} mice in vivo. Treatment with a selective nNOS inhibitor abolished the differences in contractile function between wild type and PMCA4^{-/-} mice demonstrating that our observed changes in contractility were due to altered nNOS activity and a marked downregulation of nNOS was demonstrated. In PMCA4 overexpressing mice, basal haemodynamic parameters were not different compared to wild type littermates. However, the inotropic response following isoproterenol was significantly attenuated. Interestingly, when we overexpressed PMCA mutant ct120, which does not interact with nNOS, these changes did not occur. Moreover, treatment with a selective nNOS inhibitor reduced the beta adrenergic response in wild type and PMCA4ct120 mice to levels comparable with PMCA4 overexpressors, suggesting that modulation of nNOS was likely the mechanism responsible for this phenotype. In conclusion, our data provide the first in vivo evidence that PMCA4 regulates cardiac contraction and beta adrenergic signalling by modulating nNOS activity. Through its novel regulatory role for cardiac contractility and inotropic response, alterations in the activity of PMCA may be relevant in the development of new treatment modalities for heart failure.

YOUNG INVESTIGATORS' AWARD SESSION THROMBOSIS

918 Factor Seven Activating Protease expression enhanced by differentiation of human monocytes into macrophages and accumulated in coronary atherosclerotic plaques

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Introduction and hypothesis: Factor seven activating protease (FSAP) is a novel plasma serin protease and it is considered to be a potent activator of factor VII independent of tissue factor, and suggested to be predictor for the evolution and progression of atherosclerosis. Little is known about the physiologic or pathophysiological cellular expression of this protease. The present study was performed (i) to characterize FSAP expression in immunocompetent cells and (ii) to investigate whether FSAP is present in coronary atherosclerotic plaques and normal vessels.

Methods: FSAP gene and protein expression was analyzed in stimulated and un-stimulated cultured human monocytes, monocyte-derived macrophages, monocyte-derived dendritic cells, lymphocytes, endothelial cells and coronary smooth muscle cells with the use of real-time RT-PCR, Western blot techniques, immunoprecipitation and immunocytochemistry. Directional coronary atherectomy specimens from 23 lesions were analyzed by using the immunohistochemistry, real-time RT-PCR and Western blot techniques.

Results: Monocytes, macrophages, dendritic cells and lymphocytes, but not endothelial cells and coronary smooth muscle cells, were found to express FSAP on both gene and protein levels. Macrophages presented significantly higher FSAP expression than undifferentiated monocytes. In contrast, dendritic cells differentiated from monocytes strongly down-regulated FSAP expression. Pro-inflammatory cytokine IL-1 had no detectable effect on the extent of FSAP expression, but LPS had biphasically affect and IL-6 induced a time dependent increase in expression of FSAP. FSAP antigen and mRNA expression was detected in coronary atherosclerotic lesion as demonstrated by ex vivo analysis of human coronary atherectomy specimens. Gene analysis showed that the FSAP gene was significantly more expressed ($p < .001$) and FSAP antigen had an increased positive staining both intracellularly and extracellularly ($p < .004$) in acute coronary syndrome cases compared with stable angina cases. FSAP accumulated focally also in lipid-rich areas within the necrotic cores of the atherosclerotic plaques of human internal mammary artery, but not in normal vessels.

Conclusions: This is the first study to demonstrate that immunocompetent

cells such as monocytes, macrophages, dendritic cells and lymphocytes express FSAP on both protein and mRNA level. The detection of FSAP within coronary atherosclerotic lesions identifies a so far unrecognized procoagulant mediator in the diseased coronary vessel wall and may be related to the pathogenesis of plaque vulnerability and thrombogenicity.

919 Ximelagatran/melagatran versus conventional anticoagulant therapy: meta-analysis of 13 randomized controlled trials enrolling 22639 patients

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Background: The risk-benefit profile of the oral direct thrombin inhibitor ximelagatran, and its active form, melagatran (X/M), versus conventional anticoagulant therapy (CAT) is still largely debated. We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing X/M to CAT.

Methods and Results: Major medical databases were searched for RCTs in any clinical setting. Major adverse events (MAE: all cause death, nonfatal myocardial infarction, nonfatal thromboembolic stroke, pulmonary embolism), major bleeds (MB), minor bleeds, and the rate of hepatotoxicity (HT) were compared. Out of 140 potentially relevant citations, 13 RCTs, enrolling 22639 patients, were included. Indications for treatment were: 1) perioperative prophylaxis of deep vein thrombosis (DVT); 2) management of DVT; and 3) stroke prevention in atrial fibrillation. Overall, the risk of MAE (OR 0.98[0.83-1.17]), MB (OR 1.01[0.69-1.47]), minor bleeds (OR 0.99[0.83-1.18]) and HT (OR 1.89 [0.64-5.61]) was not significantly different for X/M compared to CAT. In pre-specified analyses restricted to individual clinical settings, X/M was associated with a lower risk of MB but a higher risk of HT, both in the management of DVT (OR for MB 0.51[0.27-0.98]; OR for HT: 5.86[3.38-7.89]) and in the prevention of atrial fibrillation-related stroke (OR for MB 0.71[0.55-0.92]; OR for HT 8.31[5.65-12.23]).

Conclusions: X/M is comparable to CAT in preventing MAE, with a lower risk of serious bleeding but a higher risk of HT in settings requiring prolonged treatment. Further investigations should aim at identifying clinical and biochemical predictors of hepatic toxicity by X/M.

920 Genetic polymorphisms on the $\alpha 2$ subunit of platelet integrin $\alpha 2 \beta 1$ affect the release of sCD40L and P-selectin during acute myocardial infarction and increase cardiovascular risk

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Platelet membrane integrin $\alpha 2 \beta 1$ (I- $\alpha 2 \beta 1$) has an important role in platelet activation during the acute phase of myocardial infarction (MI), as a receptor for collagen. Platelets activation is characterized by both the release of soluble CD40L (sCD40L) and P-selectin (P-Sel). Although silent genetic polymorphism C807T on the $\alpha 2$ subunit affects the density of I- $\alpha 2 \beta 1$ on platelet surface and G1648A determines the platelet Bra/b antigen system, their actual role on platelet activation during MI is unknown.

Aim: We investigated the role of C807T and A1648G on the risk for MI and the release of sCD40L and sP-sel during the acute phase of MI and one year after the event.

Methods: The study population consisted of 606 young subjects of the Caucasian race (aged 48.8 ± 3.2 years): 219 young patients with premature acute MI and 387 healthy controls. A sub-population of 67 patients and 232 matched controls were recalled one year after the event, to participate in the follow-up study. Distribution of C807T and G1648A polymorphisms were investigated with PCR, and plasma levels of sCD40L and P-Sel were measured by ELISA.

Results: The genotypes distribution were for 807TT/CT/CC: 34/112/73 in patients and 30/214/143 in controls ($p < 0.05$) and for 1648GG/AG/AA: 161/50/8 in patients and 300/77/10 in controls ($p = NS$). The risk for MI in 807TT was 2.296(1.187-4.440) $p = 0.014$ after adjustment for potential confounders. During the acute phase of MI, both plasma sCD40L and P-sel were significantly higher in 807CT+TT (12.77 ± 1.22 pg/ml and 68.2 ± 4.9 ng/ml respectively) compared to CC (7.12 ± 0.93 pg/ml and 39.9 ± 3.67 ng/ml respectively, $p < 0.01$ for both). One year after the event, although sCD40L and P-sel were decreased in all genotypes, they remained higher in CT+TT (8.73 ± 0.97 pg/ml and 51.1 ± 3.6 ng/ml) compared to CC (4.35 ± 0.93 pg/ml and 37.2 ± 2.6 ng/ml respectively, $p < 0.01$ for both). The increase of sCD40L and P-sel from rest (at one year) to the acute phase levels was significantly higher in CT+TT compared to CC ($p < 0.01$). In healthy controls, sCD40L and P-selectin was not different in CC (4.19 ± 0.48 pg/ml and 31.1 ± 3.1 ng/ml respectively) compared to CT+TT (5.3 ± 0.33 pg/ml and 35.8 ± 1.8 pg/ml for both). G1648A had no effect on sCD40L and P-sel levels.

Conclusions: Genetic polymorphism C807T on platelet integrin $\alpha 2 \beta 1$ is a risk factor for premature MI, and it affects the release of sCD40L and P-selectin during the acute phase of MI, an effect sustained in the same patients one year after the event. These findings suggest that C807T polymorphism may modify platelets activation, especially during the acute phase of myocardial infarction.

921 The effect of ramipril on platelet function in patients with high cardiovascular risk: A double-blind randomized placebo-controlled evaluation of ramipril on platelet nitric oxide responsiveness

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Background: Angiotensin-converting enzyme inhibitors (ACEi) have previously been shown to have beneficial effects in preventing acute ischaemic events (HOPE and PROGRESS studies); however, these studies were not designed to elucidated mechanisms. We have previously shown that patients with myocardial ischaemia have impaired platelet responses to the anti-aggregatory effects of nitric oxide (NO resistance), and that NO resistance is an adverse prognostic marker. More recently we have shown that short-term ACEi therapy increases platelet NO responsiveness in patients with congestive heart failure. Therefore current study was designed to test the hypotheses that in a high risk (HOPE study-type) patient cohort (a) ramipril sensitizes platelets to NO, and (b) that the putative effects of ramipril are accentuated in the presence of NO resistance.

Methods: In a double-blind study of 3-months duration patients (n=119) who either had known ischaemic heart disease or diabetes + additional coronary risk factor(s) were randomized to ramipril (10mg/day; n=60) or placebo (n=59). Platelet aggregation, its inhibition by the NO donor sodium nitroprusside (SNP) and arterial stiffness (expressed as augmentation index [AIx]) were assessed at baseline and 3 months after randomization. Responses to SNP were corrected for changes in ADP response during the study. Platelet NO resistance was defined as baseline SNP response <35% inhibition of aggregation. Plasma levels of asymmetric dimethyl arginine (ADMA) were measured as an index of endothelial dysfunction.

Results: Mean patient age was 67±9 (SD) years. Ramipril therapy significantly increased ΔSNP: ΔADP response relative to placebo in the entire group (p=0.002, ANCOVA), and also reduced AIx (p=0.02) and ADMA levels (P=0.05). Interestingly, changes in response to SNP occurred entirely in the NO resistant patient subgroups (n=28 ramipril versus n=21 placebo), with change in SNP response for ramipril/placebo groups of 33.1±6.3/13.5±5.1% inhibition of aggregation for NO resistant patients (p=0.02) versus -11.2±5.5/-5.0±4.9% for the remainder of the patients (p=ns).

Conclusions: In a HOPE study-type patient population ramipril sensitizes platelets to NO. However, this effect largely reflects amelioration of responses in patients with severe NO resistance. Thus it is possible that reversal of platelet NO resistance contributes to the beneficial effects of ramipril.

YOUNG INVESTIGATORS' AWARD SESSION CORONARY PATHOPHYSIOLOGY AND MICROCIRCULATION

923 Restoration of coronary microvascular function in the infarct-related artery by bone marrow-derived progenitor cells after acute MI: results from the double-blind, placebo-controlled REPAIR-AMI trial

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In patients (pts) with acute myocardial infarction (AMI), dysfunction of the coronary microcirculation promotes death of myocytes in the infarct border zone. The resulting infarct extension is associated with further deterioration of left ventricular function and, consequently, a poor prognosis. Recently, intracoronary (i.c.) infusion of bone marrow-derived progenitor cells (BMC) in pts with reperfused AMI has been shown to augment cardiac function and prevent endsystolic volume expansion. This was partially attributed to an improved progenitor cell-mediated neovascularization, but clear evidence from studies in humans is missing so far. Therefore, the "i.c. Doppler substudy" of the randomized, double-blind, and placebo-controlled REPAIR-AMI trial (Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction) aimed to investigate the effects of an i.c. BMC therapy on coronary blood flow regulation in pts with reperfused AMI. In this substudy, a total of 54 pts were enrolled (BMC group: n=28; placebo group: n=26). Coronary blood flow regulation in the infarct artery as well as in a reference vessel was assessed by i.c. Doppler at the time of study therapy and at 4 months follow-up.

Results: At the time of study therapy (4.3±0.1 days after AMI), coronary flow reserve (CFR) was reduced in the infarct artery as compared to the reference vessel in both groups (BMC: 2.0±0.1 in the infarct artery vs. 2.9±0.2 in the reference vessel, p<0.05; placebo: 1.9±0.1 in the infarct artery vs. 2.8±0.2 in the reference vessel, p<0.05). At 4 months follow-up, CFR in the infarct artery had slightly improved in the placebo group (+0.88±0.18; p<0.001 vs. initial), but was markedly increased by 90% (+1.80±0.25; p=0.005 vs. placebo) in BMC-treated pts resulting in a complete normalization of CFR in the infarct-related artery (3.8±0.2, p<0.001 vs. initial and placebo). In the infarct artery, adenosine-induced mini-

mal vascular resistance declined slightly in the placebo group (from 1.77±0.12 to 1.52±0.15 mmHg*s/cm, p<0.05), but considerably decreased by -29±6% in the BMC group (from 1.86±0.19 to 1.20±0.12 mmHg*s/cm, p<0.05 vs. initial and placebo).

Conclusion: Intracoronary BMC therapy after AMI normalizes coronary flow reserve in the infarct-related artery. The restoration of microvascular function was associated with a significant improvement of maximal vascular conductance capacity. These data provide clinical proof-of-concept that progenitor cell transplantation promotes vascular repair, either through paracrine mechanisms or directly due to an improved neovascularization.

924 Cardiac troponin I elevation following successful percutaneous coronary intervention: effects of an acute oral loading dose of Trimetazidine

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Background: In the setting of percutaneous coronary intervention, the magnitude of troponin I (cTn I) elevation directly correlates with irreversible myocardial injury assessed by cardiovascular magnetic resonance imaging and has an independent prognostic value. Trimetazidine (TMZ) reduce per-procedural myocardial cells ischemia during coronary angioplasty.

Purpose: We hypothesized that a loading dose of TMZ would reduce the frequency and the intensity of minor myocardial necrosis because of its beneficial effects on several mechanisms involved in cardiac protection against ischemia.

Methods: 582 consecutive patients undergoing successful single vessel stenting were prospectively studied in a double-blind, controlled randomised trial. Patients were randomly assigned to receive orally an acute loading dose (60mg) of TMZ before angioplasty. cTn I levels were measured before angioplasty and 6, 12, 18 and 24 hours after the procedure to measure myocardial injury.

Results: To compare the total amount of cTn I release after angioplasty between the two groups, we calculated the area under the curve (AUC) of post procedural cTn I serial measurement (figure 1). The AUC appears to be significantly higher in the control group than in the TMZ group (p<0.05). The total amount of cardiac myonecrosis after coronary angioplasty is significantly reduced by an oral loading dose of TMZ. This cardio-protective effect was found despite the fact that the TMZ group exhibited higher risk profile for complications considering both clinical and angiographic data.

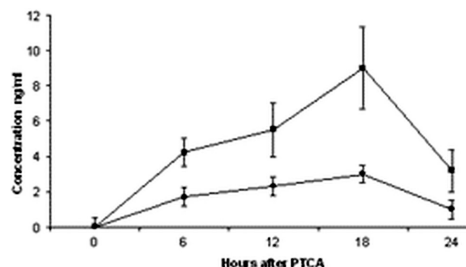


Fig. 1. Levels of cTn I before (0) and 6, 12, 18 and 24 hours after angioplasty in the TMZ group (circle) and in the control group (square).

Conclusions: To our knowledge, this is the first study demonstrating the efficiency of a loading dose of TMZ before coronary angioplasty to prevent myocardial damage and may enhance long term outcome.

925 Inflammatory and anti-inflammatory variable clusters and risk prediction in acute coronary syndrome patients. A factor analysis approach

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Introduction: Numerous inflammatory mediators such as C-reactive protein (CRP), fibrinogen, interleukin-18 (IL-18), and inter-cellular adhesion molecule-1 (ICAM-1) have been proposed for risk stratification in acute coronary syndrome (ACS) patients. However, interactions between these markers have made it difficult to assess their true role in risk prediction. Factor analysis is a multivariable statistical technique that reduces large numbers of interrelated variables to a smaller set of independent clusters, underlining physiological relationships. The aim of this study was to investigate, using factor analysis, the predictive role of a clustering of: pro-inflammatory markers, anti-inflammatory cytokines i.e. interleukin -10 (IL-10), and HDL cholesterol, regarding recurrent coronary events in ACS patients.

Methods We assessed 320 consecutive ACS patients (236 men, 67 years of age

IQ range 58-74 years). The composite of cardiac death and re-hospitalization with non-fatal myocardial infarction, or ACS, was the pre-specified study end-point. Serum CRP, fibrinogen, HDL cholesterol, IL-10, IL-18 and ICAM-1 levels were measured at study entry. We assessed independent predictors of the combined end-point during a 1 year follow up using multiple logistic regression analysis.

Results Factor analysis identified 3 clusters which we classified as 1) "systemic inflammation" cluster, with positive loadings of CRP and fibrinogen, 2) "local inflammation/endothelial dysfunction" cluster, with positive loadings of IL-18 and ICAM-1 and 3) "anti-inflammatory" cluster comprising IL-10 and HDL cholesterol. We found that only the "anti-inflammatory" cluster was a significant predictor (OR 0.66 95%CI 0.49-0.89) of adverse cardiac events during a 1 year follow up, and remained to be a significant predictor (OR 0.65 95%CI 0.48-0.88) in a multivariate model that included all 3 factors.

Conclusion Although inflammatory markers such as CRP have been shown to predict future cardiovascular events in ACS patients, when all inflammatory mediators are taken into account in a prospective analysis of risk, markers reflecting anti-inflammatory mechanisms appear to be better prognostic markers.

926 Increased mast cell accumulation and activity contribute to angiogenesis and preserve microvascular function after coronary microembolization



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Enhancement of angiogenesis after coronary microembolization (CME) might prevent progressive microvascular dysfunction. Mast cells (MCs) are rich source of angiogenic cytokines that contribute to angiogenesis. However, the role of MCs on angiogenesis and microvascular function after CME is unclear.

Methods: We induced CME in 27 miniswine by selective infusion of 15×104 microspheres (45µm) into left anterior descending artery (LAD). At Day 1 (D1), 7 (D7) and 30 (D30), we measured 1) expression of von-Willebrand factor (vWF) as index of angiogenesis; 2) MC s density and degranulation and collagen fraction using immunohistological staining. Coronary flow reserve (CFR) was assessed by Doppler wire over LAD at D1, D7, D30 after CME. Four animals with injection of saline to LAD were served as control group.

Results (vs. control/baseline, *P<0.05): After CME, the number of MCs, degranulated MCs, collagen fraction, and capillary density (vs. control) increased significantly at D1 & D7 and persistently elevated in D30 (Table). CFR decreased significantly at D1 (vs. baseline) after CME but restored to baseline at D7 & D30 (Table). There are significant positive correlations between the number of MCs (r=0.80, p<0.01) and activated MCs (r=0.78, p<0.01) with LV angiogenesis.

Table

	Control/Baseline	Day 1	Day 7	Day 30
CFR	2.4±0.3	1.7±0.3*	2.8±0.7	2.3±0.6
MCs No/HPF	3.2±0.4	7.8±1.9*	11.5±2.2*	13.8±2.1*
De-MCs No/HPF	0.06±0.02	2.6±0.7*	4.7±0.9*	5.8±1.3*
vWF No/HPF	1.7±0.6	2.4±1.6	5.4±1.8*	10.5±2.0*
Collagen fraction (%)	0.04±0.01	0.7±0.2*	4.6±1.0*	10.3±2.3*

Conclusions: MCs accumulation after CME was associated with an increased LV angiogenesis, and restoration of CFR. These findings suggest that MCs contribute to angiogenesis and preserve microvascular function after CME.

YOUNG INVESTIGATORS' AWARD SESSION CLINICAL SCIENCE

928 Effects of exercise training on mobilization of BM-CPCs and migratory capacity



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Background: Bone marrow-derived circulating progenitor cells (BM-CPCs) are mobilized in adult peripheral blood (PB) during the acute myocardial infarction period and contribute to the regeneration of infarcted myocardium. We examined the influence of physical training on the mobilization and the migratory activity of the BM-CPCs as well as on the left ventricular function (LVEF) after acute myocardial infarction (AMI).

Methods: In this study 33 patients with AMI were analyzed in two groups: In the first group 22 patients with standardized exercise training for 3 weeks 14±4 days after AMI; in the second group 11 patients control subjects without exercise training. Peripheral blood concentrations of CD34/45+ and CD133/45+ were measured by FACS. The migratory activity of BM-CPCs was analyzed by migration assay. BNP in PB and the functional investigations; spiroergometry (VO2 and PaO2) and stress echocardiography (LVEF) were determined in both groups.

Results: We found an significant increase in both concentrations CD34/45+ and CD133/45+ (CD34/45+: p=0.004, CD133/45+: p<0.001) also in migratory capacity of BM-CPCs (VEGF<0.001, SDF<0.001) after 3-weeks of exercisetraining, which was significant decreased 3 months after completion of exercise training. No significant difference was observed in control group without exercise training (CD34/45+: p=0.45, CD133/45+: p=0.65, VEGF: p=44, SDF: p=0.95). In the functional investigations were showed spiroergometric a significant increase of VO2 as well as PaO2 after exercise trainings, wich was decreased in control group without exercise training. There was no difference stress echocardiographic LVEF at rest in both groups. On the other hand interestingly, our findings showed that the increase of LVEF at peak stress was significant higher after exercise training as compared to control group (p=0.02). Moreover, we found significantly decrease in BNP-values after exercise training (p=0.04) as well as 3 months after AMI (p=0.01). No difference was found in control group.

Conclusions: Our study demonstrates that the exercise training for 3 weeks after AMI lead to a significant Mobilization as well as increase of functional activation of BM-CPCs after AMI in human. Moreover, the regular exercise training might contribute to the positive effects on the regenerative potency after AMI.

929 Flt-1 as an early diagnostic marker in acute coronary syndromes



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Background: Recent experimental and first clinical data have shown a potential role of the vascular endothelial growth factor family and its fms-like tyrosine kinase (Flt)-1 receptor in acute coronary syndromes (ACS). This study was designed to evaluate the diagnostic and prognostic value of Flt-1 in ACS patients.

Methods: In 1839 consecutive patients with documented CAD (1096 with stable angina and 743 with ACS) baseline concentrations of Flt-1 were measured along with the classical indicators of ACS i.e. troponin I, creatin kinase MB, myoglobin and additionally B-type natriuretic peptide. Biomarker concentrations were evaluated for the time categories 0-6hours and over 6hours after symptom onset against 264 normal control subjects. During a follow-up of 2.5 years (median) cardiovascular events were registered.

Results: Flt-1 concentration peaked early (0-3hours) after chest discomfort onset and rapidly decreased in its plasma concentrations afterwards. In comparison with control individuals (median (25th/75th interquartile range) concentration: 28.5 (17.7/41.8) ng/ml) and stable angina patients concentration: 56.8 (27.3/157.9) ng/ml) Flt-1 levels were higher in ACS patients (137.3 (51.0/358.9) ng/ml) (p<0.001). Flt-1 correlated well with troponin I and creatine kinase MB. Further analysis was restricted to patients with non-ST-elevation myocardial infarction and unstable angina. The Receiver Operating Characteristic (ROC) curve analysis revealed that within the first 6 hours after symptom onset the area under the curve (AUC) for the detection of ACS was highest for Flt-1 (0.909, (95% confidence interval 0.816-1.000)) in comparison with control subjects. For troponin I the AUC was 0.833, (0.705-0.961). After 6 hours its AUC declined towards 0.834. Similar results were observed for Flt-1 in unstable angina patients only. Within the first 6 hours this marker revealed an AUC of 0.917 for the detection of ACS. In the differential diagnosis against SAP patients Flt-1 (AUC: 0.797) was the second strongest marker after troponin I (AUC: 0.844) within the first 6 hours and the strongest in the unstable angina subgroup (AUC: 0.762). No significant association was observed between event free survival and Flt-1 baseline concentrations. **Conclusion:** The current prospective study for the first time demonstrates that Flt-1 is elevated early in acute coronary syndromes and may provide important diagnostic information in the differential diagnosis of acute chest pain in addition to necrosis markers. Flt-1 levels were not significantly associated with cardiovascular outcome in CAD.

930 Five year follow-up in patients after therapy stratification based on intracoronary pressure measurement



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The aim of this study was to retrospectively evaluate the long-term safety of therapy stratification in patients with intermediate coronary lesions based on the fractional flow reserve (FFR). Earlier studies demonstrated the usefulness of FFR for identifying patients in whom deferring an intended percutaneous coronary intervention (PCI) would be more beneficial than performing the planned procedure. The long-term safety of FFR-based therapy stratification however, remains unknown.

Methods and Results: We included 80 patients presenting with a 50-75% angiographic stenosis by visual assessment and a negative, inconclusive, or missing stress test within the study period from 6/1998 to 6/2000. In patients with normal FFR values [i.e., FFR ≥ 0.75] (group 1), no intervention was performed. In patients with an FFR < 0.75 (group 2), intervention of the target segment was

performed. The primary endpoint was the occurrence of major adverse cardiac events during a five-year follow-up period, which was obtained in all patients. Mean follow-up was $1,883 \pm 442$ days. During follow-up, 35 events occurred (11 events, 0.3 per patient in group 1; 24 events, 0.6 per patient in group 2). Event-free survival at five years was 73% in group 1 and 50% in group 2, respectively ($p = 0.05$). Target vessel event-free survival was 93% vs. 65% (group 1 vs. group 2, $p < 0.05$).

Conclusion: The findings of the present study demonstrate the long-term safety of deferring PCI in patients with intermediate coronary lesions in whom the FFR is not critically reduced. Whether this hypothesis will hold true in the era of drug eluting stents merits further evaluation.

931 Matrix metalloproteinase-3 genotype is associated with higher coronary plaque burden, positive remodelling and increased risk of unstable disease



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Objectives: Matrix metalloproteinases (MMPs) are plausible candidates for susceptibility to acute coronary syndrome. We hypothesised that common MMP polymorphisms would relate to corresponding MMP plasma levels, coronary plaque characteristics and unstable clinical presentation.

Methods: 201 patients with de novo presentation of coronary artery disease undergoing coronary angiography were classified into unstable coronary syndrome ($n=122$) and stable angina pectoris ($n=79$) groups using Braunwald criteria. Patients were genotyped for 4 common MMP promoter polymorphisms (MMP-1 -1607 1G/2G, MMP-2 -1306 C to T, MMP-3 -1171 5A/6A, MMP-9 -1562 C to T). Plaque characteristics were assessed in a sub-group of 40 patients using intravascular ultrasound.

Results: The 6A allele of the MMP-3 polymorphism was associated with unstable clinical presentation ($p=0.007$). Furthermore, 6A allele carriers had higher plasma MMP-3 concentration (15.8 ± 12.5 versus 11.7 ± 7.2 , ng/mL, $p=0.01$), maximum coronary stenosis ($89 \pm 15\%$ versus $80 \pm 23\%$, $p=0.02$), plaque area (12.0 ± 5.2 versus 7.5 ± 3.6 mm², $p=0.03$), percentage plaque burden (82 ± 7 versus $71 \pm 13\%$, $p=0.003$) and remodeling ratio (1.03 ± 0.23 versus 0.83 ± 0.12 , $p=0.003$). Other genotypes did not relate to either plaque characteristics or clinical presentation.

Conclusions: The MMP-3 6A allele promotes positive coronary remodeling associated with greater plaque burden and increased susceptibility to unstable coronary syndromes in humans.

YOUNG INVESTIGATORS' AWARD SESSION POPULATION SCIENCES

933 Circulating leptin as an independent predictor of resting heart rate in the general population



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Background: Resting pulse rate (RPR) is a powerful indicator of cardiovascular mortality. Obesity is associated with increased RPR. Decreased physical activity, insulin resistance, subclinical inflammation and sympathetic activation have been implicated in this association. Leptin has recently been proposed as possible mediator of obesity-induced increased RPR through sympathetic activation and direct effects on the heart. We assessed the relationship between leptin and RPR in the US population.

Methods: We used weighted multiple regression to examine the relation between RPR and serum leptin levels among 2264 males and 2545 females enrolled in the Third US National Health and Nutrition Examination Survey.

Results: In both males and females, leptin was positively associated with RPR. After adjustment for age, ethnicity, physical activity, body mass index, insulin resistance, triglycerides, HDL cholesterol, C-reactive protein and creatinine clearance, leptin independently predicted RPR in both males ($\beta=6.7$; 95%CI=2.8-10.6; $p<0.0001$) and females ($\beta=5.97$; 95%CI=2.8-9.4; $p<0.0001$).

	Estimate	95% Confidence Interval	P value
Males (n=2264)			
(Log) Leptin	6.67	2.75 to 10.6	0.001
(Log) CRP (mg/dL)	5.52	2.64 to 8.39	<0.001
HOMA-IR	0.29	-0.22 to 0.8	0.26
Physical Activity	-0.007	-0.012 to -0.002	0.006
Females (n=2545)			
(Log) Leptin	5.97	2.8 to 9.14	<0.001
(Log) CRP (mg/dL)	1.41	-0.99 to 3.81	0.24
HOMA-IR	0.55	0.23 to 0.86	0.001
Physical Activity	-0.008	-0.014 to -0.002	0.007

All models included age, ethnicity, Ainsworth physical activity score, body mass index, insulin resistance (HOMA-IR), triglycerides, HDL cholesterol, C-reactive protein (CRP) and creatinine clearance.

Conclusions: Our study demonstrates a positive correlation between RPR and

serum leptin in the general adult US population, which is independent of physical activity, body mass index, metabolic and inflammatory factors and support the role of leptin as a mediator of obesity-related increase in RPR.

934 Differences in the risk associated with gender and other risk factors for cardiovascular disease in the presence of self-reported diabetes: the SCORE project



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Diabetes mellitus is a known risk factor for cardiovascular disease (CVD). The SCORE risk prediction charts do not include diabetes as a separate risk factor, and suggests that the calculated 10 year risk of fatal CVD should be multiplied by two in diabetic men and four in diabetic women. We examined the risks associated with self-reported diabetes in men and women, and the impact of diabetes on the relative effects of other risk factors in the SCORE study cohorts.

The constituent cohorts of the SCORE dataset questioned patients on whether they had diabetes, or whether a doctor had told them that they had diabetes. Cohorts with information on men only, or with no diabetes information, were excluded. The Finland, Norway, Scotland, Denmark, Germany, Italy and Belgium cohorts were included. Subjects with prior coronary heart disease were excluded. Using a Cox model, with age as time variable, and stratified by cohort, the hazard ratios for systolic blood pressure (SBP), serum cholesterol, smoking and sex were compared in the diabetic and the non-diabetic groups.

Results: Of a total population of 179,185 subjects, 3,814 (1,672 women and 2,142 men) had self reported diabetes. The hazard ratios associated with diabetes were higher in women (HR=4.4, 95% CI 3.7 - 5.3) than in men (HR=2.5, 95% CI 2.1 - 2.8). The relative effects of other risk factors (SBP, smoking and male sex) were significantly higher in non-diabetics compared with diabetics in a multivariate Cox analysis (Table 1).

Table 1. Effect of conventional risk factors in subjects without prior coronary heart disease, by diabetic status

Variable	Hazard Ratio in Diabetics (95% CI)	Hazard Ratio in Non-Diabetics (95% CI)	P value for interaction
SBP (per 10 mmHg)	1.10 (1.05 - 1.15)	1.21 (1.20 - 1.23)	0.00
Serum chol (mmol/l)	1.18 (1.10 - 1.27)	1.22 (1.20 - 1.25)	0.80
Smoking	1.28 (1.01 - 1.63)	2.24 (2.10 - 2.38)	0.00
Male sex	1.55 (1.24 - 1.94)	2.98 (2.80 - 3.21)	0.00

Stratified by cohort.

Conclusions: Self-reported diabetes is a much stronger risk factor for fatal CVD in women than in men. Risk factors such as SBP, gender and smoking behave differently in the presence of diabetes. This will affect the use of diabetes as a "multiplier" in risk modelling.

935 Predicting in-hospital mortality for STEMI in the UK using patient administration characteristics



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Purpose: Risk models help medical decision-making for patients with acute coronary syndromes (ACSs). Though several exist, they are either not derived from the population to which they are applied or include complex baseline variables. We used the MINAP database, a UK registry of ACSs, to determine simple factors that may predict in-hospital death for STEMI.

Methods: We had data for 187,069 patients and studied those clinical variables based on other studies and our experience that may be easily collected on admission to hospital.

Results: There were 20,968 patients with STEMI who had an all-cause in-hospital mortality of 8.2%. We found that delays to thrombolysis and out-of-hospital thrombolysis (paramedic and GP administered) were independent predictors of death. Outcome was also determined by type of practitioner administering the therapy. Established predictors including age, systolic BP and heart rate

Predictors of death post STEMI

Admission characteristic	Odds Ratio	95% CI	P value
Any delay in thrombolysis (e.g. hypertension, consent, cardiac arrest)	1.162	1.036 to 1.304	0.011
Thrombolysis given in hospital (vs before admission)	1.588	1.065 to 2.367	0.023
Thrombolysis given by medical team (vs A&E staff, specialist nurse, cardiologist or GP)	1.384	1.227 to 1.561	<0.001
Age per 10-year increase	2.196	2.094 to 2.304	<0.001
Systolic BP per 20 mmHg increase	0.756	0.730 to 0.783	<0.001
Heart rate per 30 bpm increase	1.559	1.466 to 1.658	<0.001
History of diabetes	1.364	1.194 to 1.558	<0.001

at admission were strong independent predictors of outcome and corroborated the EMMACE risk model of death post STEMI. The derived risk model offered a good discriminative ability of death with a c-index of 0.800, $P < 0.001$.

Conclusion: Though timing of thrombolysis is an important determinant, several easily collected admission characteristics have been shown to be strong predictors of death after admission for an STEMI.

936 Regular exercise corrects altered heart rate variability in obese people



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Background Altered heart rate variability (HRV), a measure of cardiac autonomic control, is a strong predictor of death and nonfatal cardiovascular events. We determined the effect of Body Mass Index (BMI), change in BMI over 11 years and exercise on different dimensions of HRV.

Methods SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) is a cohort study with baseline assessment in 1991. In 2001-2003, 24-hour electrocardiograms (ECG) have been recorded in a random sample of the participants aged 50 and over. Subjects with recordings of less than 18 hours were excluded, leaving 1718 recordings for analyses. Blood pressure, height and weight were measured and information about cardiovascular risk factors and exercise was obtained in an extensive interview. BMI in 1991 was based on measured height and reported weight. The influence of these variables on heart rate variability and heart rate was analyzed in multiple regression models adjusting for sex, age, age squared, educational level, diabetes and hypertension. Interaction between BMI and exercise was investigated, also looking at the part of HRV which is independent from heart rate.

Results Obese subjects (BMI > 30 kg/m²) not exercising had significantly lower HRV (9% lower SDNN; $p=0.003$) than normal weight subjects not exercising. Compared to obese subjects not exercising, obese subjects exercising at least 2 hours per week had significantly increased time and frequency domain parameters of HRV (total power: 35%, $p=0.002$; high frequency (HF): 33%, $p=0.039$; low frequency: 32%, $p=0.017$; SDNN: 21%, $p=0.000$; SDANN: 21%, $p=0.000$). In addition, obese subjects exercising at least 2 hours per week had a 40% ($p=0.007$) higher HF and 8% ($p=0.038$) higher SDNN than normal weight subjects not exercising regularly. Normal weight subjects and subjects having gained weight over the past 11 years who were exercising at least moderately had increased low frequency values compared to subjects not exercising, indicating effects on both the sympathetic and parasympathetic nervous system. A similar picture emerged when considering heart rate as endpoint of our analyses. However, exercise seemed to have an effect on HRV over pathways not involving heart rate that might even be stronger in the obese subjects.

Conclusions: Our results support the hypothesis that regular exercise has positive effects on cardiac autonomic control especially in the obese and that the respective beneficial effects of physical exercise may be stronger than the corresponding opposite effects of weight gain.

STENT THROMBOSIS IN THE DRUG-ELUTING STENTS ERA: INCIDENCE, PREDICTORS, MECHANISMS

1011 Morphologic predictors of drug eluting stent thrombosis in man



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Background: Although drug-eluting stents (DES) reduce the need for repeat revascularization compared to bare metal stents (BMS), animal and clinical data suggest the window of thrombotic risk for DES extends far beyond that for BMS. We examined coronary arteries of human DES implants to determine the long-term effects of DES on coronary arterial healing and identify mechanisms underlying late stent thrombosis (LST).

Methods: From a registry of 48 autopsies of drug eluting stents (79 stents), 27 DES cases (20 Cypher, 25 Taxus) of > 30 days duration were compared to 25 matched autopsies of BMS implantation (36 stents). LST was defined as an acute thrombus within a stent that had been in place > 30 days. Cases of ST were separated into occlusive and subocclusive thrombi and evaluated for inflammation, healing and hypersensitivity.

Results: Of 27 patients with DES in place > 30 days, 17 had evidence of LST (8 with Taxus, 9 with Cypher). Taxus demonstrated significantly greater fibrin

deposition as compared to Cypher and BMS (55.8 ± 30.1 vs. 38.0 ± 25.8 and $23.8 \pm 21.7\%$, $p < 0.001$) whereas Cypher showed significantly more eosinophils per strut as compared to Taxus and BMS (10.1 ± 14.7 vs. 1.5 ± 2.2 and 0.6 ± 0.3 , $p < 0.0002$). Both DES showed delayed healing characterized by poor endothelialization ($47.2 \pm 27.6\%$ for Taxus vs. 43.3 ± 35.5 for Cypher and 88.7 ± 22.0 for BMS, $p < 0.0001$) and fibrin deposition. In 6 of 14 patients suffering late DES ST, antiplatelet therapy had been withdrawn. Additional procedural and pathologic risk factors for late DES thrombosis were 1) local hypersensitivity reaction; 2) ostial and/or bifurcation stenting; 3) malapposition; 4) restenosis and 5) strut penetration into a necrotic core.

Conclusions: The two currently FDA approved DES result in delayed arterial healing when compared to BMS of similar implant duration. The cause of late DES thrombosis is likely multi-factorial with delayed healing in combination with other clinical and/or procedural risk factors playing an important role.

1012 Late stent thrombosis following drug-eluting stent implantation: data from a large, two-institutional cohort study



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Background: Late stent thrombosis (LST) has emerged as an eminent safety concern with the use of drug-eluting stents (DES). There is no large-scale study focusing on LST. We therefore analyzed data from a large cohort to determine: 1) Differences between early (0-30 days) and late (>30 days) ST with DES.

2) Differences in the incidence of LST between sirolimus-eluting (SES) and paclitaxel-eluting (PES) stents.

Methods and Results: Between April 2002 and December 2005, a total of 8668 pts underwent PCI with DES (SES: $n=3817$, PES: $n=4851$) at two academic referral hospitals. The overall incidence of angiographically documented ST was 1.8% ($N=157/8668$) encountered at a median of 9 days (range 0-1074) after stent implantation. Early ST (median 4, range 0-28) was observed in 93 (59%) pts, and LST (median 453, range 31-1074) in 64 (41%) pts, with the majority of LST cases (59%) occurring more than 1 year after the index PCI. The incidence of ST was similar for SES ($N=70$, 1.8%) and PES ($N=87$, 1.8%, $p=ns$), as was the distribution of early and late ST among the two stent types (SES, early/late=1.50; PES, early/late=1.42, $p=ns$). At the time of ST, dual antiplatelet therapy was taken by 89% of early and 25% of LST pts ($p < 0.001$). Premature discontinuation of any anti-platelet therapy, defined as cessation of either aspirin or clopidogrel prior to the recommended duration of prescription, was more frequent in late than early ST pts (22% vs 6%, $p=0.004$). LST pts were more frequently smokers ($p < 0.0001$), hypertensive (0.003), and hyperlipidemic (0.004) compared with early ST pts. There were no differences in procedural characteristics between early and late ST pts. Target vessels of early ST pts. were smaller at baseline (RVD: 2.67 vs 2.84 mm, $P=0.07$), had a smaller minimal luminal diameter (2.39 vs 2.57 mm, $P=0.03$) and a larger residual diameter stenosis (18 vs 13%, $P=0.04$) after the intervention compared with LST pts.

Conclusions: Angiographically documented ST occurred in 1.8% of 8668 patients treated with DES. The overall incidence and the occurrence of LST was similar for SES and PES. Nearly half of all ST cases were encountered late, and the majority of these very late (> 1 year). Current recommendations for the duration of dual antiplatelet therapy after DES implantation are insufficient for the prevention of LST, which can unpredictably occur at any time point.

1013 Sustained increase of platelet activation indices following sirolimus-eluting stents implantation



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Purpose: Despite the proven superiority of sirolimus-eluting stents (SES) compared to bare metal stents (BMS), recent data demonstrates that stent thrombosis after successful SES implantation is substantially higher. In patients treated with SES or BMS we measured serial changes in sP-selectin and soluble CD40 ligand (sCD40L) - as indices of platelet activation, von Willebrand factor (vWf) - as an index of endothelial damage and levels of factor VIII, fibrinogen and d-dimer - as indices of fibrinolytic response.

Methods: We evaluated 45 patients (30 male, 64 ± 18 years) with stable angina > 6 months and single vessel coronary artery disease, who underwent elective percutaneous coronary intervention (PCI). SES were implanted in 25 patients and BMS in the remainder. All patients were on dual antiplatelet therapy with 75 mg clopidogrel and 100mg aspirin. Blood samples were taken before PCI, 48 hours and 1 month later to evaluate plasma concentrations of sP-selectin, sCD40L, vWf, factor VIII, fibrinogen and d-dimer each time.

Results: All procedures were successful. Circulating levels of vWf, factor VIII, fibrinogen and d-dimer did not differ significantly between the two groups ($p=NS$). However, a significant increase of sCD40L and sP-selectin levels was detected in the SES group that was maintained until the end of the 1 month (Table 1).

Table 1

	SES			BMS		
	before	48 hours	1 month	before	48 hours	1 month
sCD40L(pg/ml)	142 ±78	197 ±68*	182 ±71*	156 ±92	132 ±54	144 ±70
sP-selectin (ng/ml)	41 ±18	57 ±22	62 ±25*	51 ±27	49 ±17	44 ±29

*: p < 0.05 compared to baseline

Conclusions: Patients treated with SES showed a sustained increase in platelet activation indices compared to those treated with BMS. This finding may emphasize the need for more aggressive antiplatelet therapy in patients with SES.

1014 One-year stent thrombosis rate in the EVASTENT registry: is this the patient, the procedure or drug_related?



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Background: The rate and causes of sub-acute (SAT) and late (LAST) stent thrombosis after implantation of a DES still remain under debate, although this rate is higher in real life than in randomized studies. EVASTENT is a nationwide matched-cohort registry allowing a direct comparison of diabetic (db+) and non-diabetic patients, with optimal follow-up of the patients and on-site monitoring for every patient. The on-label use of DES was recommended but not always followed. Aspirin + clopidogrel were recommended for at least 3 months. A "proven" ST was defined as a ST confirmed by angio or autopsy. A "highly probable" ST was defined by the Critical Event Committee (leading to acute death for all of these pts except one). One year F-up is complete for 98% of pts.

Results: The one-year mortality rate was 3.2%, 2.4 times significantly higher in db+ patients than db- pts. ST rates are shown in table 1. At baseline the significant univariate predictors of stent thrombosis (confirmed + suspected) were: being female, a low EF, previous stroke, presence of diabetes (ST 3.0% vs. 1.8%) and particularly insulin-dependant diabetes, renal failure, MVD (ST 3.6 vs. 1.5%), off-label stenting, calcified lesion, pre-dilatation of the lesion and longer stent length implanted. In multivariate analysis the independent predictors for stent thrombosis were female (RR 2.1), low EF (RR 0.97 per unit), previous stroke (RR 4), renal failure (RR 3.4), calcified lesions, and length of implanted stents (RR 1.02 per mm). During follow-up, complete (for 7 patients) or partial withdrawal of the bi therapy Aspirin +Clopidogrel was the strongest predictor of ST, especially for very (> 90 days) LAST. However some ST occurred in pts under dual therapy with an apparent good compliance of the patient to the treatment.

ST (confirmed and overall) rates

	Acute (< 48 hrs)	Sub-acute	LAST (30-90 days)	Very LAST (> 90 days*)	Total
Confirmed	5 (.03%)	11 (.06%)	1	13 (.08%)	30 (1.7%)
Confirmed + very probable	6 (.03%)	18 (x%)	2 (.01%)	19 (1.1%)	45 (2.6%)

Conclusion: dual antiplatelet therapy must probably be continued for at least one year after implantation of a DES, particularly in pts with a presence of baseline predictors of future ST. The 3-year follow-up results of these pts is ongoing.

1015 Angioscopic evaluation of process of neointima after drug-eluting stent (DES) compared with bare metal stent (BMS)



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Background: Process of neointima formation after bare metal stent (BMS) implantation was previously elucidated by angioscopic observations, which revealed that white thick neointima covered most of BMS after 6 month. However, the process after the implantation of drug-eluting stent (DES) has not been clarified. Therefore, we compared the angioscopic appearance of neointima over DES and BMS at 6 months after implantation.

Methods: A series of patients who received the implantation of BMS (n=13) or Sirolimus DES (n=24) were included. Angiographic and angioscopic examination was performed at 6months. Color of stented lesion (white or yellow), coverage of stent by neointima (not-covered, covered by thin layer, or buried under neointima), and thrombus at stented lesion(presence or absence) were angioscopically evaluated.

Results: DES was not covered in 11 (46%) lesions, covered by thin layer in 21 (88%) lesions, and buried under neointima in 11 (46%) lesions, at least in part. BMS was not covered in 1 (8%) lesion, covered by thin layer in 4 (31%) lesions, and buried under neointima in 13 (100%) lesions, at least in part. Prevalence of stent buried under neointima (46% vs. 100%, p=0.001) was lower and prevalence of thrombus (42% vs. 8%, p=0.03) higher at DES compared with BMS implanted lesions. Prevalence of thrombus (64% vs. 17%, p=0.005) was higher at the lesions with yellow plaque when DES was implanted.

Conclusion: Sirolimus DES, compared with BMS, was poorly covered by neoin-

tima and was accompanied by thrombus especially when there was yellow plaque under stent.

1016 Platelets response to combined aspirin and clopidogrel drug therapy and 1-year mortality after elective coronary stenting



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Background: We evaluated the predictive value of platelets response to combined aspirin and clopidogrel drug therapy, for the incidence of 1-year death following elective coronary stenting (CS).

Methods: A total of 612 consecutive pts who underwent elective CS for stable or unstable coronary artery disease were studied. All patients preloaded with aspirin and 300mg of clopidogrel at least 24 hrs before the procedure. Platelets response to dual antiplatelet therapy was measured preprocedurally by the platelet function analyzer (PFA-100) closure time (CT). Patients were divided into 3 groups according to the tertiles of preprocedural values of PFA-100 CT.

Results: By the 1-year 47 (4.7%) pts died. Although, there were not significant differences in baseline clinical, angiographic and CS related data among the 3 groups, patients at the first tertile of preprocedural values of PFA-100 CT (lower response to dual antiplatelet therapy) had the higher risk of 1-year death than those in the second (10.2% vs 2.4; RR=4.9; p=0.001) or third (10.2% vs 1.5; RR=5.2; p<0.001) tertile (Fig 1).

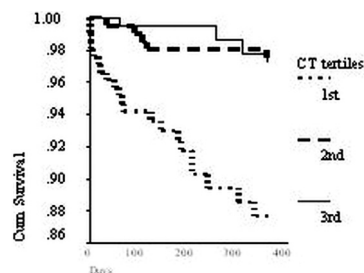


Fig. 1

Conclusions: The present results have shown that attenuated platelets response to combined therapy with aspirin and clopidogrel portend an increased risk for 1-year death after CS.

DISTAL EMBOLISATION PCI: PREVENTION RISK ASSESSMENT AND TREATMENT

1017 Plaque volume and the occurrence and location of peri-procedural myocardial necrosis following PCI: Insights from delayed enhancement MRI, TIMI myocardial perfusion grade analysis and IVUS



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Background: Myocardial necrosis can occur during percutaneous coronary intervention (PCI) despite optimal adjunctive pharmacology and careful technique. Using angiographic analysis of side branch impairment and assessment of TIMI myocardial perfusion grade, coupled with two- and three-dimensional intravascular ultrasound (IVUS) evaluation of plaque volume, we investigated the mechanisms of procedural infarction using delayed enhancement MRI (DE-MRI).

Methods: Fifty two patients (64 vessels) who underwent complex PCI were studied. All patients were preloaded with clopidogrel and received IIb/IIIa inhibitors. "Adjacent" myonecrosis was defined as the presence of an area of new gadolinium hyperenhancement (HE) close to the stent, presumptively due to side branch impairment. "Distal" myonecrosis was defined as situated at least 10 mm downstream from the stent, possibly due to distal embolism.

Results: Fifteen (23%) vessels had evidence of new HE post-PCI. Of these, 8 (12%) had the "distal" type, while 7 (11%) had the "adjacent" type. IVUS showed a significantly greater reduction in plaque area (2.6 ± 0.8 mm² vs 0.3 ± 0.6 mm² vs 0.4 ± 0.2 mm², p<0.001) and plaque volume (91.6 ± 51.5 mm³ vs 8 ± 14 mm³ vs 20 ± 35 mm³, p<0.001) in the group with distal HE, as compared to patients without new HE or adjacent HE. In the entire population, a significant correlation was seen between changes in plaque area (r=0.45, p<0.001) and volume (r=0.58, p<0.001) after PCI and the mass of new necrosis measured by MRI. TIMI perfusion grade assessment of a "closed microvasculature" post PCI carried an odds ratio (OR) of 8 (95% CI 1.4-46.1, p=0.02) for the occurrence of HE, while

side branch occlusion was associated with an OR of 16.2 (95% CI 2.6-102.5, $p=0.03$). However, a "closed microvasculature" was only associated with distal HE ($p<0.01$), while side branch occlusion was associated with adjacent pattern of HE ($p=0.02$).

Conclusions: These data suggest that distal embolization of plaque material occurs in contemporary PCI of native coronary arteries causing areas of new myocardial infarction. The volume of embolized material relates directly to the volume of new necrosis detected by MRI. Myocardial necrosis also occurs in areas adjacent to the stent but this is related to occlusion of small side branches. Efforts to minimize procedural necrosis may require careful review of side branch anatomy and/or use of distal protection during extensive coronary stenting.

1018 Relationship Between Admission Blood Glucose and Microvascular Injury in Patients With Acute Myocardial Infarction and No Previous Diabetes



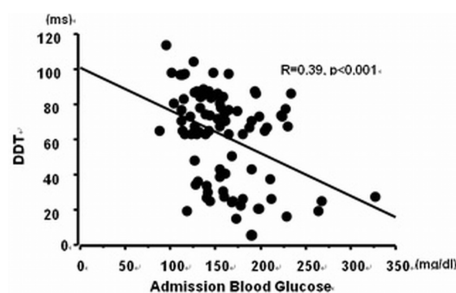
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Background: Previous studies have reported that acute hyperglycaemia at hospital admission is associated with adverse outcomes after acute myocardial infarction (AMI) in patients without diabetes mellitus. However, its underlying mechanism remains unclear. Recent studies have shown that severe microvascular injury can be assessed from coronary flow velocity (CFV) patterns with a rapid diastolic deceleration time (DDT). The purpose of this prospective study was to examine the relationship between admission blood glucose and microvascular injury in AMI patients without diabetes.

Methods: The study population consisted of 88 consecutive patients with no diagnosis of diabetes and a first anterior AMI successfully treated with percutaneous coronary intervention (PCI). We examined the CFV pattern immediately after coronary intervention using a Doppler guidewire. Acute hyperglycaemia was defined as a blood glucose level of ≥ 190 mg/dl at admission.

Results: Acute hyperglycaemia was found in 20 patients (23%). In patients with hyperglycaemia, DDT was shorter (480 ± 281 vs 634 ± 247 ms; $p=0.02$), and the peak value of CPK was higher (5346 ± 3161 vs 3666 ± 2843 IU/l; $p<0.01$). By regression analysis, the values of admission blood glucose significantly correlated with DDT ($r=0.39$, $p<0.001$). Multivariate analysis showed that acute hyperglycaemia was an independent predictor of severe microvascular injury (odds ratio 3.37, $p<0.03$).



Admission blood glucose and DDT

Conclusion: Admission blood glucose is related to severe microvascular injury after reperfusion in patients with AMI and no previous diabetes.

1019 Influence of TIMI grades before percutaneous coronary intervention on microvascular injury in patients with acute myocardial infarction



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Background: In patients with acute myocardial infarction (AMI), attaining TIMI grade 3 flow before percutaneous coronary intervention (PCI) leads to an improvement of left ventricular function in chronic-phase. On the other hand, microvascular dysfunction following successful percutaneous coronary intervention (PCI) impairs the recovery of left ventricular function. However, the relationship between the TIMI grades before PCI and the microvascular dysfunction has not been elucidated. The purpose of this study was to examine the influence of TIMI grades before PCI on the microvascular injury in patients obtained TIMI grade 3 flow after PCI.

Methods: Consecutive 140 patients with first-time anterior AMI were studied after successful PCI ($\leq 25\%$ residual stenosis with TIMI grade 3 flow). The TIMI grade before PCI was determined by the conventional coronary angiography. The microvascular injury was evaluated on the basis of coronary flow velocity (CFV) patterns using Doppler guide wires. In accordance with our previous reports, we defined microvascular dysfunction as the presence of systolic flow reversal and the diastolic deceleration time (DDT) of ≤ 600 ms.

Results: The relationship between the TIMI flow grade before PCI and the severity of microvascular injury after PCI was as follows: the microvascular dysfunction was observed in 21/70 (30%) for grade 0, in 1/7 (14%) for grade 1, in 4/41 (10%) for grade 2, and in 0/22 (0%) for grade 3. The subjects were divided into 3 groups according to the TIMI flow grade before PCI: grade 0, grade 1-2, and grade 3 groups. The TIMI flow grade before PCI was related to DDT and the peak systolic velocity: the lower the TIMI grade flow before PCI, the shorter the DDT (568 ± 238 vs. 674 ± 202 vs. 838 ± 142 ms, $p<0.05$) and the lower the peak systolic velocity (-6 ± 31 vs. 6 ± 20 vs. 18 ± 12 , $p<0.05$).

Conclusions: Patients showing a poor TIMI grade before PCI were more frequently complicated by severe microvascular injury. In contrast, none of the patients with TIMI grade 3 flow before PCI developed the microvascular dysfunction. Although TIMI grade 3 flow could be achieved in the current PCI procedures, TIMI flow grades before the procedure critically determine the microvascular circulation.

1020 Distal myocardial protection with intracoronary propranolol is effective when added to a Gp IIb/IIIa inhibitor: final acute results of the RABBIT II Trial



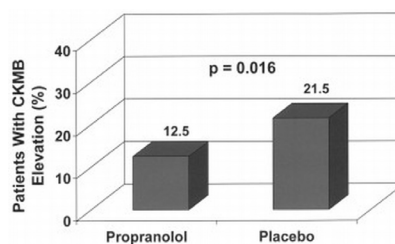
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Myocardial infarction (MI) after percutaneous coronary intervention (PCI) is associated with worsened late patient outcome. We previously showed in a prospective randomized double blind trial with Gp IIb/IIIa inhibitor (Gp) use at operator discretion that intracoronary (IC) propranolol (0.015 mg/kg) to the at-risk myocardium distal to the lesion prior to PCI decreased MI incidence as evidenced by an elevation in CKMB and improved long-term patient outcome.

Methods: To determine if IC propranolol is effective in decreasing MI frequency with uniform Gp use, we performed the Randomized Assessment of Beta Blocker Intracoronary Trial II (RABBIT II) in 400 patients (200/group) using the same methodology as the previous study with the exception that all patients received eptifibatide using the ESPRIT dosing protocol.

Results: The overall risk reduction for MI was 42% (CI: 0.37 - 0.91; $p=0.016$). Risk reduction was seen in all pre-specified subgroups including gender, age, multivessel intervention, clinical syndrome, prior use of oral beta blocker, and presence of diabetes.



Conclusion: These results demonstrate that IC propranolol can decrease the incidence of MI in the setting of optimal antiplatelet cardioprotection and recommend its routine use during PCI.

1021 Distal protection during interventional treatment of coronary vein grafts: the FIRST trial



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Interventions in coronary vein grafts can cause acute procedural complications due to distal embolisation of debris.

By using a distal endovascular protection device a 42% relative reduction of Major Adverse Cardiac Events (MACE) was achieved in the SAFER trial.

In the FIRST (First European Investigation Regarding the Systematic use of the TriActiv device) multicenter trial the new distal endovascular protection system TriActiv III (Kensey Nash) was evaluated during intervention of coronary vein grafts. The TriActiv III System blocks, flushes and aspirates the debris generated during PCI of diseased vessels.

196 patients in 17 centers in Germany with significant disease of a vein graft that provided at least TIMI I flow and allowed a protection device to be seated were enrolled. Inclusion and exclusion criteria were comparable to the SAFER trial. Acute procedural success was achieved in 98% of cases. Aspirated debris was found in 95% of pts with an average particle size of 73 μ m.

Primary endpoint was the rate of MACE at 30 days after the index procedure (a combined clinical endpoint defined as: death, Q-wave or Non Q-wave MI, emergent bypass surgery, repeat target lesion revascularisation) that occurred in 7.0% of pts. (16.5% in SAFER control pts, $p<0.0026$). No pt died and 5.7% of pts suffered from MI (5.1% non-Q-wave, 0.6% Q-wave; 14.9% in SAFER control pts, $p<0.0024$). The rate of early revascularization was 1.2 vs. 2.5% (n.s.) resp.

Secondary endpoints comprised the rate of cardiac and cerebrovascular events (MACCE) at 30 days after the index procedure (9.7%) and at hospital discharge (8.2%).

The TriActiv® system for distal protection during PCI of venous bypass grafts is safe and effective. Normal post procedural flow can be preserved and major adverse events (death, MI, early TVR) can be reduced by 50% with distal protection. The FIRST study supports the growing belief that PCI of venous bypass grafts should be performed with protection systems.

1022 Thrombus aspiration prior to coronary intervention improves myocardial microcirculation in patients with ST elevation acute myocardial infarction, the VAMPIRE study



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Purpose: The Vampire study (VAcuum asPIration thrombus REmoval) is a multi-center prospective randomized design to evaluate safety and efficacy of thrombus and plaque aspiration using TVAC (Thrombus Vacuum Aspiration Catheter, Nipro, Japan) in patients with STEMI.

Methods: Patients were randomly assigned to primary PCI with or without thrombus aspiration. Patients with cardiogenic shock, left main disease, and renal failure were not included in the study. Primary end-points are success and complication rates of thrombus aspiration therapy and damage of myocardial microcirculation assessed by final TIMI flow, corrected TIMI frame count, and myocardial blush score.

Results: A total of 368 patients were enrolled in the study from May 2003 to May 2005. There were no differences in clinical and angiographic characteristics between TVAC group (n=189) and the control group (n=180). Procedural success rates were 99% in both groups. Crossing the lesion with TVAC as a primary device was successful in 85% of the cases and TIMI-3 flow was achieved in 69% immediately after the aspiration. Procedural time, fluorescence time and amount of contrast were not different between the two groups. In-hospital MACE were 0.7% in the TVAC and 2.0% in the control group (p=NS). Blush grade-3 was achieved in 44% in TVAC group, whereas 16% in the control group (p<0.001). Final TIMI-3 flow was not different between the two groups (84.8% in the TVAC group, 80.2% in the control group). However, in cases with late reperfusion (>12 hours from the onset), TIMI-3 flow was more achieved in the TVAC group than control group (90.3% vs 63.9%, respectively). Follow-up results at 8 months will be available at the time of the meeting.

Conclusions: Aspiration therapy prior to primary PCI may preserve myocardial microcirculation without any deleterious effects and is effective especially in patients with late reperfusion.

BURNING QUESTIONS IN PAEDIATRIC CARDIOLOGY

1023 Left ventricular hypoplastic development in left heart obstructive lesions during fetal life



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Background: Left ventricular (LV) remodeling in prenatal diagnosed left heart obstructive lesions (LHOL) such as aortic stenosis (AS) and aortic coarctation (AC) plays a critical role in prenatal counseling and postnatal surgical management.

Purpose: to analyze the spectrum and the progression of different LV remodeling patterns and to identify prenatal signs susceptible to be used as markers of development of hypoplastic left heart syndrome (HLHS).

Methods: We prospectively studied 29 fetuses with LHOL: 13 with isolated AS, 14 with isolated AC and 2 with combined AS and AC. All fetuses did not have LV hypoplasia (LV end diastolic diameter z-score>-2) at first antenatal echocardiography (24.5±3.6 wks). Echocardiographic evaluation was performed 4 and 8 weeks after the first observation and at the birth.

Results: Fetuses were divided in two groups: group A (n=25), left ventricular end-diastolic volume (LVEDV) at the birth >20 ml/m²; group B (n=4), LVEDV at the birth <20 ml/m² (LV hypoplasia). At first echocardiographic evaluation groups A and B showed a significantly different aorta/pulmonary ratio (0.44±0.08 vs 0.86±0.14; p<0.001); other left-heart echocardiographic features were not significantly different in two groups. Despite the normal left-heart structures dimensions at the initial evaluation, the growth of mitral annulus (0.43±0.28 vs 0.10±0.02 mm/week; p<0.02) and aortic annulus (0.26±0.14 vs 0.08±0.01 mm/week; p<0.05) was significantly slower in group B.

Conclusions: Our data suggest that left heart obstructive lesions can pro-

gressively evolve in left ventricular hypoplasia during pregnancy. A smaller aorta/pulmonary ratio was the only significant difference at initial echocardiographic evaluation in the two groups. However, serial echocardiographic studies are necessary to recognize fetuses at risk of developing HLHS as a subnormal growth rate of mitral and aortic annuli.

1024 Pulmonary atresia with intact ventricular septum. Management, outcomes and risk factors for death and subsequent biventricular repair



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Management strategy of pulmonary atresia with intact ventricular septum (PAIVS) is usually determined by morphology of the right ventricle (RV) and coronary circulation. The purpose of this work is to report one centre experience and to assess risk factors for death and subsequent biventricular repair.

From January 1990 to September 2005, 38 consecutive patients were referred for PAIVS. Echocardiography showed a tripartite RV (n = 25), a bipartite RV (n = 11) and unipartite RV (n = 2). Tricuspid valve Z-score was -1.13 ± 1.65 (-4.0 to +1.5). Coronary artery fistulas were suspected in 14 patients. Interventional perforation of the pulmonary valve was attempted in 23 patients. Procedure was successful in 12 pts and failed in 11. These children underwent neonatal surgery: pulmonary valvotomy (n = 9) and creation of a Blalock-Taussig anastomosis (n = 2). Fifteen other patients were operated as a primary procedure: surgical valvotomy (n = 3) and Blalock anastomosis alone (n = 12). Four patients died in neonatal period (1 after successful interventional perforation, 3 after creation of a shunt). Five other patients with a shunt died suddenly during follow-up. Risk factors for time-related death were: RV anatomy (p = 0.0017), existence of coronary artery fistulas (p = 0.0202), smaller tricuspid annulus (p = 0.04). At latest follow-up, 18 patients evolved to a biventricular repair with 8 of them requiring complementary procedures after initial valvotomy; 11 other patients evolved to a cavo-pulmonary connection, including 4 patients who had undergone initially a strategy of biventricular repair. The only predictive factors noticed at birth in favour of subsequent biventricular repair were: larger diameter of the tricuspid annulus on echocardiography (10.8 ± 2.32 mm versus 6.39 ± 1.47 mm, p = 0.008) or larger tricuspid valve Z-score (0.1 ± 1.16 versus -2.16 ± 1.3, p = 0.005), and the morphology of the RV (p = 0.0001) with more tripartite, less bipartite and no unipartite RV in the biventricular group.

To conclude, biventricular repair could be achieved in about 50% of patients presenting with PAIVS. Smaller RV or tricuspid valve and existence of coronary artery fistulas are risk factors for death and/or subsequent functionally univentricular repair.

1025 Critical left ventricular volume in aortic stenosis in first year of life: its importance in patients selection to univentricular surgical correction post-valvotomy

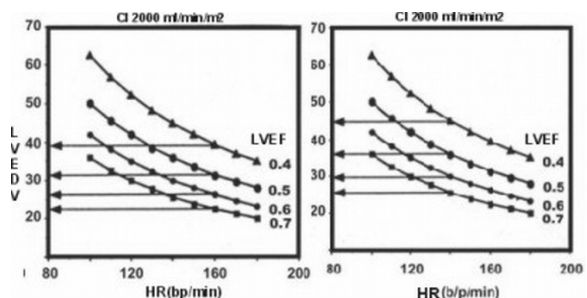


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Objective: To analyze the critical end diastolic left ventricular volume (EDLVV), assumed like a minimal acceptable volume to maintain the cardiac output, in selection of patients with aortic stenosis candidates to univentricular surgical correction post-valvotomy.

Patients and Method: This is a retrospective study in 21 patients with aortic stenosis during the first year of life compared to 232 from the literature. It was assumed 20-60 ml/m² as the normal EDLVV. We compared the EDLVV between survivors and deceased patients. We performed a correlation between EDLVV and age at the time of valvotomy. Finally, we evaluated the critical EDLVV through the theoretical relationship between the EDLVV and heart rate for different ejection fractions and designated cardiac indexes: 2,000 and 2,500 20-60 ml/min/m².

Results: We found a high statistic relationship between the EDLVV and survivors when the EDLVV were less than 20 ml/m² and great than 60 ml/m² (p=0.0001). However in the range between 20-60 ml/m² the statistic relationship was minor. There was higher incidence of death in patients who presented in the first week of life. A cardiac index of 2,000 ml/min/m² and heart rate of 140 beats/min would



require a minimal EDLVV of 26 ml/m² if the ejection fraction was 0.70 and 44.5 ml/m² for an ejection fraction of 0.40. The same cardiac index and heart rate of 160 beats/min would require an EDLVV of 22 ml/m² if the ejection fraction was 0.70 and 39 ml/m² for an ejection fraction of 0.40.

Conclusion: The evaluations of the critical EDLVV can add one more parameter in selection of patients with aortic stenosis post-valvotomy, candidates to univentricular surgical repair.

1026 use of balloon expandable stents in aortic coarctation



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The use of stents for the treatment of native and postsurgical coarctation of the aorta is a therapeutic modality of recent development. We would like to communicate our immediate results, the complications and mid term follow up.

In a 7 year period, we performed 51 angioplasties with stent (S) in 47 patients with the diagnosis of coarctation of the aorta, among them 37 were native and 10 postsurgical. Mean age was 13 years (range, 6 to 37 years) and mean weight was 46 kg (range, 24-75 kg). We implanted 51 stents in 47 consecutive patients with conventional catheter balloons in 21 and with balloon in balloons (BIB) in the other 26 patients. 31 Palmaz and 20 CP stents were implanted. Among them, 4 were covered CP stent. We got gradient reduction from a mean of 33±17 mmHg (range, 10-84 mmHg) to 0±5,16 mmHg (range 0-30 mmHg) and gained at the site of the coarctation from x: 5,5±2,7 mm (range 1,7-12,2 mm) to x: 15± (range 5,2 -18,3 mm). We had 3 mayor and 8 minor complications. We had 2 conventional balloon ruptures. 3 patients had wrong positioning of the stent, 2 of them underwent a second stenting in proper position and another 2 had late distal migration and underwent a new procedure with correct stenting. In the mid term follow up between 1 month and 6.8 years (mean 3.8 years), we lost the data of 15 patients and 32 were evaluated by usual means. 2 patients were redilated and another 2 are waiting for angioplasty with high pressure balloons. We conclude that stenting in native and postsurgical coarctation of the aorta is an effective and safe procedure. The morbidity of the method is progressively diminishing with the development of better materials. The learning curve is a very important issue.

1027 Cryomapping offers advantages for ablation near the atrioventricular junction in pediatric patients



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Background: Ablation in young children using radiofrequency (RF) energy can be challenging when the arrhythmia substrate is located in close proximity to the atrioventricular (AV) node due to a significant risk for inadvertent AV block. Cryomapping can theoretically decrease the occurrence of iatrogenic AV block.

Aim: To determine the effect of cryomapping during ablation of arrhythmia substrates located in the triangle of Koch in a pediatric patient group.

Methods: This was a single center, prospective, non-randomized study. During the study period (August, 2004-November, 2005) a total of 59 pediatric patients (age range: 7.5 to 17.7 years) were screened for supraventricular arrhythmias. After a diagnosis of AVNRT or AVRT with an antero-septal accessory pathway (AP) was made, cryomapping was performed cooling the catheter tip temperature to a max. of -40°C. Mapping was performed either during ongoing tachycardia or in sinus rhythm. Ablation was performed only if cryomapping terminated the tachycardia or blocked the AP conduction without prolongation of the AV conduction.

Results: In 14/59 pts (24%) RF ablation was abandoned because of arrhythmia substrate in close proximity to AV node (11 antero-septal AP, 3 AVNRT's). Cryoablation was successful in all 3 pts with AVNRT. Elimination of AP conduction without AV block was observed in 5/11 pts and cryoablation was performed successfully. In 6/11 pts high degree AV block developed simultaneously with elimination of AP conduction with during cryomapping in patients with antero-septal AP's. Cryoablation was not attempted in these cases. This resulted in an acute success rate of 57% for cryoablation (8/14 pts). No permanent complications related to the use of cryoenergy were observed. Only one (12%) patient experienced recurrence of AP conduction during a 12 months follow up period.

Conclusions: 1. Cryoablation is a safe alternative to RF ablation in pediatric patients, when the arrhythmia substrate is located in close proximity of the AV node. 2. Cryomapping improves success rate on an intention to treat basis. 3. Cryomapping identifies high risk patients for inadvertent AV block, but results in a considerable decrease of the overall ablation success rate.

1028 The contegra bovine jugular vein graft versus the shelhigh pulmonic porcine xenograft for reconstruction of the right ventricular outflow tract



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Background: The expanding possibilities of correcting complex congenital cardiac malformations create an increasing demand for conduits to reconstruct the

right ventricular outflow tract (RVOT). The advent of two readily available grafts, the Contegra bovine jugular vein graft and the new generation Shelhigh Pulmonic porcine xenograft overcomes the lack of availability of homografts but raises questions in terms of durability. Aim of this study was to determine the short- and medium-term outcome of the Contegra bovine jugular vein graft and the new generation Shelhigh Pulmonic (NR-4000PA) xenograft in patients in need for RVOT-reconstruction.

Patients and Methods: From 10/1999 to 12/2005 69 patients (mean age 7.2 years, range 0-63 years) underwent reconstruction of the RVOT using the Contegra bovine jugular vein graft (n=39, 12-22mm) or the new generation Shelhigh Pulmonic porcine xenograft (n=30, 12-25mm). The Contegra graft was implanted in patients with TOF (n=20), pulmonary atresia (n=3), DORV with pulmonary stenosis (n=3), d-TGA with VSD and pulmonary stenosis (n=3), truncus arteriosus (n=3), pulmonary insufficiency (n=2) and in patients with other complex malformations (n=5). The Shelhigh Pulmonic graft was used in patients with TOF (n=20), pulmonary atresia (n=1), DORV with TGA (n=1), d-TGA (n=1), truncus arteriosus (n=2), pulmonary stenosis (n=2) and in patients with aortic stenosis who underwent a Ross procedure (n=3). The primary endpoints of the study were cardiac death, re-operation, re-intervention or significant conduit stenosis defined as a RV-PA-gradient of more than 30mmHg.

Results: Follow-up was performed using two-dimensional echocardiography and magnetic resonance imaging when appropriate. During a mean follow-up period of 33 months 8 patients (20.5%) with Contegra sized 12mm (n=2), 14mm (n=2), 16mm (n=1), 18mm (n=1), 22mm (n=2) compared to 2 Shelhigh patients (6.7%) with sizes 14mm and 23mm, needed replacement of their stenosed conduit (p=.16).

Conclusion: The Contegra conduit seems to have a greater tendency to degenerative stenosis than the Shelhigh conduit with a higher risk for premature reoperation in these patients. Further evaluation of the Shelhigh conduit is warranted to determine its potential advantages.

ADVANCES IN HEART TRANSPLANTATION

1029 Malignancies as a major cause of death after heart transplantation: follow up of the German heart transplantation tumor data base



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Purpose: An increasing incidence of malignant disease after heart transplantation (HTX) had to be recognized over recent years. Aim of the ongoing German malignancy data base was to assess frequency, time point, pattern of organ involvement as well as the impact on prognosis of malignancies following HTX.

Methods: Since 2004 a total of 2717 heart transplant recipients (2199 male, mean age 58 + 14 years) from 7 centres were assessed in an internet based tumor registry, documenting each patient transplanted in the individual programs. Underlying disease before HTX was dilated CMP in 61% and ischemic CMP in 31% (other 8%).

Results: A total of 1855 pts were treated with an antibody induction therapy early after transplantation. Immunosuppressive therapy was administered in form of Cyclosporine in 63%, Tacrolimus in 24%, Sirolimus/Everolimus in 6%, Azathioprine in 38%, Mycophenolate Mofetil in 28% and Steroids in 84% of pts. In 772 out of 2717 pts (28.4%) solid malignancies were detected. The highest incidence was found for skin cancer (51%), followed by haematological malignancies (15%), lung cancer (10.8%), urogenital- (9.5%) gastrointestinal cancer (7.4%). A total of 867 pts died during follow up, malignancies were identified as cause of death in 106 (20.3%) of all deceased patients in this cohort. A potential association to immunosuppressive therapy and clinical follow up of diseased patients is under further investigation.

Conclusions: Ongoing results of this registry underline the high prevalence and prognostic relevance of malignancies post heart transplantation. Further analysis of is aimed to develop new surveillance strategies in order to prevent or at least anticipate the high risk of malignancy.

1030 Beating donor heart explantation and low pressure perfused ultrastructure in extracorporeal long term preservation with a modified Langendorff system



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Objective: In heart transplantation a well preserved myocardial ultrastructure

is an important precondition for functional recovery. The aim of the study is to compare the ultrastructural findings in a new established model of extracorporeal beating heart perfusion system.

Method: (I) Hearts of six pigs were arrested with cardioplegia (Bretschneider), explanted and followed by 30 minutes of cold ischemia. Afterwards they were connected to a circulating constant pressure Langendorff-system (80-90 mmHg) consisting of an oxygenator and a centrifugal pump. The perfusate consisted of a modified Tyrode solution with 1000 ml leukocyte depleted autologous blood. Left atrial and aortic root pressures were kept constant. (II) Beating hearts of seven pigs were explanted without cardioplegia and cold ischemia. They were connected immediately to the Langendorff-system as in group I and the perfusion pressure was reduced (40-50 mm Hg). 55 left ventricular biopsies (group I n=29, group II n=26) were taken in situ and within 12 hours of perfusion, fixed in glutaraldehyde and prepared for transmission electronmicroscopy.

Results: Cardioplegia and hypothermia (group I) induced marked mitochondrial edema and myofibrillar degeneration in cardiomyocytes as well as severe endothelial edema. During four hours of reperfusion, in cardiomyocytes increasing mitochondrial edema, myofibrillar, and sarcolemmal damages were seen. Severe endothelial degeneration, moderate interstitial edema and hemorrhages appeared. After eight hours reperfusion endothelia and cardiomyocytes were severely damaged. Interstitium was severely edematous and showed intensive hemorrhages, numerous polymorphonuclear granulocytes, and some bacteria. In contrast, in group II after six hours of reperfusion endothelia showed only mild alterations. In cardiomyocytes mild-moderate myofibrillar and minimal mitochondrial degeneration were seen. Interstitial edema and hemorrhages were mild. After eight hours reperfusion cardiomyocytes showed moderate lesions, whereas capillary endothelia were predominantly intact.

Conclusion: Beating heart explantation and low pressure perfusion led to an improved long term preservation of the ultrastructure and could be a promising tool for donor heart preservation. However, additional variations are necessary and reimplantation experiments will be the next step to confirm these findings.

1031 The influence of immunosuppressive drugs on T- and B-cell apoptosis via p53-mediated pathway in-vitro and in-vivo: a novel human whole blood assay



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Objective: This study was designed to assess the effects of inhibitors of calcineurin and inosine-5-monophosphate-dehydrogenase on p53-pathway-apoptosis in T- and B-cells in vitro and in human heart-transplanted-recipients (HTx-R).

Methods: First part: peripheral blood for 6 experiments for each drug was collected from healthy volunteers and treated either with 1 µM cyclosporin A (CsA), 10 µM mycophenolic acid (MPA) or 100 nM tacrolimus (TRL). Second part: peripheral blood was collected from HTx-R undergoing CsA-MPA (n=11) or TRL-MPA (n=11) therapy before (0h) and after (2h) acute drug application and from healthy volunteers (n=11) without drug therapy. Whole blood (part 1+2) was stimulated (24h) with eight different concentrations of actinomycin-D (0-800 nM), an apoptosis inductor acting via p53-pathway. Apoptotic lymphocytes were measured by TUNEL and expression of Annexin-V using FACS. Drug effects were calculated by taking the effects of actinomycin-D as baseline values.

Results: In-vitro drug treatment with CsA, MPA and TRL significantly ($p < 0.05$) decreased the apoptotic effect of actinomycin-D in T-cells in a non-competitive manner. In HTx-R undergoing drug therapy there was a similar anti-apoptotic effect observed in both T- and B-cells ($p < 0.05$). Differences between 0h and 2h after acute drug application did not exist. Apoptosis induced by actinomycin-D can be completely blocked by caspase-inhibitor zVAD-FMK.

Conclusion: Our results suggest that an inhibition of calcineurin and inosine-5-monophosphate-dehydrogenase by CsA, TRL or MPA leads to inhibition of T-and B-cell apoptosis via p53-pathway in-vitro and in-vivo. This assay may be helpful to assess the pharmacodynamic effects of immunosuppressants for therapy surveillance in HTx-R.

1032 Evolution of endothelial-dependent forearm vasodilation after heart transplantation and its relationship with graft vasculopathy



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Background: Endothelial dysfunction (ED) has been found in patients (pts) with severe heart failure. Whether peripheral ED improves after heart transplantation (HT) or can be useful to predict graft vasculopathy (GV) remains unknown.

Objective: To assess forearm endothelium-dependent vasoreactivity after HT and whether ED correlates with GV.

Methods: 29 patients (pts) (53 ± 10 years), were studied at 1, 6 and 12 months after HT. High resolution brachial artery ultrasound was used to assess flow-mediated dilation (FMD) induced by reactive hyperemia and nitroglycerin (NTG). FMD was used as an index of endothelium-dependent vasodilation and was calculated as the percent change in brachial artery mean diameter after reactive

hyperemia over that obtained at baseline. An increase in FMD $> 4\%$ was considered normal. GV was assessed with IVUS performed at one year by monitored pullback in the left anterior descending (LAD) at 0.5 mm/s. The total length of LAD images was 40 mm. Frames were selected for measurement at 1 mm intervals. Plaque, lumen, vessel and plaque volume index were measured. TNF-alpha levels were assessed at 1 and 12 m.

Results: At the first month after HT, FMD was impaired in 25 pts (86%) and at 12 m in 21 (72%). FMD significantly improved at 6 and 12 months. There was no significant correlation between with % change in FMV and parameters that measured GV by IVUS at 1 year. TNF-alpha values were significantly lower at 12 m (59 ± 30 vs 39 ± 20 pg/ml, $p = 0.03$).

	1m	6m	12m
FMD(%)	1.95 ± 2.6	$3.3 \pm 3.2^*$	$5.1 \pm 3.4^{**}$
NTGdil(%)	15 ± 7.7	12.8 ± 6.0	14.3 ± 7.7

(* $p = 0.005$, 1 vs 6m), (** $p = 0.0001$, 1 vs 12 m)

Conclusion: 1. Impairment of peripheral FMD is present in a high percentage of pts at 1 m after HT. 2. Significant improvement of FMD was seen at 12 m of HT. 3. Peripheral ED did not correlated with GV at 1 year. 4. The reduction in TNF-alpha values at 12 m could play a role in the improvement of ED.

1033 Eprosartan versus Diltiazem in the primary prevention of cardiac allograft vascular disease: a double blind prospectively randomized study using intravascular ultrasound



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Purpose: Myointimal hyperplasia in coronary arteries of transplanted hearts, known as cardiac allograft vasculopathy (CAV), is one of the most accelerated progressing coronary syndromes in humans. Recent data provide increasing evidence, that activation of the renin-angiotensin system is involved in pathogenesis. To investigate the hypothesis, that blockade of AT1 receptors may result in antiproliferative and anti-inflammatory effects, we performed a pilot study in de novo heart transplant recipients evaluated by intravascular ultrasound and intracoronary doppler.

Methods: A total of 40 patients (35 male, mean age 54.0 ± 10.3 years) were randomized to receive either 600 mg Eprosartan od. (n=19) versus 90 mg Diltiazem bid. (n=21), beginning 5-21 days after a first heart transplantation (HTX). Treatment was well tolerated. Using intravascular ultrasound during protocol based heart catheterization, plaque-, lumen-, and vessel area as well as volumes were evaluated at baseline and after 12 and 24 months.

Results: Most pronounced treatment differences were observed after 12 months. Plaque volume and plaque area increased from 46.3 mm^3 (3.2 mm^2) to 59.1 mm^3 (4.1 mm^2) in the Eprosartan group versus a more marked increase from 39.2 mm^3 (2.5 mm^2) to 75.7 mm^3 (4.6 mm^2) in the Diltiazem group ($p = 0.08$). Focal stenosis in terms of a more than 50% luminal obstruction (angiography) was not observed during follow up of 2 years. Coronary flow reserve as assessed by endothelium independent vasodilatation with adenosine was found to increase in both groups within the first 12 months: CFR 2.56 to 3.05 in Eprosartan and CFR 2.25 to 2.99 in Diltiazem treated patients ($p = \text{ns}$).

Conclusions: This pilot study demonstrates a reduced increase in myointimal hyperplasia in patients treated with Eprosartan versus Diltiazem. However, neither differences in plaque area nor in coronary flow reserve reached statistical significance in this small study cohort.

1034 Does female sex affect the prognosis of heart transplantation? An analysis of survival, rejection and neoplasia among a series of 482 patients



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Background: Although female recipients of heart transplants (HTs) seem to have a stronger immunological response and a greater incidence of rejection episodes than male recipients, it is not clear that female sex is a risk factor for death after HT.

Aim To compare the survival and morbidity (rejection and neoplasia) rates of male and female HT patients.

Methods: Retrospective analysis of a series of 482 HT patients (83% male) from a single institution. The dependent variables were: survival, number of rejection episodes, and number of neoplasias. Independent pre-HT variables other than sex that were included in the analysis because of their possible effect on survival were: recipient age, aetiology of the cardiopathy, renal dysfunction, previous cardiac surgery, anticoagulation, urgency status, diabetes mellitus, hypertension, donor age, donor ischaemic time, and date of HT (1991-1995; 1996-2000 or 2001-2005).

Results: The actuarial survival rates of men ($n=404$, mean age 55.05 ± 12.0 years) vs women ($n=78$, mean age 54.8 ± 11.0 years) at 1, 5, 10 and 14 years were 78% vs 81%, 66% vs 75%, 53% vs 60% and 42% vs 60% (p NS). Multivariate analysis showed that pre-HT diabetes, renal dysfunction and previous cardiac surgery increased the risk of death, but female sex did not. The incidence of rejection episodes (defined as the percentage of patients with any rejection episode after HT) was 49.8% for men as against 48.7% for women (p NS), and the incidence of neoplasia was 16.7% for men as against 7.0% for women (p NS).

Conclusions: The prognosis of HT, in terms of survival, rejection and neoplasia, seems to be no worse for women than for men.

MORE ON LONG-TERM PROGNOSIS OF ACUTE CORONARY SYNDROMES

1035 Relationship of baseline hemoglobin levels with short term outcome in acute coronary syndromes. Insights from the OASIS 5 and 6 trials



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Background: Baseline hemoglobin levels have been shown to be independently associated with outcome in the short term in a large subset of patients suffering from acute coronary syndromes (ACS), but these reports remain unconfirmed.

Methods: To determine whether baseline hemoglobin level is related to outcome, the rates of death, death+myocardial infarction (MI) and major bleeding were analysed in 32,170 patients included in the OASIS 5 and OASIS 6 trials, according to quartiles of baseline hemoglobin levels. OASIS 5 ($n=20,078$) tested the respective efficacy and safety of fondaparinux (fonda) vs enoxaparin (enox) in NSTEMI-ACS. OASIS 6 ($n=12,092$) tested the efficacy of fonda vs unfractionated heparin (UFH) or no heparin, (depending on indication or no indication for anti-thrombin treatment) in ST elevation ACS

Results: At 30 days, lower baseline hemoglobin levels were associated with significantly higher rates of death, death+MI in the population as a whole (table), and in each treatment group. Death rate was significantly lower in the fonda group as compared to enox/UFH/placebo in lowest and highest quartiles (Q1: 7.1 vs 8.6%, $p<0.02$; Q4: 3.1 vs 4.1%, $p<0.03$). Lower baseline hemoglobin levels were associated with higher rates of major bleeding. Bleeding rates were significantly lower in the fonda group for each quartile of hemoglobin. All observations at 30 days were maintained at 180 days.

Baseline Hb	N	Death (%)	Death+MI (%)	Maj.bl. total (%)	Maj.bl.fonda (%)	Maj. bl. enox/UFH/placebo (%)
<12.7	7773	7.8	10.7	4.8	3.9	5.7*
12.7 - <13.9	8061	5.2	8.1	3.5	2.7	4.3*
13.9 - <15	8207	4.1	7.0	3.1	2.7	3.5*
>15	8129	3.6	6.3	2.3	1.8	2.8*

Hb=hemoglobin, g/dL. * $p<0.04$ vs fonda. Maj.bl.=major bleeds

Conclusion: These findings confirm that lower baseline hemoglobin levels are significantly related to outcome and risk of bleeding, which is significantly lower with fonda than with enox/UFH/placebo. Further analysis is warranted to determine whether hemoglobin level is an independent predictor of risk.

1036 Effect of nadir hemoglobin during hospital course on the long-term risk of death in survivors of acute myocardial infarction



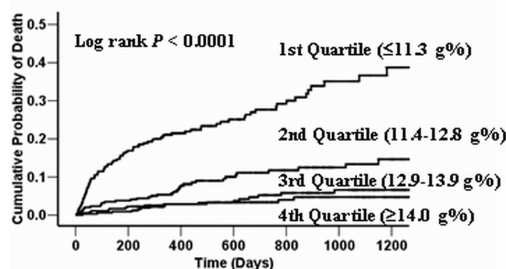
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Background: Anemia on admission is associated with short-term mortality in patients (pts) with acute myocardial infarction (AMI). Anemia can develop or worsen during hospital course, but the long-term impact of changes in hemoglobin (Hb) levels is not known.

Methods: We prospectively studied 1390 pts with AMI who survived the acute event. The relationship between baseline Hb, nadir Hb during hospital course, pre-discharge Hb and the primary endpoints of all-cause mortality were evaluated using Cox models.

Results: Using the WHO definitions (Hb < 13 g/dL in men and < 12 g/dL in women), anemia was present in 248 pts on admission (17.8%). Median nadir Hb concentration was 1.3 g/dL lower [interquartile range 0.6-2.2] compared to baseline Hb ($P < 0.0001$), and the number of pts with anemia increased to 667 (48.0%). During a median follow up of 23 months (6 to 48), 157 pts died (11.3%). Nadir Hb during hospital course was a stronger predictor of outcome than baseline or pre-discharge Hb. In a Cox model adjusting for clinical variables, renal function and pre-discharge ejection fraction, there was an inverse independent

association between nadir Hb and mortality: Adjusted HRs of pts with nadir Hb in the 3rd, 2nd and 1st quartiles, compared with pts in the 4th, were 1.1 [95% CI, 0.5 to 2.1], 2.0 [95% CI, 1.1-3.9], and 3.3 [95% CI, 1.8 to 6.3], respectively (P trend < 0.0001; Figure).



Mortality according to nadir Hb.

Conclusions: Worsening anemia frequently occurs during the course of hospital stay in pts with AMI. The prognostic implications of low Hb concentrations extend beyond the early phase of infarction. Nadir Hb during hospital course is a predictor of long-term mortality in survivors of AMI and provides prognostic information beyond conventional risk factors and left ventricular ejection fraction.

1037 Plasma aldosterone in acute myocardial infarction predicts adverse clinical outcome (The Aldosterone-OPERA study)



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The role of the renin-angiotensin-aldosterone pathway has been established in STEMI complicated by heart failure. However the role of aldosterone as an early marker of outcome in MI, with or without ST elevation (ESC definition of MI), independently of the presence of heart failure, remains unknown. In 29 French centers, 471 patients with an acute MI underwent measurement of aldosterone, CRP, BNP, and troponin levels within the first 24 hours of admission and again 72 hours after admission. Male gender (80%) was predominant and mean age was higher in women (70 ± 14 vs 61 ± 13 yrs, $p<0.0001$). STEMI and NSTEMI represented 75.5% vs. 24.5% of the population, respectively. Time from symptom onset to hospitalization was 6 ± 5.3 hrs (mean $\pm$ SD). In-hospital revascularization (PCI or CABG) was performed in 74.3% of patients. Ejection fraction was $54 \pm 12\%$ (mean $\pm$ SD). Within 24 hrs of admission, plasma level (median [95%CI]) of aldosterone was 42 [22;104] pg/mL, troponin I was 36 [11;76] mcg/L, CRP was 6 [3;16] mg/L and BNP was 207 [106;389] pg/mL. A prior history of heart failure was not correlated to aldosterone levels. Adverse in-hospital outcome was defined as the composite end-point of death, resuscitated cardiac arrest, recurrent MI, recurrent ischemia, heart failure or stroke. Adverse in-hospital outcome occurred in 15.9% of the study population. In the highest quartile of aldosterone measured at 24 hours (>103.6 pg/mL), 32% of patients reached this composite end point compared to <14% patients in every other quartile. All demographics, risk factors and biomarkers that were significant after univariate analysis, were entered in a stepwise logistic regression analysis which identified three independent correlates of adverse in-hospital outcome: age ($p<0.0001$), dyslipidemia ($p=0.0078$) and 24hr-aldosterone plasma level ($p<0.0001$). A long-term follow-up was performed and the same model identified three significant independent predictors of death, resuscitated cardiac arrest, recurrent MI, recurrent ischemia, heart failure or stroke at 1-year: current smoking ($p=0.0017$), 24hr-aldosterone level ($p=0.0143$), and 24hr-BNP level ($p=0.0003$). Median levels of aldosterone decreased from 42 pg/mL at 24 hrs to 32 pg/mL at 72 hrs but this late measurement remained a significant predictor of adverse outcome both in-hospital ($p=0.0011$) and at 1-year follow-up ($p=0.0310$). In conclusion, in acute MI, aldosterone appears to be a strong and independent correlate of serious adverse clinical outcome both in-hospital and at 1-year follow-up. Considering the possible therapeutic consequences, these findings deserve further exploration.

1038 Multimarker risk approach for predicting 6-months prognosis in non-ST-elevation acute coronary syndromes



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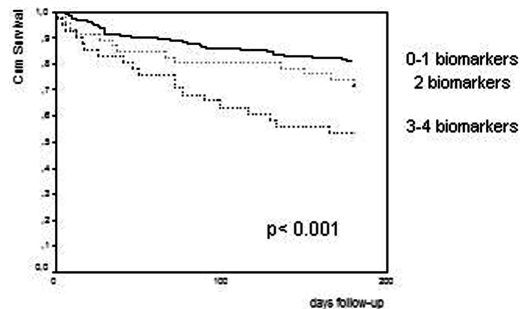
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Biomarkers have emerged as interesting predictors of risk in non-ST elevation acute coronary syndromes (non-ST ACS). However, non-ST ACS as a complex

disease, probably involves many different factors that might interact to result in an additive or a synergistic effect. The aim of this study was to define the utility of the combined measurement of troponin T, C-reactive protein, NT-proBNP and D-dimer to predict adverse events, in order to assess different pathways in the ACS.

Methods: We included 331 consecutive patients (67.5±12.1 years) admitted in two Hospitals for non-ST ACS. Baseline measurements of troponin T, C-reactive protein, NT-proBNP and D-dimer were performed. Positive troponin T was considered $\geq 0.1\text{ng/mL}$, whereas positive C-reactive protein, NT-proBNP and D-dimer were considered upper than fourth quartile in our population. The risk for major events (death, new ACS, revascularization and heart failure) at sixth months follow-up was analyzed.

Results: Survival curves are presented in Figure. After adjusting for baseline characteristics and electrocardiographic changes, (Cox analysis) multimarker risk approach was associated with adverse events at sixth months. The presence of 3-4 positive biomarkers showed a Hazard Ratio: 2.59 [IC 95%1.37-4.91] ($p=0.004$).



Survival curves

Conclusions: Multimarker approach based in troponin T, C-reactive protein, NT-proBNP and D-dimer provides independently prognostic information in non-ST ACS.

1039 Incidence and clinical relevance of right bundle-branch block in patients with acute ST and Non-ST elevation myocardial infarction



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Background: Left bundle branch block has been associated with poor outcome in patients with myocardial infarction. However, the prognostic role of right bundle branch block (RBBB) in acute ST elevation (STEMI) and Non-ST elevation myocardial infarction (NSTEMI) is not well known. Aim of the study was to evaluate the incidence and clinical relevance of RBBB in patients with acute STEMI and NSTEMI.

Methods: From the German prospective multicenter registries "Maximal Individual Therapy of Acute Myocardial Infarction" (MITRA PLUS) 20,233 consecutive patients with STEMI and 6,403 patients with NSTEMI were analyzed. Patients with left bundle branch block were excluded.

Results: 894 (4.4%) patients with STEMI and 455 (7.1%) patients with NSTEMI presented with RBBB.

	STEMI		NSTEMI	
	RBBB+ (N=894)	RBBB- (N=19339)	RBBB+ (N=455)	RBBB- (N=5948)
Age (years)	71	66*	73	69*
Female	28%	32%*	23%	35%*
Diabetes	28%	23%*	36%	30%*
Prior MI	21%	15%*	29%	25%*
Prior stroke	4.7%	3.0%*	12%	8%*
Cardiogenic shock	16%	6.6%*	8%	4%*
Acute reperfusion	57%	70%*	21%	33%*
Beta blocker	71%	80%*	78%	85%*
Statins	51%	59%*	69%	75%*
1-year mortality	19%	9.2%*	13.6%	10.9% (ns)

Baseline characteristics, acute in-hospital treatment and 1-year mortality (* $p<0,05$ RBBB+ versus RBBB-)

Conclusion: 1. 7% of patients presenting with NSTEMI and 4.4% with STEMI have a RBBB. 2. Patients with RBBB are older, have increased comorbidities and less often receive optimal acute in-hospital treatment. 3. In STEMI, patients with RBBB have a doubled 1-year mortality rate whereas in NSTEMI there is no difference of outcome in patients with RBBB compared to those without RBBB.

1040 CK-elevation in consecutive patients with NSTEMI - change from a diagnostic to a prognostic marker: results of the ACOS-registry



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Background: After the re-definition of myocardial infarction in 2000 the troponins replaced the CK as biomarker for the diagnosis of especially non-ST-elevation myocardial infarction (NSTEMI).

Methods: Between 2000 and 2002 a total of 16816 consecutive patients with acute coronary syndromes were enrolled into the multicenter ACOS-registry in Germany. We examined the impact of the CK-elevation on hospital mortality in 6334 consecutive patients presenting with NSTEMI in clinical practice comparing 3188 patients with CK $> 2x$ upper normal limit (NSTEMI CK+) with those 3148 without CK $> 2x$ upper normal limit (NSTEMI CK-).

Results: Patients with NSTEMI CK+ were younger and less often female than patients with NSTEMI CK-. Patients with NSTEMI CK+ significantly less often had prior myocardial infarctions and coronary interventions as well as concomitant diseases. Even after adjustment for these differences by multivariate regression analysis, the CK-elevation $> 2x$ upper normal limit was associated with a significant higher hospital mortality (OR 1.96, CI 1.53-2.50).

CK-elevation in NSTEMI

	NSTEMI CK-(n=3148)	NSTEMI CK+(n=3186)	p-value
Age (years)	69.8	67.8	< 0.001
Female Gender	37.4%	30.7%	< 0.001
Prior MI	27.6%	22.1%	< 0.001
Prior PCI	14.2%	10.0%	< 0.001
Prior CABG	10.6%	7.8%	< 0.001
Hypertension	72.1%	68.3%	< 0.001
Diabetes	31.1%	30.0%	= 0.345
Hyperlipidemia	66.9%	63.2%	= 0.002
pAVD	10.3%	8.4%	= 0.013
Smoking	24.0%	26.8%	< 0.001
Hospital Mortality	3.6%	6.4%	< 0.001
Hospital MACCE (Death/MI/Stroke)	7.5%	11.6%	< 0.001

Conclusion: Although patients with NSTEMI CK+ were younger and less often had prior coronary interventions as well as concomitant diseases, hospital mortality was twice as high as compared to NSTEMI CK-. CK-elevation $> 2x$ upper normal limit is a simple and valuable risk marker for NSTEMI in clinical practice.

IMPROVING YIELD, VIABILITY AND ENGRAFTMENT OF STEM CELLS IN THE HEART

1041 Human Cardiac Stem Cells: reproducible isolation and functional characterization of their in vitro and in vivo biological properties and regenerative potential



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Purpose: The recent discovery that the mammalian heart harbors resident stem cells has opened a new exciting field for cardiac biology and pathophysiology. However, many questions remain unanswered, particularly the realistic exploitation of these cells in the clinical arena. To this aim, an easy reproducible model of isolation and characterization of human CSCs is needed.

Methods: Human myocardial samples and biopsies were obtained during cardiac surgery or percutaneous LV catheterization from patients with stable and unstable angina and mitral regurgitation. Explants from right and left atria and ventricles were cultured for an average of 2 weeks to extract and then expand cardiac cells. These were then sorted to isolate c-kit-positive cells and analyzed for the expression of 'stemness' genes by real time RT-PCR, western blot, immunohistochemistry and FACS.

Results: We isolated c-kit-positive cardiac cells from all the four cardiac chambers. These cells were cloned and have been expanded more than 40 passages so far. After these passages, these cells retain telomerase activity and normal telomere length, without cellular and/or molecular evidence of senescence. When grown in suspension, human c-kit-positive CSCs form cardiospheres, i.e. pseudoembryoid bodies, a marker of multipotency. Importantly, when grown in conditioned medium, they differentiate into beating cardiomyocytes, vascular smooth muscle and endothelial cells. Furthermore, all the human clones of c-kit-positive CSCs, obtained so far, highly express recognized 'stemness' genes; c-kit, MDR-1, Oct-4, Nanog, Bmi-1, TERT, Wnt-1, beta-catenin, Notch, and Hedgehog. When injected into infarcted nu/nu rat hearts, c-kit-positive CSCs regenerate histological and functional human myocardium. This phenotype is similar to the one we have described previously for rodent CSCs.

Conclusions: The human heart harbors CSCs that express stemness genes, are clonogenic, self-renewing, multipotent and are competent to regenerate damaged myocardium. They can be successfully and routinely isolated from small myocardial samples, expanded to large numbers and maintained undifferentiated and/or differentiated in culture.

1042 Label retaining cells in the adult mouse heart

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Recent reports have provided increasing evidence for the existence of resident stem cells or cardiac progenitors in adult hearts. Bromodeoxyuridine (BrdU)-label retention has been used to identify stem cells as slow cycling cells in various tissues (e.g., skin, colon); however, this approach has not been applied to the heart yet. We have investigated whether adult mouse hearts contain BrdU label-retaining cells (LRCs) using a BrdU pulse (2 weeks) and chase-protocol. Adult mouse hearts were analyzed immunohistochemically at different time points of chase, ranging from 0 to 12 months. The number of LRCs decreased from 12% immediately after the BrdU pulse to ~0.25% at 4 months of chase, but it remained stable between 4 and 12 months. Histologically, LRCs were widely distributed across the heart; although preferential localization at the apex and in the atria was observed. They were small-sized, located in the interstitium between myocytes, and their cytoplasm stained negative for alpha-actinin (arrows, Figure 1). They were mostly negative for differentiation markers of cardiac, endothelial cell, smooth muscle cell, and fibroblast lineages. Cardiac cells expressing the stem cell antigen-1 (Sca-1) accounted for $9.2 \pm 4.5\%$ of non-myocytic cells in the mouse hearts and were predominantly (70%) positive for the stem cell marker c-kit as well. By flow cytometry analysis, LRCs were enriched by a factor 2.5 in the Sca-1-positive vs. Sca-1-negative cell population.

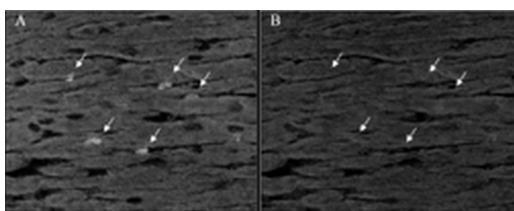


Fig. 1. Characterization of LRCs.

In conclusion, the adult mouse heart contains LRCs that retain the BrdU label for more than 1 year and are enriched in the Sca-1 positive subset, consistent with putative stem cells.

1043 Improved system for selection of ES cell-derived cardiomyocytes allowing for visualisation of myofibril formation in viable cells

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Embryonic stem (ES) cells give rise to all cell lineages including cardiomyocytes (CMs). Isolation of CMs from heterogeneous ES cell-derived populations is required. Towards this goal, previous studies used either a fluorescent marker or antibiotic resistance genes expressed from CM-specific promoters. We have developed a novel system that provides for CM selection and direct visualisation of myofibril formation. Nine bicistronic constructs containing cDNAs encoding a myosin light chain 2v (MLC2v)-green fluorescent protein (GFP) fusion molecule (for CM epitope tagging) and blasticidin deaminase (for drug selection) were used (Figure; panel A). Gene expression was driven by different CM-specific promoters: alpha-myosin heavy chain (MHC), MLC2v, Na⁺-Ca²⁺ exchanger 1 (NCX1), and cardiac troponin I (cTnI). Some constructs also contained a HS2 enhancer from the globin Locus Control Region to prevent gene silencing. Transient and stable transfections were performed in rat neonatal CMs and mouse ES cells, respectively. In neonatal CMs, the hierarchy of promoter activities was MLC2v > cTnI > alpha-MHC and NCX1. The HS2 enhancer increased GFP⁺ CMs from 7% to 48%. In embryoid bodies (EB; differentiation-day 10) exposed to blasticidin for 3 days, all surviving cells were found within beating aggregates or attached to the dish surface and contracting. GFP⁺ beating areas were found in 3 clones in EBs containing the alpha-MHC promoter construct, but not in clones containing other constructs. GFP⁺ cells showed sarcomeric GFP localisation (Figure; panel B), positive alpha-actinin staining, and normal growth in culture.

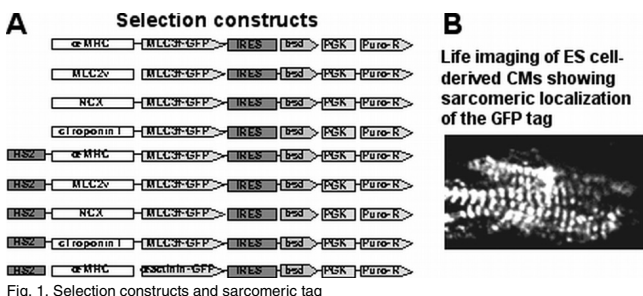


Fig. 1. Selection constructs and sarcomeric tag

Conclusions: This novel selection system allows for simultaneous selection and monitoring of myofibril formation and cell differentiation in viable ES cell-derived CMs.

1044 Increase of cardiac load by transaortic constriction leads to upregulation of bone marrow-derived endothelial progenitor cells, neoangiogenesis and proliferation of cardiomyocytes

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Background: Left ventricular function in myocardial hypertrophy is determined by cardiac blood supply in proportion to size and number of cardiomyocytes. Bone marrow derived endothelial progenitor cells (EPC) have been shown to contribute to cardiovascular repair and angiogenesis. We therefore examined the role of EPC during pressure-induced myocardial hypertrophy.

Methods and Results: Transaortic constriction (TAC) of C57/Bl6 mice (360 μ m for 35 d) increased left ventricular systolic pressure from 54 ± 3 mmHg in sham operated animals to 94 ± 17 mmHg in TAC. The ratio of heart to body weight increased from SHAM $4.16 \pm 0.09\%$ to TAC $7.1 \pm 0.4\%$, $p < 0.01$, $n = 15$ per group. Consistent with hypertrophy, the number of cardiomyocytes (CM) decreased from 673 ± 30 to $565 \pm 33/\text{mm}^2$. Lung weight (SHAM 182 ± 17 mg, TAC 263 ± 55 mg) as well as liver weight increased. Ki67 immunostaining was performed to identify proliferating cells. No Ki67⁺ cardiomyocytes were found in SHAM, whereas TAC showed 0.41 ± 0.07 Ki67⁺ CM/ mm^2 . In non-cardiomyocyte cells, hypertrophy increased Ki67⁺ cells from SHAM $432 \pm 67/\text{mm}^2$ to $1749 \pm 264/\text{mm}^2$ ($n = 8$, $p < 0.001$). EPC, defined as Sca-1/VEGFR-2 positive mononuclear cells, were quantified by FACS analysis. TAC increased circulating blood EPC to $210 \pm 17\%$ of SHAM ($p < 0.05$). Similarly, EPC in the bone marrow were upregulated to $221 \pm 37\%$ of SHAM ($p < 0.05$). As an additional method of EPC quantification, DiLDL/lectin positive EPC were expanded from spleen-derived mononuclear cells. In TAC mice, cultured EPC increased to $195 \pm 12\%$ ($p < 0.05$). To study the functional effects of EPC upregulation during myocardial hypertrophy, neoangiogenesis was evaluated in vivo by quantification of new vessel in-growth in subcutaneously implanted polyvinyl sponges (21d) by perfusion with fluorescent microspheres ($0.2 \mu\text{m}$): TAC increased the area of neoangiogenesis by 40%.

Conclusion: Pressure-induced, non-ischemic myocardial hypertrophy in mice is associated with increased numbers of endothelial progenitor cells circulating in the blood as well as in the bone marrow, enhanced extra-cardiac neoangiogenesis and increased proliferation of cardiomyocytes. Regulation of bone-marrow derived cells may represent an important systemic - and potential cardiac - effect of increased cardiac afterload.

1045 Effect of FGF2 on statin-mediated mobilization of endothelial progenitor cells

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Background: Bone marrow-derived endothelial progenitor cells (EPC) contribute to repair mechanisms of the endothelium. Statins are known to mobilize EPC from bone marrow to peripheral blood, enhance the clonogenic potential of progenitor cells, and improve reendothelialization after focal endothelial cell damage. Fibroblast growth factor-2 (FGF2) is an important mediator of angiogenesis and influences endothelial cell growth, endothelial cell migration, and reendothelialization. Here we investigate the underlying mechanisms of statin-mediated EPC mobilization.

Methods and Results: In order to study the role of FGF2 on stem and progenitor cell mobilization, FGF2^{-/-} knock out mice were treated with the HMG-CoA reductase-inhibitor rosuvastatin (10mg/kg body weight s.c.) or placebo. We measured the number of Sca1/Flk-1 positive EPC within peripheral blood and bone marrow using flow cytometry. In contrast to wild type mice (WT), FGF2^{-/-} mice did not show a statin-mediated mobilization of EPC into peripheral blood. FGF2^{-/-} mice showed an accumulation of Sca1/Flk-1 positive EPC within the bone marrow indicating a mobilization defect in these animals. In order to study the functional effect of insufficient EPC mobilization in FGF2^{-/-} mice, mice received an injury of their common carotid artery. In WT mice, statin-induced EPC mobilization was associated with a reduction in neointima formation mediated by an enhanced reendothelialization. In rosuvastatin-treated FGF2^{-/-} mice, EPC mediated inhibition of neointima formation was not observed. In order to study the functional effects on neoangiogenesis we studied angiogenesis in a subcutaneous disk model. Statin-mediated improvement of neoangiogenesis was only observed in WT mice and was missing in FGF2^{-/-} mice.

Conclusion: FGF2 plays a major role in statin-mediated mobilization of stem and progenitor cells from bone marrow into peripheral blood. The lack of EPC mobilization in FGF2^{-/-} mice is associated with a reduced reendothelialization after focal endothelial cell damage and with a reduction in neoangiogenesis in a subcutaneous disk model. The results underline the pivotal role of EPC in reendothelialization and neoangiogenesis. FGF2^{-/-} mice are an important model to study the vasculoprotective role of EPC.

1046 Shock waves treatment induces differentiation of cardiac primitive cells in vitro



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The identification of resident stem cells and progenitors of cardiomyocytes, endothelial and smooth muscle cells in the adult human heart has triggered the studies of new treatment options influencing their proliferation, migration and differentiation. It has been recently made known that shock waves (SW) therapy enhances the expression of VEGF and its receptor Flt-1 in human umbilical vein endothelial cells in vitro and proves beneficial in patients with coronary artery disease. We assessed the hypothesis that shock waves can have positive effects on precursors of all cardiac cell populations, namely cardiomyocytes, endothelial, smooth muscle cells and fibroblasts.

We used bioptic pieces from normal adult hearts (n=10) and from human hearts explanted due to the ischemic cardiomyopathy (n=14) to obtain the outgrowth of cardiac cells in vitro. The precursors and progenitors of cells of cardiac lineages were identified and quantified by immunocytochemistry. The cell proliferation and expression of differentiation markers were then examined by immunocytochemistry and western blot, both without and after exposition to 800 shots of SW at 0.1 mJ/mm².

The growth rate of cardiac cells was slowed down by the SW treatment due to the decrease of fibroblast relative number in the cell culture (83% vs. 56%, $p < 0.05$). The expression of Flk-1 increased significantly in the primitive cells from both normal and diseased hearts after SW treatment (4-fold and 2-fold, respectively). Similarly, the SW treatment increased nearly 2-fold the expression of smooth muscle actin, while the increase of α -sarcomeric actin and MHC expression was not significant. The expression of MLC-1 decreased significantly after SW treatment of normal cells and increased in the cells from pathological hearts, while MLC-2 decreased in both cell types. Importantly, the number of primitive cells and expression of differentiation markers were always significantly higher in the control cells from pathological hearts when compared with the normal hearts.

The results indicate that differentiation of primitive cells in the myocardium is markedly enhanced in chronic pathological conditions. The SW treatment influences positively differentiation and maturation of cardiomyocytes, endothelial and smooth muscle cells, reducing the relative number of fibroblasts in vitro, possibly due to the influence on growth factor production and release, enhancing their auto- and paracrine action. The effects of SW therapy were markedly more prominent in the cells from normal hearts, therefore its use may be recommended in the early stages of heart failure.

ANYTHING NEW ON SMOKING

1112 GSTM1, GSTT1 and CYP1A1 detoxification gene polymorphisms and susceptibility to smoking-related coronary artery disease



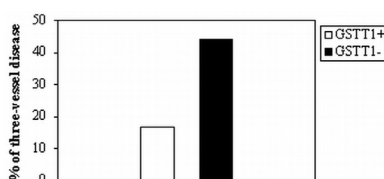
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Background: Cigarette smoking is a powerful risk factor for atherosclerosis, but the degree of damage varies from individual to individual. Genetic polymorphisms of relevant xenobiotic metabolising enzymes may determine the susceptibility of an individual response to environmental toxicants.

Aim: To assess whether the inheritance of polymorphic genes encoding cytochrome P450 1A1 (CYP1A1) and glutathione S transferase (GSTM1 and GSTT1) have an effect in modulating smoking-related coronary artery disease (CAD) risk.

Methods: CYP1A1 (6235T>C) polymorphism and the GSTM1, GSTT1 null genotypes were evaluated by PCR-restriction fragment length polymorphism (RFLP) in a group of 164 smoker patients (143 male, 57.8±10.3 years) consecutively referred to our Department for coronary angiography investigation. Significant CAD was >50% diameter reduction in at least 1 major coronary vessel.

Results: Significant CAD was detected in 115 patients (70.1%). Gender ($p < 0.0001$), diabetes 2 ($p = 0.0023$), hypertension ($p = 0.005$) and dyslipidemia ($p < 0.0001$) were significant risk factors for CAD. The frequency of GSTM1 null genotype ($p = 0.5$) and 6235T>C polymorphism ($p = 0.13$) were not significantly different between patients with or without CAD. The frequency of the GSTT1 null genotype was 42.6% in the CAD patients compared with 24.5% in the no-CAD group ($p = 0.03$). After adjustment for traditional risk factors, the presence of GSTT1 null genotype was significantly associated with an increased risk of CAD



(OR=2.6; 95% CI: 1-6.8, $p = 0.04$). Moreover, smokers with the null GSTT1 genotype had a significant increased risk for three-vessel disease than those with the positive genotype ($\chi^2 = 15.5$, $p = 0.002$): (Figure).

Conclusion: Smokers carrying null GST genotype have an increased susceptibility to the smoking related CAD.

1113 The impact of cigarette smoking on low-grade inflammation and thrombosis/fibrinolysis system in essential hypertensive subjects: shedding more light to the smoking-related vascular disease



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Purpose: Despite the fact that smoking has numerous effects that promote atherosclerosis, the data regarding its association with inflammatory processes and thrombosis/fibrinolysis system in the setting of untreated essential hypertension are rather scarce. In the present study we investigated the interactions between smoking and high-sensitivity C-reactive protein (hs-CRP), fibrinogen and plasminogen-activator inhibitor type 1 (PAI-1) levels in essential hypertensive subjects.

Methods: 295 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [192 men, mean age=50 years, office blood pressure (BP)=148/95] were classified according to their smoking habits as current smokers (>or=1 cigarette/day, n=127) and the remaining subjects as non-smokers (n=165). All subjects underwent ambulatory BP monitoring and venous blood sampling was performed for estimation of metabolic profile, hs-CRP fibrinogen and PAI-1 concentrations.

Results: Hypertensive current smokers compared to non-smokers had increased office diastolic BP (96 ± 9 vs 94 ± 7 mmHg, $p < 0.05$) and 24-h diastolic BP (84.7 ± 10 vs 80.8 ± 9 mmHg, $p = 0.001$), whereas did not differ regarding age, sex, body mass index (BMI), and left ventricular mass index ($p = \text{NS}$ for all). Although groups exhibited no difference regarding metabolic profile ($p = \text{NS}$), smokers compared to non-smokers were characterized by higher levels of hs-CRP (3.18 ± 0.95 vs 2.29 ± 0.48 mg/l, $p < 0.005$), fibrinogen (316.2 ± 62.6 vs 292.7 ± 66.9 mg/dl, $p = 0.01$) and PAI-1 (38.08 ± 9.54 vs 25.5 ± 23.9 ng/ml, $p = 0.002$). In the entire population, hs-CRP was associated with BMI ($r = 0.281$, $p < 0.0001$), pack-years index ($r = 0.184$, $p < 0.005$), 24-h systolic BP ($r = 0.144$, $p < 0.05$), and fibrinogen ($r = 0.138$, $p < 0.05$), whereas PAI-1 exhibited a positive correlation with pack-years index ($r = 0.248$, $p < 0.005$) and 24-h diastolic BP ($r = 0.220$, $p = 0.006$). Regarding fibrinogen, it was related to pack-years index ($r = 0.176$, $p < 0.05$) and daytime pulse pressure ($r = 0.185$, $p < 0.005$). Analysis of covariance revealed that hs-CRP, fibrinogen and PAI-1 concentrations remained significantly different between the two groups after adjusting for confounding factors ($p < 0.05$ for all).

Conclusions: Smoking in essential hypertension is accompanied by increased inflammatory processes and impairment of thrombosis/fibrinolysis system, as reflected by hs-CRP, fibrinogen and PAI-1 levels. These findings may partially elucidate the complex mechanisms linking smoking with increased cardiovascular risk, in this setting.

1114 Homozygosity for the 894T allele on endothelial nitric oxide synthase gene, interacts with cigarette smoking increasing the risk for myocardial infarction in young individuals



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Genetic polymorphism G894T on endothelial nitric oxide synthase (eNOS) has been associated with increased cardiovascular risk. However its pathophysiologic significance is still unclear, since it has been associated with endothelial dysfunction in high-risk patients and especially in smokers, but not in healthy, low-risk individuals.

Aim: We aimed to examine whether G894T modifies the smoking-associated risk for premature myocardial infarction (MI).

Methods: The study population consisted of 228 patients with first event of premature MI (aged 46.96 ± 0.4 yrs old) and 519 age- and sex- matched controls. Smokers were defined as those smoking at least 10 cigarettes per day for at least the last 1 year. "Heavy" smokers were defined as those with ≥ 20 pack-years and "light" smokers those with < 20 pack-years. G894T polymorphism was detected by PCR.

Results: The prevalence of smoking was higher in patients (200, 87.7%) compared to controls (301, 57.9%, $p < 0.001$). The frequencies of GG, GT and TT were 97 (42.5%), 99 (43.5%) and 32 (14%) in MI and 255 (49.1%), 217 (41.8%) and 47 (9.1%) in controls. The risk for MI in smokers was $4.623(2.936-7.280)$ $p < 0.001$ compared to non smokers $1.982(1.105-3.738)$ $p = 0.034$ for "light" and $5.963(3.758-9.462)$ $p < 0.001$ for "heavy" smokers. Among 894TT, the smoking-associated risk for MI was $13.248(2.655-66.095)$ $p = 0.002$ ($6.750(0.547-83.231)$ $p = 0.136$ for "light" and $17.834(3.647-87.215)$ $p = 0.001$ for "heavy" smokers). Among 894GT, the smoking-associated risk for MI was $4.079(2.047-8.130)$ $p = 0.001$ ($1.790(0.677-4.755)$ $p = 0.240$ for "light" and $5.176(2.569-10.430)$ $p < 0.001$ for "heavy" smokers). In 894GG, the smoking-associated risk was $4.774(2.372-9.612)$ $p < 0.001$ ($2.00(0.729-5.491)$ $p = 0.178$ for

"light" and 6.348(3.102-12.988) $p=0.0001$ for "heavy" smokers). The unadjusted risk for MI of 894TT homozygotes in the overall population was 1.640(1.015-2.647) $p=0.043$ compared to 894GT+GG, and it was elevated to 2.508(1.364-4.611) $p=0.003$ after exclusion of non-smokers.

Conclusions: The G894T polymorphism on eNOS gene increases the smoking-associated risk for premature myocardial infarction. This finding suggests that homozygotes for the 894T allele, are more vulnerable to the deleterious effects of cigarette smoking, and it is more likely to develop premature myocardial infarction compared to carriers of the 894G allele.

1115 Microcirculation damage was prominent in smokers with vasospastic angina



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Background: Endothelial dysfunction is considered one of the mechanisms underlying vasospastic angina (VSA). It is also known that smokers have abnormality in endothelial dysfunction. Although smoking is a major risk factor for coronary artery disease, microvascular abnormalities have not been well shown. We here investigated clinical characteristics and coronary reactivity with adenosine triphosphate (ATP) in smokers with VSA.

Methods: Consecutive 22 patients whose coronary spasm was documented in left anterior descending coronary artery (LAD) with acetylcholine were enrolled in this study. Coronary blood flow responses were also evaluated by intracoronary Doppler flow velocity recordings in LAD. Average peak velocities (APV) were measured at baseline and intracoronary administration of ATP (50µg) in smokers (N= 11, 60±9 yrs, 8 males) and non-smokers (N= 11, 61±10 yrs, 5 males). CFR was calculated by the ratio of baseline to hyperemic APV.

Results: Multi-vessel spasm was demonstrated in 6 smokers and only 2 non-smokers ($P<0.05$). Resting APV with smokers (13.4±3.0cm/s) was similar to non-smokers (13.5±2.9cm/s). However, CFR with smokers (2.6±0.7) was significantly lower compared to non-smokers (3.4±0.8, $p<0.05$).

Conclusion: In clinical settings, multi-vessel spasm was demonstrated more in smokers. Microcirculation damage precedes endothelial dysfunction in smokers with VSA.

1116 The role of maternal cigarette smoking habit in the onset of early coronary atherosclerotic lesions in fetuses and infants



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Lipid profile and cigarette smoking are well established as major exogenous risk factors for the development of atherosclerosis. However, there are few and controversial reports regarding the foetal origin of coronary artery lesions.

Aim: To evaluate features of early atherosclerotic lesions in victims of unexpected fetal deaths (UFD) and SIDS and its possible correlation with maternal cigarette smoking.

Methods: 22 UFD and 36 SIDS victims were autopsied. Before and during pregnancy 48% mothers (28/58) were smokers. The major epicardial coronary arteries were isolated along their whole length, embedded in paraffin and serially cut for histologic examination. Sections were stained with H&E, Azan, Alcian blue (pH 0.5 and 2.5), and Weigert. Sections were immunotyped for CD68, CD34, anti-alpha actin, PCNA, c-fos, and TUNEL method (apoptosis).

Results: Multifocal coronary lesions of varying entity were detected in 83% of fetuses (10/12), and 94% of infants (15/16) of smoking mothers. In only 5 cases belonging to non-smoker mothers (2/10 foetus and 3/20 infants) were also observed coronary lesions ($p<0.0001$). Findings ranged from focal areas with mild myointimal thickening in prenatal life to early soft parietal plaques reducing arterial lumen up to 30-40% in infants. Smooth muscle cells (SMC) showed loss of polarity, forming columns perpendicular to the media axis, infiltrating the subendothelial connective tissue through the rupture of the internal elastic membrane. There were increased amounts of mucoid ground substance at this level. Macrophages were observed penetrating the endothelium in the intimal border of the lesions. No neoangiogenesis was detected. Early atherosclerotic lesions presented c-fos gene activation in the SMC of the tunica media. Some of these, were also positive for apoptosis. These findings suggest that c-fos gene over-expression could promote a proliferative process, as testified by the PCNA positivity.

Conclusion: Early intimal coronary arteries alterations are already detectable in the prenatal period, and are associated with maternal tobaccoism.

1117 Passive smoking impact on adiponectin and resistin plasma levels in healthy non-smokers



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Introduction: Smoking is one of the primary modifiable risk factors for CAD, while hypo adiponectinemia and hyperresistinemia may contribute to chronic inflammatory process, insulin resistance, endothelial dysfunction and accelerated atherogenesis.

Aim of our study was to estimate the effect of passive smoking on adiponectin and resistin plasma levels, in healthy non-smokers, (non-active non-passive, NNP), and to compare the findings to those of healthy non-smokers, (non-active, passive exposure, NAPE), matched for age, sex, body mass index and the rest of risk factors.

Methods: Forty NAPE (18M, 22F), mean age 48±7 yr with passive exposure to smoke>10yr (group A) and 46 NNP (20M, 26F), mean age 47.5±8 yr (group B), were studied. Adiponectin and resistin plasma levels were determined in both groups (ELISA method).

Results: Our findings and the comparisons between the two groups are shown in table 1.

Table 1

Parameters	Group A (n=40)	Group B (n=46)	p
Adiponectin (µg/ml)	6.5±2.2	10±3.7	<0.01
Resistin (ng/ml)	11±3.5	7±3.8	<0.001

Conclusions: Our findings suggest that healthy non-smokers, (non-active, passive exposure) have significantly lower adiponectin levels and significantly higher resistin levels compared to healthy non-smokers, (non-active non-passive). This may represent another possible mechanism due to which passive smoking plays an important role in atherosclerosis process.

SUCCESSFUL INITIATIVES IN CARDIOVASCULAR NURSING

1118 The European Heart Failure Self-Care Behavior Scale: data from clinical and research populations



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Background: Improvement of self-care behaviour is an aim of several non-pharmacological interventions for patients with heart failure (HF). These interventions are often evaluated based on their effects on readmission, costs and quality of life. However, it is also important to know how patients changed their self-care behaviour as a result of such interventions. The European Heart Failure Self-Care Behavior Scale (EHFScB scale) was developed and tested in 2001 and is available in 11 languages in 2006. The aim of this study was to further determine reliability and validity in 7 different samples from 5 countries.

Method: Data of 2307 HF patients (63% male, mean age 73 years) were analyzed from 2 clinical and 5 research samples from Sweden, Netherlands, United Kingdom, Italy and Spain. Internal consistency was determined by Cronbachs alpha. Validity was explored by content analysis interviewing 16 individuals diagnosed with heart failure in New York Heart Association Class (NYHA) II-III on their self-care behaviours. Discriminant validity was determined by comparing the total score on the EHFScB scale with two Quality of life instruments, the EuroQol (EQ) and the Minnesota Living with Heart Failure Questionnaire (MLWHFQ).

Results: Internal consistency of the scale was 0.77 for the total population and ranged from 0.71 to 0.85 for the separate samples. Two items were lowering the alpha in most samples; they were items concerning a flu shot and getting regular exercise. There were no items of this 12-item scale that were missing > 1% of the data and patients were able to choose a score between totally agree and totally disagree on all items for at least 80%.

Content analysis revealed that all items -except for getting a flu shot- of the EHFScB scale were mentioned by patients as relevant self-care behaviours. Items that were also mentioned by patient but that are not in the scale were all related to general non HF-specific self care such as a healthy diet, avoiding emotional distress and good sleeping habits. Scores of EHFScB scale were not significantly correlated to the EQ and MLWHFQ ($r=0.05$, ns), suggesting these are indeed different concepts.

Conclusion The European Heart Failure Self care Behaviour Scale - and several of its officially translated versions - is an internally consistent and reliable scale that both can be used in clinical research and clinical practice.

1119 Evaluation of nurse-led rapid access chest pain clinics - are they safe and effective?



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Introduction: Rapid access chest pain clinics allow rapid assessment and investigation of suspected new onset angina. Typically, these clinics are led by Doctors. In January 2002 specialist nurse-led rapid access chest pain clinics were established at a District General Hospital (Wigan Royal Infirmary) in the North West of England.

Objective: To assess safety and efficacy of these specialist nurse-led rapid access chest pain clinics.

Method: GPs were invited to refer patients with recent onset chest pain, suggestive of angina. Patients were seen within 2 weeks of referral. They were reviewed by 3 specially trained cardiac specialist nurses who followed a special protocol. After taking history and examining the patient, exercise was undertaken on a treadmill utilising the standard Bruce protocol. Retrospective data was collected from all patients attending the specialist nurse-led clinics from January 2002 to June 2005.

Results: General Practitioners referred 920 patients (450 males and 470 females) to the specialist nurse-led clinics. Mean age was 54 years for males and 55 for females. Eight hundred and forty three (92%) patients were seen within the 14 day Government target. 910 patients underwent exercise tolerance testing and 146 (16.1%) were positive (95 males and 51 females). 78 patients underwent cardiac catheterisation (55 males, 23 females) and coronary artery disease was found in 64 patients (53 males, 11 females). Twenty of these patients (31%) were treated medically and 44 patients (69%) underwent revascularisation. Apart from one patient who had atrial fibrillation post-exercise, there were no complications. All exercise tests were reviewed later by cardiologist. Only 4 results were disputed, the nurses labelling these as equivocal while the cardiologist diagnosed these as negative. No clinic was cancelled.

Conclusion: This study demonstrates that specialist nurse-led rapid access chest pain clinics are safe and effective. Identifying high risk patients earlier allows early medical and surgical intervention thus reducing patient morbidity and mortality. These clinics reduce the burden on doctors and ensures that hospitals can meet Government targets.

1120 The impact of the Angina Plan on misconceptions and mood



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Purpose: The aim of this study was to evaluate the Angina Plan, a cognitive-behavioural nurse-facilitated self-help intervention as a method of supporting patients admitted to hospital with an acute exacerbation of angina.

Methods: A pragmatic randomised-controlled trial was carried out (August 2003 - June 2005) involving 218 patients and 55 partners admitted with an acute exacerbation of angina in two hospital sites in an Acute Scottish Hospital Trust. Participants were randomized to receive the Angina Plan, an in-hospital consultation and telephone follow-up post discharge or Standard Care. Assessments made pre-discharge and at 6 month follow-up by interview included demographic and clinical data, the Hospital Anxiety and Depression Scale and the York Angina Beliefs Questionnaire.

Results: Analysis showed that patients receiving the Angina Plan reported a comparative increase in knowledge and a reduction in misconceptions, $F(1, 216)=33.88$ $p=.00$. There were no reliable effects on mood. Once patients with high depression scores pre-discharge ($N=13$) were removed from the analysis, AP patients showed a significant reduction in depression levels compared to the SC patients $t(203)=2.23$, $p=.027$. In a further sensitivity analysis, when patients receiving CABG or PCI were excluded, effects on knowledge and misconceptions remained and between-group changes in depression approached significance. In partners of the study participants, no between-group differences in partners' knowledge and misconceptions were found. However, between group differences were found in partners levels of depression with the AP group reporting lower levels of depression at 6-month follow-up.

Conclusions: The use of the Angina Plan in a secondary care setting produces similar benefits to its reported use in primary care with patients with newly diagnosed angina. Initiating the Angina Plan in a secondary care setting seems to be beneficial not only for newly diagnosed angina patients but also for patients with established coronary heart disease.

1121 The influence of structured home visits on anxiety and depression after coronary artery bypass grafting (CABG). Results of the HINCAB study



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Introduction: Anxiety and depression symptoms are known to be quite common

after CABG and often appear at the same time. Further the symptoms reinforce each other. Anxiety and depression are shown to be independent risk factors for morbidity and mortality in heart patients. Studies underline that CABG patients, especially the first month after surgery, need more information and guidance by health care providers than they currently get.

Aim: The aim of the present study was to evaluate the effects of a home based intervention program; the Home based Intervention Nursing Coronary Artery Bypass grafting (HINCAB) study. The hypothesis was that such an intervention program would reduce anxiety and depression symptoms.

Method: A randomized controlled trial (RCT) recruited 203 patients undergoing elective CABG. The participants were allocated to an intervention group ($n = 101$) or a control group ($n = 102$). The intervention consisted of two structured home visits 2 and 4 weeks after surgery, according to an intervention protocol. Anxiety and depression symptoms were measured at baseline, after 6 weeks and 6 months by the self-rating instrument HADS (Hospital Anxiety and Depression Scale) that was mailed to the participants. The study was approved by the Regional Ethical Committee.

Results: A total of 185 patients completed the study; intervention group ($n = 93$) and control group ($n = 92$). At 6 months follow-up improvement was found in both groups for anxiety as well as depression symptoms. These improvements did not differ significantly between the groups. However, in a predefined sub-analysis in patients with anxiety and/or depression symptoms at baseline ($n = 65$), these improvements were significantly larger in the intervention group ($n = 29$) than in the control group ($n = 36$) after 6 months ($p < 0.05$ for both). Intra-group analysis showed significant improvement in anxiety scores for both groups and in depression scores in the intervention group.

Conclusion: In the total study group the improvement of symptoms did not differ significantly between the intervention group and the control group. However, among patients with anxiety and/or depression symptoms at baseline, these improvements were significantly larger in the intervention group. These findings indicate that preoperative screening by HADS should be used to pinpoint a subgroup of CABG patients that could benefit from home visits by a qualified and experienced nurse.

1122 Successful motivational interviewing for smoking cessation in a secondary cardiovascular prevention clinic



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Introduction: Although, the use of specialised nurses may lead to a decline in smoking patients, it is still difficult to integrate structural lifestyle intervention in daily usual care. Therefore, we recently introduced, a standardized Lifestyle Inventory with Feedback (LIFE) procedure for physicians as new element of regular care for cardiovascular patients.

Purpose: To investigate the additional effect on smoking cessation with Motivational Interviewing by specialised nurses on top of LIFE in an outpatient secondary prevention setting.

Methods: After being exposed to LIFE, all smoking patients ($n=116$), selected out of 449 consecutive patients with cardiovascular disease, were randomised for either Motivational Interviewing, i.e. extended Minimal Intervention Strategy (L-MIS) by specialised nurses or regular care (solely LIFE). Informed consent was obtained for final urine cotinine determination. Cumulative individual time investment was recorded.

Results: After 3 months follow-up, abstinence rate in the solely LIFE group was 6.8%, whereas 42.3% in the LIFE plus Motivational Interviewing group quit smoking ($p<0.0001$). Only 1.8% of all participants in both groups used additional supportive medication. On average each completed Motivational Interviewing session took 77.8 minutes. NNT appeared 2.8.

Conclusions: Motivational Interviewing Strategy (L-MIS) on top of a structured Lifestyle Inventory with Feedback procedure (LIFE) significantly increases smoking cessation to a larger extent. Direct cardiovascular risk reduction due to smoking cessation, managed in this way by specialised nurses in an outpatient secondary prevention setting, is successful and might be cost-effective.

1123 Ultimate cost-benefits of altering the natural history of chronic heart failure via multidisciplinary, home-based intervention: Ten-year follow-up of typically old and fragile patients



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Background: The short to medium-term benefits of nurse-led, multidisciplinary home-based interventions (HBI) in chronic heart failure (CHF) are now well documented. However, their ability to deliver cost-benefits over the longer-term is unknown; particularly given their ability to prolong survival and the subsequent increased risk, therefore, of surviving CHF patients requiring recurrent hospitalisations before an inevitable death.

Methods: We examined the long-term effects of a nurse-led multidisciplinary HBI in a typically old and fragile cohort of CHF patients discharged home from acute hospital care randomly allocated to HBI ($n = 149$) or usual post-discharge care (UC: $n = 148$). Study patients were followed-up for up to 10 years (minimum 7.5 years) following an index admission to derive actual all-cause mortality, event-free survival (readmission or death) and recurrent hospitalisation data during this period. These data were then used to calculate the long-term cost-effectiveness of HBI (expressed as the cost per life-year saved).

Results: During prolonged follow-up, median survival in the HBI cohort was almost twice that of UC (40 vs. 22 months, $p < 0.001$) and fewer HBI patients died overall (77% vs. 89%; adjusted RR 0.74, 95% CI 0.53 to 0.80; $p < 0.001$). Nearly every patient (98%), however, required an unplanned admission to hospital or died. As previously reported, HBI was associated with prolonged event-free survival (median of 4 vs. 7 event-free months, $p < 0.01$) and, overall, a 24% reduced risk of such an event occurring in the longer-term (adjusted RR 0.76, 95% CI 0.61 to 0.96, $p < 0.01$). Due to more prolonged survival (30 more patients lived beyond 5 years), HBI patients ultimately accumulated more unplanned readmissions (560 vs. 550 admissions associated with 4312 vs. 4,671 days of hospital stay): the HBI group took 7 years to reach the UC group. However, on an adjusted basis, both the rate of readmission and hospital stay was significantly lower in the HBI group (2.04 ± 3.23 vs. 3.66 ± 7.62 admissions and 14.8 ± 23.0 vs. 28.4 ± 53.4 days/patient/year: $p < 0.05$ for both comparisons). Overall, HBI was associated with 120 more life-years per 100 patients treated compared to UC (405 vs. 285 years) at an individual cost of \$AU1,729 (1,072 Euros) per additional life-year gained when accounting for the cost of all hospital activity and applying HBI.

Conclusion: In altering the natural history of CHF relative to UC (via prolonged survival and reduced frequency of recurrent hospitalisation), HBI is a remarkably cost and time-effective strategy over the longer-term.

ANEMIA AND IRON DEFICIENCY IN HEART FAILURE

1124 Recombinant human erythropoietin improves left ventricular diastolic and systolic function, and reduces plasma biomarkers of neurohormonal activation in patients with chronic heart failure and anemia

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Aim: Anemia is a frequent comorbid condition in chronic heart failure (CHF) affecting adversely patient prognosis. Erythropoietin (EPO) administration seems to restore hemoglobin (Hb) levels and improve exercise capacity of CHF patients. We sought to investigate if recombinant human EPO (rhEPO) affects beneficially markers of left ventricular (LV) diastolic and systolic function, and neurohormonal activation in patients with CHF and anemia (Hb < 12.5 g/dL).

Methods: Twenty-six CHF patients [NYHA class: 3.0 ± 0.7 ; LV ejection fraction (EF): $26 \pm 5\%$; Hb: 11.2 ± 0.8 g/dL; serum creatinine < 2.5 mg/dL] were randomized (2:1) to receive either 3-month rhEPO ($n=17$) (darbepoetin- α : $1.5 \mu\text{g/kg}$ every 20 days s.c.) plus ferrum orally or placebo ($n=9$) plus ferrum orally. Echocardiographic markers of LV diastolic (E, A filling velocities, ratio E/A, deceleration time DT of E, tissue Doppler imaging e wave, ratio E/e) and systolic function [LVEF, end-systolic wall stress (ESWS)], plasma B-type natriuretic peptide (BNP), serum C-reactive protein (CRP), and 6-min walk test were assessed before and after the 3-month treatment.

Results: DT of E (152 ± 65 vs 171 ± 67 msec, $p=0.05$), ratio E/e (11.7 ± 3.3 vs 9.6 ± 3.6 , $p<0.01$), LVEF (23 ± 5 vs $30 \pm 6\%$, $p<0.01$) and ESWS (147 ± 64 vs 113 ± 34 g/cm², $p<0.01$) were improved only in the rhEPO-treated group. Additionally, in rhEPO-treated patients, BNP (1280 ± 128 vs 824 ± 93 ng/mL, $p<0.01$) and CRP (12.1 ± 8.7 vs 9.2 ± 5.7 ng/mL, $p<0.05$) levels were significantly reduced, while Hb (11.0 ± 0.8 vs 12.9 ± 1.5 g/dL, $p<0.01$) and 6-min walk distance (231 ± 108 vs 318 ± 109 m, $p<0.01$) significantly increased. No significant changes of all these parameters were observed in the placebo-treated arm. RhEPO-induced increase of Hb was significantly correlated with the respective reduction of BNP ($r=-0.55$, $p<0.05$) and ESWS ($r=-0.60$, $p<0.05$).

Conclusions: RhEPO administration improves markers of LV diastolic and systolic function in CHF patients with anemia, reducing also peripheral neurohormonal response and improving patient exercise capacity.

1125 Randomized, double-blind, placebo-controlled trial to assess the impact of darbepoetin alfa treatment on exercise tolerance in anemic patients with symptomatic heart failure: results from STAMINA-HeFT

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Background: Patients with heart failure (HF) and anemia have severe symptoms and poor outcomes, but no large randomized, double-blind, placebo-controlled trial (RCT) has assessed the safety and benefits of raising hemoglobin (Hb) in these patients. STAMINA-HeFT is a multicenter RCT evaluating the effect of treating anemia with darbepoetin alfa (DA) in HF.

Methods: Patients with NYHA class II-IV, LVEF $\leq 40\%$, and Hb ≤ 12.5 g/dL were randomized to placebo or DA subcutaneously every 2 weeks for 1 year (target Hb 14.0 ± 1.0 g/dL). Endpoints were change in exercise time (ET), NYHA class, Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score at 6 months; HF hospitalization and mortality at 1 year; safety.

Results: Baseline characteristics of DA and placebo groups were similar. Most subjects had NYHA class II (35%) or III (61%) and received beta blockers (78%); mean $\pm$ SD age was 69 ± 11 years, Hb was 11.4 ± 0.8 g/dL. Although DA treatment was not associated with a significant overall increase in ET, a significant Hb-dependent increase was observed: delta Hb < 1.0 g/dL ($n=23$), delta ET +14.8 sec; delta Hb $1-2$ g/dL ($n=61$), delta ET +40.5 sec; delta Hb > 2.0 g/dL ($n=52$), delta ET +95.3 sec; $p=0.003$. Hazard ratio (95% CI) for first HF hospitalization or mortality was 0.68 (0.43, 1.08; $p=0.10$).

Results Table

	Placebo (n=157)	Darbepoetin alfa (n=162)
Mean Changes from Baseline (SD or 95% CI)		
Hb, g/dL	0.45 (1.11)	1.80 (1.20)
Exercise time, sec (primary endpoint)	46.5 (25.9, 67.2)	57.3 (37.5, 77.1)
NYHA class	-0.13 (-0.22, -0.04)	-0.19 (-0.28, -0.10)
MLHFQ total score	-7.1 (-10.8, -3.4)	-9.3 (-12.4, -6.1)
Specific Adverse Events, n (%)		
Hypertension	10 (6)	13 (8)
Deep vein thrombosis	2 (1)	0 (0)
Exacerbation of HF	45 (29)	38 (23)

Conclusion: In anemic HF patients, treatment with DA was well tolerated, effectively increased Hb and Hb-dependent exercise duration and was suggestive of a benefit in clinical outcomes. These data support the initiation of a large outcomes trial to assess anemia treatment as a potential new therapeutic option in HF.

1126 Safety and efficacy of darbepoetin alfa treatment in anemic patients with symptomatic heart failure: a pooled analysis of two randomized, double-blind, placebo-controlled trials

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Background: Anemia in heart failure (HF) is associated with worse symptoms and outcomes. Its treatment has not been assessed in randomized, double-blind, controlled trials (RCT). This prespecified analysis reports pooled results from 2 multicenter RCTs evaluating the safety and efficacy (and clinical outcomes) of darbepoetin alfa (DA) treatment in anemic HF subjects.

Methods: Patients with symptomatic HF, LVEF $\leq 40\%$, hemoglobin (Hb) $9.0-12.5$ g/dL were randomized to placebo or DA subcutaneously every 2 weeks for up to 1 yr (target Hb 14.0 ± 1.0 g/dL). Endpoints: change from baseline in NYHA class, Patient's Global Assessment (PGA), Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores at 6 months (individual studies); HF-related hospitalization, all-cause mortality, all-cause mortality or HF-related hospitalization (composite), safety at 1 yr (pooled analysis).

Results: Baseline characteristics of placebo and DA groups were similar. The mean (SD) age was 70 (11) yrs, LVEF 33 (10)%, Hb 11.4 (0.8) g/dL. Treatment with DA effectively raised Hb. The decrease in the risk of the composite endpoint and of HF-related hospitalization in the DA group approached statistical significance. Improvements were seen in the DA groups vs placebo in NYHA class and MLHFQ total score, but not PGA (individual studies). The number of adverse events was similar in both treatment groups.

Conclusion: Treatment of anemia with DA in HF subjects effectively raised Hb and was well tolerated. The data suggest that DA treatment may improve symptoms and may decrease the risk of HF-related hospitalization and death. The

Pooled analysis results

	Placebo n=209	Darbepoetin alfa n=266	p value
Outcomes hazard ratio (95% CI)			
Composite endpoint		0.67 (0.44, 1.03)	0.064
HF-related hospitalization		0.66 (0.40, 1.07)	0.091
All-cause mortality		0.76 (0.39, 1.48)	0.418
Specific adverse events, n (%)			
Hypertension	12 (6)	15 (6)	
Deep vein thrombosis	2 (1)	0 (0)	
Exacerbation of heart failure	53 (25)	50 (19)	

findings support the conduct of a Phase 3 trial to examine anemia treatment as a potential new therapeutic option in HF.

1127 Iron deficiency frequently occurs in heart failure and predicts exercise intolerance



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Background: Iron deficiency (ID) is a common pathology in humans, but its relevance in chronic heart failure (CHF) has not yet been investigated. We evaluated the prevalence and clinical correlates of ID in an unselected population of CHF patients.

Methods: We studied 218 symptomatic, consecutive CHF patients (181 men, age: 63±11 years [mean±SD], LVEF: 30±7%; ischaemic CHF aetiology: 69%) under optimal pharmacological therapy. ID was diagnosed when serum ferritin level <100 µg/L or when ferritin 100-300 µg/L and transferrin saturation (TSat) <15%. The following indices of body iron status were also measured: serum iron levels, soluble transferrin receptors (sTfR) and total iron binding capacity (TIBC).

Results: One hundred and one (46%) patients fulfilled laboratory criteria for ID. The following parameters differentiated those with and without ID: peakVO₂ (1151±487 vs. 1350±446 mL/min), ventilatory response to exercise (VE-VCO₂ slope; 43.8±20.0 vs. 37.1±11.7), serum levels of NT-proBNP (6366±8134 vs. 4622±6875 pg/mL) and hs-CRP (14.3±21.3 vs. 8.1±12.7 mg/L) (patients with vs. without ID, respectively, p<0.05 in all comparisons). There were no differences in age, gender, CHF aetiology, comorbidities, therapy, LVEF and renal function between these 2 groups. Among indices of iron status patients with ID demonstrated: decreased iron level (69±37 vs. 110±52 µg/dL, p<0.0001) and increased sTfR (2.18±0.107 vs. 1.73±0.55 mg/L, p<0.01). Interestingly, the presence of anaemia (haemoglobin level <12 g/dL, 36 patients) had only marginal influence on the prevalence of ID: 61% in anaemics vs. 43% in non-anaemics (p=0.052). We additionally investigated the relationship between iron status and exercise intolerance, and found that among laboratory indices characteristic for ID, low TSat and elevated sTfR predicted decreased peakVO₂ (p=0.048 and p=0.026, respectively) and augmented VE-VCO₂ (p=0.05 and p=0.024) when adjusted for the other established exercise capacity predictors in the multivariate models.

Conclusions: Iron deficiency frequently coexists with CHF irrespectively of anaemia. ID may reflect status of low grade inflammation and independently predicts exercise intolerance. Whether correction of iron status would be beneficial for CHF patients needs to be investigated.

1128 Effect of intravenous iron sucrose on exercise tolerance in anaemic and non-anaemic iron deficient patients with chronic heart failure: a randomised, controlled, observer-blinded trial (FERRIC-HF)



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Background: Iron deficiency anaemia is common in patients with chronic heart failure (CHF) and associated with exercise intolerance. Iron deficiency may diminish exercise performance even in the absence of anaemia. We tested the hypothesis that iron repletion with intravenous (IV) iron sucrose would safely improve exercise tolerance in anaemic and non-anaemic iron deficient CHF patients.

Methods: Thirty-five patients with CHF (age 64±13y, 25 male, 26 ischaemic aetiology, 12 diabetic, peak oxygen consumption [pVO₂]/kg 14.0±2.7 mL/min/kg, NYHA class II [n=18]/III [n=17], LVEF 30±7% [all <45%], creatinine 107±40 µmol/L) and iron deficiency (ferritin <100 ng/mL or ferritin 100-300 ng/mL with transferrin saturations <20% or soluble transferrin receptors >1.76 mg/L) were randomly assigned to 16 weeks of IV iron or no treatment in a 2:1 ratio. Randomisation was stratified according to haemoglobin levels (<12.5 g/dL vs 12.5-14.5 g/dL) and centre. Treatment comprised of 200 mg IV iron sucrose weekly until iron repletion (total iron repletion dose = weight (kg) x 2.4 x [15 - haemoglobin (g/dL)] + 500 mg) and 200 mg monthly thereafter. The observer-blinded primary endpoint was the change in absolute pVO₂ from baseline to end of study.

Results: The difference (95% confidence interval [CI]) in the mean changes from baseline to end of study between IV iron and control groups was 273 ng/mL

(151, 396) for ferritin (P<0.0001), 0.1 g/dL (-0.8, 0.9) for haemoglobin (P=0.9), 96 mL/min (-12, 205) for absolute pVO₂ (P=0.08), 2.2 mL/kg/min (0.5, 4.0) for pVO₂/kg (P=0.01), 60 sec (-6, 126) for treadmill exercise duration (P=0.08), -0.8 (-1.3, -0.3) for NYHA class (P=0.003), and 1.7 (0.7, 2.6) for patient global assessment (P=0.002). In the anaemic subgroup, the difference in the mean changes between IV iron (n=12) and control (n=6) groups was 204 mL/min (31, 378) for absolute pVO₂ (P=0.02), 4.0 mL/kg/min (1.1, 6.8) for pVO₂/kg (P=0.01) and 42 sec (-66, 150) for exercise duration (P=0.4). In the non-anaemic subgroup, IV iron improved exercise duration (84 sec [-9, 169], P=0.06) and NYHA class (P=0.06). The incidence of serious (P=0.8) and non-serious (P=0.1) adverse events did not differ between IV iron and control groups.

Conclusions: Iron repletion with intravenous iron sucrose was safe and associated with improvements in exercise capacity and symptom status in CHF patients with iron deficiency. Benefits were more evident in anaemic patients.

CACHEXIA IN HEART FAILURE: WHAT IS NEW?

1130 Predictive value of short-term weight loss after hospitalization and long-term survival in patients with chronic heart failure



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PUROPSE. Chronic weight loss independently predicts survival in patients with chronic heart failure (CHF). We aimed to investigate the prognostic value of weight changes in the first 3 months after hospitalization for decompensated CHF.

Methods: We prospectively followed 71 CHF patients (age 72±11 years, 56% men, 56% ischemic etiology, 80% NYHA class III/IV, glomerular filtration rate [GFR] 59±25 mL/min). Demographic characteristics and laboratory investigations were obtained during hospitalization; weight was always taken on the same scale.

Results: During the first 3 months, 39 patients (55%) experienced weight loss (range 0.1 to 8.0 kg, mean 3.1±2.4 kg) - 11 of these patients lost >6% body weight (mean loss 7.8±1.7%). There were no differences between patients with and without weight loss in terms of age, sex, treatment, NYHA class, aetiology, and appetite score (all p>0.2). Patients with weight loss had a higher GFR than those without (65±27 mL/min vs 52±22 mL/min, p=0.035). During follow-up of 815±313 days, 27 (38%) patients died (24-month mortality after the 2nd weight assessment was 27%, 95% CI 16-37%). Weight changes were more pronounced in non-survivors than in survivors (-1.77±0.78 kg vs -0.07±0.45 kg, p=0.046). In univariate Cox analysis, weight change predicted survival (RR 1.121, 95% CI 1.000-1.256 per kg weight loss, p=0.050). This remained significant after adjusting for GFR, age, NYHA class, sex, and aetiology (p=0.025). Patients with short-term weight loss had a worse long-term survival than patients without such weight loss (24-month mortality: 33% [95% CI 18-48%] vs 19% [95% CI 4-33%], RR 2.116 [95% CI 0.952-4.836], p=0.076).

Conclusion: Body wasting is present in a substantial proportion of CHF patients during the first 3 months after hospitalisation for decompensation. The degree of short-term wasting independently predicts long-term subsequent survival.

1131 Elevated apelin levels reflect catabolic/anabolic imbalance in patients with cardiac cachexia



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Background: Apelin has been shown to be a cardiac inotrope and is one of the most potent stimulators of cardiac contractility known. It is expressed in the human heart and secreted by adipocytes. In cardiac cachexia, plasma levels of apelin are elevated. The aim of our study was to investigate the relationship between apelin levels and catabolic/anabolic imbalance in cachexia associated with chronic heart failure (HF).

Methods: Plasma apelin, cortisol, and dehydroepiandrosterone sulfate (DHEAS) were measured in 60 patients with HF and in 10 control subjects. Patients with HF were divided into two groups: those with cachexia (n=18) and those without cachexia (n=42).

Results: Plasma apelin was significantly higher in HF patients with cachexia than in those without cachexia (600±168 vs. 828±201 fmol/mL, p=0.001). There were no significant differences between mean values of cortisol (19.3±5.8 vs. 21.0±5.9, p=NS) and DHEAS (100.6±103.3 vs. 51.7±49.6 µg/dL, p=0.06) between non-cachectic and cachectic pts, but the difference between both groups was significant in the cortisol/DHEAS ratio (CDR) which reflects catabolic/anabolic imbalance (0.51±0.51 vs. 1.00±0.93, p=0.01). There was a significant correlation between apelin and CDR (r=0.33; p<0.001). The cut-off value for apelin for the prediction of catabolic/anabolic imbalance (CDR>1.0) with 66.7% sensitivity and 81.2% specificity was 704 fmol/mL, as identified by receiver operating characteristic (ROC) analysis.

Conclusions: Plasma apelin not only was markedly higher in patients with cardiac cachexia but it also reflected catabolic/anabolic imbalance measured by the cortisol/DHEAS ratio.

1132 Attenuated functional capacity of tissue-derived c-kit+ progenitor cells in the skeletal muscle of patients with chronic heart failure



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Background: Patients (Pt) with chronic heart failure (CHF) are limited in their exercise capacity due to skeletal muscle (SM) alterations. However, the SM harbours a population of tissue-derived progenitor cells, which are believed to contribute to SM regeneration. It is currently unknown, whether the number and differentiation of these progenitor cells in the SM is attenuated in Pt with CHF.

Methods: c-kit+ cells, which were negative for the hematopoietic lineage markers CD45/B220, CD3, Ter119, CD11b, Gr1, were isolated from the SM using FACS sorting. The differentiation potential of c-kit+ cells was assessed in cell culture and in vivo. Additionally, the number of c-kit+ progenitor cells was determined by immunohistochemistry in SM biopsies of fifty Pt with CHF (LVEF 23±2%) and sixteen age-matched healthy subjects (HS). Myocyte-lineage and endothelial-lineage commitment of c-kit+ cells was recognized by co-expression of myocyte enhancer factor 2 (MEF2) or van Willebrand factor, respectively, cycling c-kit+ cells were identified by co-expression of Ki67 applying immunohistochemistry. Protein expression of insulin-like growth factor I (IGF-I), which is known to promote cell proliferation and survival, was determined in the SM by Western Blot.

Results: c-kit+/lineage- cells were able to adopt the phenotype of myocytes and endothelial cells in vitro and in vivo. In CHF, the number of c-kit+ cells in the SM (24±2 cells/cm² SM area) was approximately 70% lower as compared to healthy individuals (81±14 cells/cm², p<0.05 vs. CHF). This was partially the result of an impaired proliferation of c-kit+ cells (c-kit/Ki67+ cells, CHF: 4±1 cells/cm², HS: 18±6 cells/cm², p<0.05), most likely due to a blunted expression of IGF in the SM in CHF (CHF: 0.66±0.10, HS: 1.52±0.15 arb. units, p<0.05). This notion is supported by the close correlation between IGF-I expression and number of c-kit+ cells in the SM (r=0.78, p<0.05). The amount of c-kit/MEF2+ myocyte precursor cells and of c-kit/VWF+ endothelial precursor cells was found to be reduced by 63% and 56% in CHF (p<0.05 vs. HS), respectively, which is suggestive of an attenuated cell differentiation.

Conclusion: The results of the study suggest that in patients with advanced CHF the capacity of SM regeneration seems to be blunted. This might be - at least partially - due to a reduced number and function of tissue-derived c-kit+ cells.

1133 The administration of human ghrelin attenuates development of cardiac cachexia in rats with heart failure



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Background: Recently, ghrelin was observed to have potential in the treatment of severe chronic heart failure (CHF) and cardiac cachexia (CC). There have been, however, no randomized, double-blinded, placebo-controlled studies for the administration of ghrelin. We designed 2 studies to clarify the effectiveness of human ghrelin, to determine if it improves left ventricular (LV) dysfunction and attenuates CC in a rat CHF model. Investigators performing assessments were blinded to treatment assignment.

Methods: Study-1 administrated either 50 or 500nmol/kg/day ghrelin by subcutaneous pump infusion, and Study-2 administrated either 50 or 100nmol/kg/day ghrelin by subcutaneous injection (application: 3 times daily at 0800, 1200 and 1600 h). In each study, ligation of the left anterior descending coronary artery or sham operation was performed in male SD rats (weight; 215-235 g). Treatment with furosemide was started on day 14 after surgery. Four weeks after surgery, 49 animals in Study-1 and 57 animals in Study-2 were randomized into 3 groups, and either ghrelin (2 doses) or saline were administered for 4 weeks. Body weight and body composition, as measured by NMR-scanning (EchoMRI-700 for rats, Echo Medical System, Houston, USA), and cardiac function, as measured by echocardiography (Vevo 770; VisualSonics, Toronto, Canada), were investigated 1 day before randomization and again at study termination.

Results: 1) In Study-1, CHF rats treated with 500 nmol/kg/day ghrelin showed a significant increase in body weight (+25%, P<0.001). Lean mass (+16%, p<0.01) and fat mass (+17%, p=0.001) both increased significantly with high-dose ghrelin. No significant difference was observed in LV ejection fraction (EF) between CHF rats treated with or without ghrelin, regardless of the dose (LVEF 50nmole: 31.1±2.3%, 500nmole: 29.5±1.9%; Placebo: 33.8±1.3%, p>0.2). 2) In Study-2, CHF rats treated with both low- and high-dose ghrelin showed a remarkable increase in body weight (both +18%, p<0.001), lean mass (both +25%, p<0.001) and fat mass (50nmole: +43%, p<0.05; 100nmole: +45%, p<0.01) vs placebo. Again, in this study human ghrelin did not improve LVEF (50nmole: 28.4±2.0%, 100nmole: 28.9±1.7%, Placebo: 29.9±1.9%, p>0.2). 3) In neither study, did ghrelin change LV end-diastolic diameter (all p>0.2).

Conclusion: In two separate studies using our rat model of CHF, with 2 doses and 2 different drug administration routes, human ghrelin had a beneficial effect on body weight and body composition as compared with placebo. In these same studies, LVEF and cardiac dimensions did not improve.

1134 Effects of human ghrelin and the peptide analogues, BIM-28131 and BIM-28125, on body weight, food intake and body composition in a rat model of heart failure



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A serious complication of chronic heart failure is cardiac cachexia (CC) with a prevalence of 10-15% in CHF patients. The complex metabolic changes entail a catabolic/anabolic imbalance which leads to body wasting and poor prognosis. There is currently no therapeutic option for CC. Ghrelin, the natural ligand for the growth hormone secretagogue (GHS) receptor, has been demonstrated to induce food intake and is suggested to enhance cardiac function.

Methods: Human ghrelin and two peptide analogues, BIM-28125 and BIM-28131, were tested at 50 or 500nmol/kg/d versus placebo in a CHF-model induced by acute myocardial infarction (AMI). SD rats (weight at surgery 215-235g) received diuretics from day 14 after surgery. Treatment with ghrelin compounds or placebo was started on day 28 for 4 weeks using osmotic pumps. Body weight, body composition (by NMR-scanning) and cardiac function (echocardiography) were assessed on day 55/56 (end of study). Food intake was monitored until day 49.

Results: Animals with AMI gained less weight compared with sham-operated rats (311g vs 324g, p=0.013), while food intake was not different until the start of therapy (average: 6% of body weight/day). Animals treated with BIM-28131 at 50nmol/kg/d or with all three compounds at 500nmol/kg/d displayed increased weight gain as compared with placebo and sham-operated animals (all p<0.001). Food intake was increased only in rats treated with BIM-28131 at either 500nmol/kg/d (p<0.001 vs sham/placebo) or 50nmol/kg/d (p=0.023), and in those treated with BIM-28125 at 500nmol/kg/d (p<0.03 vs sham/placebo). Before treatment, body composition was similar in all groups (average: 36g fat, 248g lean). Placebo-treated rats gained no fat, but only lean body mass. The ghrelin compounds induced both fat and lean mass gain, but to a different extent. The ratio of fat to lean gain was 0.90±0.07 for BIM-28131 at 50nmol/kg/d, while at 500nmol/kg/d it was 0.76±0.07 for BIM-28131, 0.68±0.12 for BIM-28125, and 0.48±0.05 for native ghrelin (ANOVA: p=0.0001). BIM-28131 (50nmol/kg/d) showed a trend to improve left ventricular ejection fraction (39.6±3.9%, placebo 32.0±2.7%, p=0.12).

Conclusion: Ghrelin and the tested analogues improved both body weight gain and body composition, and induced increased food intake. A trend for improved cardiac function was observed only with BIM-28131. Human ghrelin mainly induced increased fat mass, whereas low dose BIM-28131 induced a balanced gain of both fat and lean mass. Taken together, the ghrelin analogue, BIM-28131, may represent a promising therapeutic option for cardiac cachexia.

1135 Poor nutritional status predicts the prognosis of patients with chronic heart failure



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Background: Nutritional abnormalities are common among patients with chronic heart failure (CHF). However, clinical implication to evaluate the nutritional status in such patients is still unknown. The aims of the study were to investigate serum albumin level (ALB), total lymphocyte count (TLC), and body mass index (BMI) and to clarify the prognostic power of these nutrition-related markers in patients with CHF.

Methods: We prospectively enrolled 280 stable patients with stage-C/D CHF since February 2000 and the follow-up surveillance was performed annually. Kaplan-Meier analysis and multivariate Cox regression analyses were conducted to evaluate the association between the mortality and the nutrition-related markers. Covariables used in the multivariate model included ALB, TLC, BMI, hemoglobin concentration, left ventricular ejection fraction, etiology of CHF, serum creatinine level, and age at the entry.

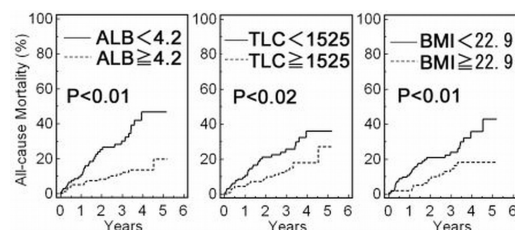


Fig. 1. Kaplan-Meier analysis.

Results: The mean age of the study population was 61.2 ± 14.9 years and the mean follow-up period was 2.4 ± 1.5 years. The mean value for ALB, TLC, and BMI was 4.1 ± 0.5 g/dl, 1517.5 ± 638.2 μ L, and 22.9 ± 4.3 , respectively. Kaplan-Meier analysis showed that the incidences of all-cause mortality in patients with lower ALB, lower TLC, or lower BMI were all significantly higher as shown in the Figure. Multivariate analysis revealed that higher TLC was an independent significant predictor of freedom from cardiac-cause death (HR 0.999, $P=0.016$) and higher ALB was significantly associated with increased survival (HR 0.563, $P=0.03$).

Conclusions: The evaluation of nutritional status may be a useful and inexpensive tool in predicting the mortality of patients with CHF. Further research is necessary to evaluate the importance of nutritional improvement in such patients.

CARDIOVASCULAR DISEASES AND AGEING

1145 Percutaneous coronary intervention with drug eluting stent in octogenarians with non-ST-elevation myocardial infarction: clinical presentation and outcomes

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Background: Drug eluting stents (DES) have recently proven to reduce restenosis rate as compared to bare metal stents for variety subset of patients and lesions. However, the safety and effectiveness of DES in non-ST-elevation myocardial infarction (NSTEMI) for the elderly have not been established. We sought to investigate, clinical outcomes of octogenarians (patients > 80 years of age) with NSTEMI undergoing DES implantation.

Methods and Results: A cohort of 1250 patients who presented with NSTEMI and underwent PCI with DES was analyzed. Of these 133 patients were octogenarians. Their in-hospital, 30-days and 6-months clinical outcomes was compared with 1117 patients < 80 years of age who underwent DES implantation for NSTEMI. Baseline characteristics revealed higher percentages of female gender ($p<0.001$), chronic renal failure ($p<0.001$) and acute heart failure ($p=0.03$) in the octogenarians group. Patients < 80 years of age had a higher prevalence of positive family history ($p<0.001$), hyperlipidemia ($p<0.001$), smoking history and obesity ($p<0.001$, respectively). In hospital outcomes were comparable for death, MI and repeat revascularization but octogenarians had more acute renal insufficiency ($p<0.001$). Outcomes at 6 months showed a comparable restenosis rate between groups and a significantly higher mortality rate in octogenarians (Table). Multivariate analysis revealed age ($p=0.01$), cardiogenic shock ($p=0.008$) and creatinine clearance ($p<0.001$) to be independent predictors of mortality.

	Patients < 80 years of age (n=1117)	Octogenarians (n=133)	P
Death at 6-months, %	3	14	<0.001
Q wave MI at 6-months, %	1	7	0.004
TLR at 6-months, %	2.4	3	0.67
TLR-MACE at 6-months, %	6	18	<0.001
Late thrombosis, %	0.3	0	—

Conclusions: DES implantation in octogenarians presenting with NSTEMI is clinically safe and associated with a low rate of in-hospital events and target vessel revascularizations at 6-months. Octogenarians, however, do have a higher mortality risk due to their multiple co-morbidities unrelated to repeat revascularization which requires special care.

1146 Mortality after acute myocardial infarction is still particularly high among the elderly. The HELIOS study group

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Background: Early outcome after acute myocardial infarction (AMI) has been considered to be adversely influenced by age, largely due to underused life-saving therapies and comorbidities.

Methods: Data from 1266 patients (77% males, 19.8% over 80 years old) hospitalized for AMI, who have been enrolled in the HELIOS Infarction Observational Study, were analyzed. The HELIOS study was organized by the Hellenic Cardiological Society to investigate the incidence and clinical course of AMI using stratified random sampling in a countrywide basis. Availability of a catheterization laboratory, geographical location and proportion of urban population were taken into consideration in the selection of the 30 centers that participated in this study.

Results: The octogenarian patients presented markedly higher in-hospital and 30-day mortality rates in univariate analysis (Table). In multivariate analysis adjusted for gender, diabetes mellitus, smoking, body mass index, thrombolysis and/or primary PCI, and advanced Killip class (III-IV), age > 80 years was sig-

nificantly and independently associated with in-hospital (RR=5.29, 95%CI=2.97-9.43, $P<0.001$) and 30-day mortality (RR=3.70, 95%CI=2.26-6.06, $P<0.001$). The abovementioned associations remained significant when treatment with aspirin, clopidogrel, statins, ACE-inhibitors and beta-blockers were also included in the model.

	Age ≥ 80 yrs (n=251)	Age < 80 yrs (n=1015)	P value
Mean age (yrs)	85 ± 5	63 ± 11	<0.001
Male gender (%)	57	82	<0.001
Diabetes (%)	37	30	0.023
Thrombolysis/Primary PCI (%)	15	44	<0.001
Killip III-IV (%)	14	7	0.001
In-hospital mortality (%)	18.8	3.4	<0.001
30-day mortality (%)	24.9	6.1	<0.001

Baseline characteristics and unadjusted mortality rates in relation to age

Conclusion: Although common life-saving therapies are underused among the elderly, and their use should be further encouraged, this fact does not fully explain their unfavorable outcome after AMI. Given the demographic trends throughout Europe, these results call for further investigation aiming to improve assessment and treatment of elderly patients with AMI.

1147 Effectiveness and safety in daily clinical practice of oral anticoagulation in octogenarian patients with nonvalvular atrial fibrillation

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Introduction and objectives: Randomised clinical trials have proven oral anticoagulation to lessen thromboembolic complication rate in nonvalvular atrial fibrillation (NVAF). However, little is known about effectiveness and safety of this treatment in octogenarian patients in daily clinical practice. Our work tries to study if a prospective protocol of oral anticoagulation in NVAF, based in ACC/AHA/ESC Guidelines is effective and safe in these patients. Patients and method: Since February, 1st 2000 to January 31st 2003, we have included in the protocol all patients aged 80 years or more with permanent NVAF attended in two general outpatient cardiology clinics, and they have been prospectively followed, analysing major events (death, stroke, transient ischemic attack, peripheral embolism or severe haemorrhage) by group of treatment.

Results: Of 152 patients included in the study, 78 were anticoagulated (51% of the whole population). Anticoagulated patients were younger than unanticoagulated patients (82 ± 2 versus 84 ± 3 years, $p<0.001$), presented a higher frequency of coronary heart disease (15% versus 3%, $p=0.007$) and a greater absolute number of cardioembolic risk factors (2.8 ± 1.2 versus 2.2 ± 1.0 , $p=0.001$). Frequencies of high blood pressure (74% versus 64%, $p=0.15$), diabetes (26% versus 18%, $p=0.23$), previous embolism (19% versus 10%, $p=0.09$), heart failure (21% versus 18%, $p=0.8$) and lone NVAF (without hypertension nor structural heart disease, 22% versus 34%, $p=0.1$) showed no statistically significant differences. Unanticoagulated patients received antiplatelet treatment in 93% of cases (94% of them, aspirin). After a follow-up of 21 ± 16 months (with follow-up data of 95.4% of patients), the probabilities of embolic events (0% versus 12.28%, $p=0.0019$) and total mortality (6.77% versus 8.51%, $p=0.049$) at 21 months (estimated by Kaplan-Meier method) were lower in anticoagulated patients than in the rest of the series, without significant differences in the probability of severe bleeding (4.59% versus 3.86%, $p=0.9$).

Conclusion: Oral anticoagulation in octogenarian patients with nonvalvular atrial fibrillation according with ACC/AHA/ESC Guidelines is effective and safe in daily clinical practice.

1148 Differences between younger and elderly patients with acute coronary syndromes

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Background: Differences in patients' age haven't been studied in detail to allow conclusions for practical guidelines pertaining to age for treatment of acute coronary syndromes (ACS).

Methods: From January 1997 to December 2005, the AMIS Plus data base included 19,461 patients with ACS admitted to 68 Swiss hospitals. We compared characteristics and outcome of patients below 50 years ($n=2848$) with those above 80 years ($n=2450$).

Results: Baseline characteristics and in-hospital outcome are presented in table 1.

Conclusion: Younger patients were mainly overweight, had dyslipidemia and were current smokers while elderly patients were dominantly hypertensive and diabetics. Elderly patients presented more frequently with dyspnea and were ad-

Table 1

N=19461	<50y (n=2848)	>80y (n=2450)	p-value
Age (years) mean±SD	44±5	85±3	0.001
Male gender (%)	86.7	52.3	0.001
STEMI/non-STEMI (%)	67/33	58/42	0.001
Delay in minutes (median)	205	310	0.020
Chest pain at admission (%)	86.4	74.7	0.001
Dyspnea at admission (%)	16.0	44.1	0.001
Killip class III&IV	2.5	15.5	0.001
Past CAD (%)	22.7	51.2	0.001
Hypertension (%)	31.8	68.1	0.001
Dyslipidemia (%)	62.3	39.6	0.001
Diabetes (%)	9.4	24.6	0.001
Current smokers (%)	72.5	10.5	0.001
Obesity (BMI > 30) (%)	20.5	9.6	0.001
Thrombolysis (%)	23.3	8.7	0.001
primary PCR (%)	50.8	13.6	0.001
Hospital stay (days) median	6	11	0.010
Re-infarction (%)	1.5	6.0	0.001
Stroke (%)	0.4	1.8	0.001
In-hospital mortality (%)	2.2	21.4	0.001

mitted with larger delays than younger patients which resulted in a less frequent use of reperfusion therapies and an increased risk of adverse events and in-hospital mortality.

1149 Elderly patients undergoing major non-cardiac surgery: perioperative and long-term risk reduction



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Background: Elderly patients undergoing major vascular surgery often experience adverse postoperative complications. We assessed whether age is independently associated with hospital and long-term mortality and whether cardiac medication can reduce the risk of mortality in elderly patients undergoing major vascular surgery.

Methods: In this observational cohort study, 1693 patients aged >65 years undergoing major non-cardiac vascular surgery were preoperatively screened for cardiac risk factors according to the Cardiac Risk Index. Chronic perioperative cardiac medication was also recorded. During a median follow-up of 8.2 years (IQ range: 5.1-10.9), mortality was noted.

Results: Mean age was 73 ± 5 years and 76% was male. Hospital and long-term mortality occurred in 137 (8.1%) and 482 (29%) patients respectively. In multivariate analysis, age was independently associated with increased hospital and long-term mortality (per year increase: OR 1.04, 95% CI: 1.01-1.08, p<0.001, HR: 1.04, 95% CI: 1.01-1.05, p<0.001, respectively). Perioperative use of aspirin, β-blockers and statins was significantly associated with a 47%, 68%, and 65% reduced risk of hospital mortality, respectively. In addition, aspirin, angiotensin-converting enzyme (ACE) inhibitors, β-blockers and statins were associated with a 35%, 26%, 39%, and 35% reduced risk of long-term mortality, respectively (Table). Tests for heterogeneity revealed a gradient decrease of mortality risk in patients from low to high age who were using statins (p=0.03).

Cardiac medication use and mortality

Multivariate analysis	Hospital mortality		Long-term mortality	
	OR (95%CI)	P-value	HR (95%CI)	P-value
Aspirin use	0.53 (0.34-0.83)	0.006	0.65 (0.53-0.81)	<0.001
β-Blocker use	0.32 (0.19-0.54)	<0.001	0.61 (0.48-0.76)	<0.001
Statin use	0.35 (0.18-0.68)	<0.001	0.65 (0.49-0.87)	0.004
ACE inhibitors use	0.69 (0.44-1.09)	0.1	0.74 (0.59-0.92)	0.008
Ca-channel blocker	0.92 (0.60-1.40)	0.7	0.80 (0.61-1.05)	0.1

Conclusion: Increasing age is a significant and independent predictor of hospital and long-term mortality in elderly patients undergoing major vascular surgery. In these patients, aspirin, ACE inhibitors, β-blockers and statins may reduce hospital and long-term mortality risk. Especially the very elderly may benefit from statin therapy.

DIABETES AND CARDIOVASCULAR OUTCOMES

1151 Gender differences in long term mortality of ischemic heart disease associated with diabetes. Results from the HUNT study



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Purpose: To assess long term mortality of ischemic heart disease (IHD) in dia-

betic compared to non-diabetic individuals and in diabetic women compared to diabetic men.

Methods: In 1984-86 a large health survey was conducted in the county of Nord-Trøndelag, Norway (HUNT 1). All inhabitants aged >20 years were invited and 74 977 (88.8%) participated making HUNT one of the largest health surveys ever performed. Persons with known diabetes were identified by self-reporting. 18 years follow-up mortality of IHD was assessed by linking HUNT1 data to the Cause of Death Registry at Statistics Norway up to 2004. Deaths caused by IHD were defined by ICD codes. Relative risk (RR) for IHD mortality in diabetic compared to non-diabetic individuals and in diabetic women compared to diabetic men were compared using Cox regression analysis.

Results: At baseline, 932 (prevalence 2.5%) diabetic men and 1168 (3.1%) diabetic women were identified with a mean age of 66.2±12.6 and 69.8 ± 14.2 years. During 18 years of follow-up, 707 (75.9%) diabetic men and 914 (78.3%) diabetic women died. IHD caused 25.6% and 22.9% of deaths in men and women, respectively. Age adjusted RR for death by IHD in diabetic individuals was 2.09 (CI 1.8-2.4) for men and 3.02 (CI 2.65-3.44) for women. When also adjusting for other cardiovascular risk factors, RR did not change in diabetic men while RR for IHD death was reduced to 2.73 (CI 2.34-3.2) in diabetic women.

Conclusions: Diabetic men have a twofold risk of fatal IHD compared to non-diabetic men. In diabetic women the RR for death from IHD is 50% higher than in diabetic men. More adverse cardiovascular risk profiles could partly explain the excess IHD mortality in diabetic women.

1152 Long-term morbidity and mortality after hospitalization for unstable coronary disease in patients with and without diabetes- Data from the Swedish Hospital Discharge Registry 1987-1999



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Aims: Patients with diabetes mellitus (DM) and acute myocardial infarction (AMI) have an adverse prognosis. The aim of the present study was to assess long-term risk of morbidity and mortality by DM status in an unselected cohort of patients with AMI or unstable angina.

Design and Methods: Data from 6676 consecutive patients including 1058 (15.8%) with previously diagnosed DM with the diagnosis of unstable angina or AMI admitted to the coronary unit at a University Hospital, during 1987-1999. The primary endpoint was the time to the first occurrence of a composite of all-cause mortality, or hospitalization for AMI, stroke, or congestive heart failure (CHF).

Results: Patients with DM were older, more often female, with adverse cardiovascular risk profiles. After adjustment for age and sex diabetes remained an independent predictor of five-year mortality (HR= 1.79; 95% CI 1.63-1.96). DM was an independent predictor of 5 years composite of all-cause mortality, or hospitalization for AMI, stroke or CHF, following ACS events. The HR was significant after adjustment for age and sex (HR 1.53; 95% CI 1.40-1.65). The 5-year event rate for CHF hospitalization was 43% among patients with DM compared with 29% among patients without DM. The rate of an AMI hospitalization among those with DM was 48% vs. 34%. Stroke was more frequent in patients with diabetes, 16.8% vs. 9.7%. After adjustment for age and sex, DM remained independently associated with a higher risk of hospitalization for CHF (HR 1.64; 95% CI 1.48-1.82), AMI (HR 1.55; 95% CI 1.41-1.71) and stroke (HR 1.88; 95% CI 1.61-2.20). The mean duration of all-cause hospital stays, from discharge through the 5-year follow-up period, as 26 days for patients with DM compared with 15 days for non-diabetic patients, adjusted for follow-up time. The average number of all-cause readmissions during follow-up was 6 among patients with DM versus 4 among non-diabetic patients. Thus, although patients with DM comprised only 15.8% of the cohort, they accounted for more than 22% of all-cause readmissions and 21% of all hospital days during 5-year follow-up

Conclusion: Diabetes is an independent risk factor for long-term mortality but also for long-term morbidity after hospitalization for an ACS event. The present study shows an independent 1.5 fold increased risk having an incident AMI, CHF, stroke or death within 5 years in patients with diabetes and unstable coronary disease.

1153 Risk factors related to development of diabetes or fasting hyperglycemia in a north indian industrial male population

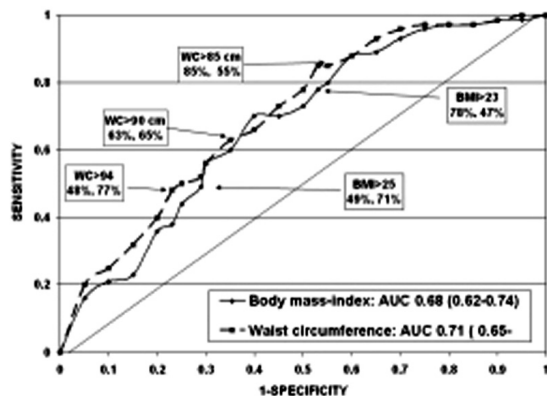


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Background: Rapid epidemiological and lifestyle changes have been observed in association with high burden of diabetes in urban India. However data on the determinants for development of diabetes in this population are not available. This study aimed to investigate the clinical determinants of development of diabetes among men in a North Indian industry.

Methods: Two cross-sectional surveys were carried out, with similar methodology, in 1995-98 (n=2458) and 2002-03 (n=2800) among all the employees (age 20-59 years) of an industry, a large majority of which were men (89.5% and 92.8% respectively). Men with no diabetes at baseline, who participated in both the surveys (N=942), constituted the sample population for this study. Development of diabetes was defined using history and fasting glucose levels ≥ 7 mmol/l.

Results: The mean age of the participants was 40 ± 2 (range 23-54) years. Diabetes developed in 8% of the study population. Individuals who developed diabetes had significantly higher age, blood pressure, body-mass index, waist circumference, fasting and post-prandial glucose, post-prandial insulin, and fasting triglycerides levels at baseline. On multi-variable regression analysis, only impaired glucose tolerance (OR 3.8, 95% CI 2.1-6.8) and waist circumference (β -coefficient 0.08, OR 1.09, 95% CI 1.02-1.16) predicted development of diabetes. Significant increase in risk was observed from a waist circumference of 84.4 cm onwards. Presence of metabolic syndrome, as defined by modified NCEP ATP III and WHO criteria, increased the odds (95% CI) of developing diabetes by 2.2 (1.3-3.6) and 4.5 (2.7-7.4) times respectively.



ROC for WC and BMI for development of DM

Conclusion: Impaired glucose tolerance, high waist circumference, and metabolic syndrome are powerful predictors of future diabetes among urban Indian men.

1154 Screening for cardiovascular risk in diabetes is warranted regardless of age and gender: a population based study of 3.3 million Danes



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Background: It is unclear when cardiovascular (CV) risk in diabetes is increased to a level, where screening for CV disease is indicated. To identify high-risk patients among diabetic subjects, we studied an unselected population of 3.3 million Danes.

Methods: Residents in Denmark, ≥ 30 years of age, were followed for 5 years (1997-2001) by individual-level-linkage of nationwide administrative registers. Diabetic subjects, receiving antidiabetic medication (tablets or insulin), with and without prior myocardial infarction (MI) (DM-PreMI and DM-noPreMI) were compared to non-diabetics, with and without prior MI (noDM-PreMI and noDM-noPreMI). CV death according to age and gender was expressed as mortality rates per 1000 personyears. Rate ratios (RR) between groups were analysed using Poisson regression adjusted for age and gender.

Results: 3,274,479 subjects were included, 71,801 (2.2%) had diabetes, 73,156

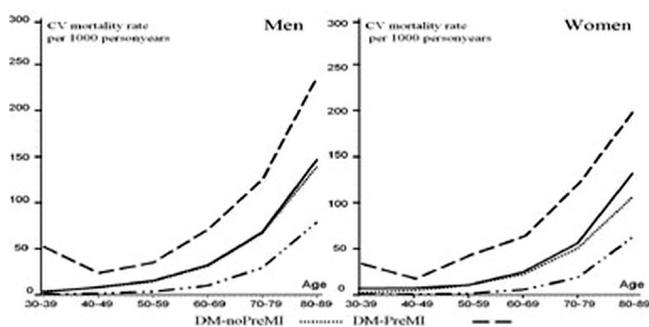


Fig. 1. Cardiovascular death.

(2.3%) and 6,419 (8.9%) had prior MI in non-diabetics and diabetics, respectively. CV death occurred in 139,985 (4.2%) of the total and 12,206 (17.0%) of the diabetic population. Diabetic subjects, irrespective of age and gender were at risk of CV death similarly to non-diabetics with a previous MI. Relative differences between groups were [RR=4.92, (95%CI 4.72-5.13)], [2.52, (2.48-2.57)] and [2.46, (2.41-2.51)] for DM-PreMI, noDM-PreMI, DM-noPreMI respectively compared to noDM-noPreMI. The rate ratios for noDM-PreMI and DM-noPreMI were similar (P=0.07) (Fig. 1).

Conclusion: Diabetic subjects regardless of age and gender, receiving antidiabetic medication are at risk of CV death similar to subjects with established CV disease. Therefore, extensive screening and treatment for cardiovascular risk factors should be implemented in all diabetic patients receiving medical antidiabetic treatment.

1155 Fasting glucose as a predictor of cardiovascular events in high-risk patients



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Background: Although patients with established diabetes mellitus (DM) and those with impaired glucose tolerance (ie fasting plasma glucose (FPG) levels < 7.0 mmol/L) are at increased cardiovascular (CV) risk, the extent to which glucose levels alone are aetiologically related or just a marker of CV risk is unknown.

Purpose: To evaluate the associations of FPG levels and CV outcomes in high-risk patients enrolled in a large scale clinical trial.

Methods and patients: Baseline FPG was assessed in 31 546 high-risk subjects with coronary, peripheral, cerebrovascular disease or with DM with end-organ damage participating in two ongoing parallel trials evaluating the effects of telmisartan, ramipril or the combination (ONTARGET [n=25 620]) and the effects of telmisartan vs placebo in ACE-intolerant patients (TRANSCEND [n=5926]). Primary outcome was the composite of CV death, non-fatal MI, stroke or hospitalization for congestive heart failure (CHF). An interim analysis, blinded for randomized treatment was performed comparing baseline FPG to the adjusted CV event rate at a mean follow-up of 886 days.

Results: Of all subjects (mean 67 years; 69% men), 11 708 patients (37%) had known DM and 1006 (3.2%) patients were diagnosed with DM at baseline. During follow-up, there was 2882 primary events (1067 CV deaths, 926 MI, 823 strokes and 668 hospitalizations for CHF). Evaluating glucose as a continuous variable, a 1 mmol/L rise in FPG was related to an increased risk of the primary outcome (RR=1.04; 95% CI 1.03-1.06; $p < 0.0001$), CV death (RR=1.05; 95% CI 1.02-1.07; $p < 0.001$), MI (RR=1.03; 95% CI 1.00-1.06; $p = 0.05$), stroke (RR=1.03; 95% CI 1.00-1.06; $p = 0.03$) and hospitalization for CHF (RR=1.05; 95% CI 1.08-1.12; $p < 0.0001$), also after multivariate adjustments.

Conclusion: Fasting plasma glucose is an independent predictor of CV death, MI, stroke and hospitalization for CHF, even after adjustments for multiple risk factors, including diabetes, with the strongest relationship to CHF. This suggests that glucose is more than a marker of diabetes and may play a causal role for the development of CV events.

1156 Newly diagnosed diabetes reduces long-term survival in patients presenting to intensive cardiac care unit



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Abnormal glucose metabolism is frequent in patients with acute coronary syndromes (ACS) and associated with impaired survival. Whether this applies to all comers presenting to intensive cardiac care unit (ICCU) remains to be established. Similarly, the impact of in-hospital newly diagnosed diabetes (NDD) on long-term survival in this unselected population is unknown.

Our aim was to evaluate how abnormal glucose metabolism impacts 6-month mortality of all comers admitted to an ICCU.

Fasting plasma glucose (g/L) was serially measured together with HbA1c (%) in 991 consecutive patients. Patients were categorized as known diabetes (KD) if on prior antidiabetic drugs, impaired fasting glucose (IFG) if $1.1\text{g/L} \leq \text{FPG} \leq 1.26\text{g/L}$, newly diagnosed diabetic (NDD) if admission glycaemia was $> 2\text{g/L}$ or $\text{FPG} > 1.26\text{g/L}$ on 2 measurements with $\text{HbA1c} \geq 6\%$. All cause mortality was assessed at 6-month follow-up.

51% of patients had abnormal glucose metabolism including IFG, KD and NDD in 16.6%, 12.7% and 22.0% of patients, respectively. It was significantly more frequent in the elderly (> 75) as compared to younger patients (60.7% vs 48.2%, $p = 0.004$, respectively). Acute coronary syndrome was the cause of admission in 63% of patients. The death rate at 6-month FU was 8.7% in the whole population. Mortality of patients with NDD was 4-fold higher (20.4% vs 5.8%, $p < 0.0001$) and 2-fold higher (20.4% vs 10.6%, $p < 0.0001$) than that of patients without abnormal glucose metabolism and patients with KD, respectively. IFG and KD displayed a

similar death rate (11.3% vs 10.6%, $p=ns$). In unadjusted analyses, high FPG and hypoglycaemia (FPG < 0.5g/L) were both significantly associated with increased 6-month all-cause mortality. After multivariable analysis, FPG > 1.1g/L (OR, 2.04; 95% CI, 1.21-3.45, $p=0.007$) and NDD (OR, 2.26; 95% CI, 1.13-4.52, $p=0.02$) were strong independent predictors of death at 6-month FU regardless of the discharge diagnosis.

Abnormal glucose metabolism is associated with impaired survival in all comers presenting to the ICCU irrespective of the admission diagnosis. Newly diagnosed diabetes is a particular detrimental condition that needs to be systematically identified.

HOW TO OPTIMIZE PROGNOSTIC ASSESSMENT IN HEART FAILURE?

1186 Presence of oscillatory ventilation during exercise independently worsens prognosis in patients with stable chronic heart failure



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Background: Breathing disorders recorded at rest are a common and ominous phenomenon in chronic heart failure (CHF). In contrast, the prevalence, clinical and prognostic significance of exertional oscillatory ventilation (EOV) has not been comprehensively studied in patients (pts) with CHF.

Methods: We examined 218 stable systolic CHF pts (age: 59 ± 11 years, 87% male, LVEF: $31 \pm 8\%$, NYHA class [I/II/III/IV]: 8/49/35/8 [%], ischaemic aetiology: 72%). All patients underwent a symptom-limited maximal cardiopulmonary exercise test (CPX) on treadmill (RER > 1.0), with the measurement of exercise time (Ex-T), peak oxygen consumption (peak $\dot{V}O_2$, mL/min/kg), ventilatory response to exercise (VE-VCO₂ slope), and the analysis of EOV. EOV was prospectively defined as the presence of ≥ 3 evident cyclic fluctuations in minute ventilation (VE) during exercise with an amplitude (the ratio of the difference between the peak and nadir in VE divided by its mean) of $\geq 15\%$ (based on literature data).

Results: EOV occurred in 161 (74%) pts with CHF. Pts with EOV, as compared to those without EOV, were mostly men (90 vs. 79%, $p<0.05$), and demonstrated only slightly higher NYHA class (2.6 ± 0.7 vs. 2.3 ± 0.7 , $p=0.05$), increased left ventricular end diastolic diameter (67 ± 7 vs. 64 ± 7 mm, $p<0.001$), excessive VE at rest (13.6 ± 3.4 vs. 11.7 ± 2.9 L/min, $p<0.0001$) and higher VE-VCO₂ slope (36 ± 12 vs. 30 ± 12 , $p<0.0001$). Between these 2 groups, there were no differences in age, CHF aetiology, Ex-T and peak $\dot{V}O_2$ (all $p>0.2$). During follow-up (mean: 1178 ± 605 days, median: 1229 days, >3 years in all survivors), 89 (41%) pts died. In univariate models, the following variables predicted survival: age, NYHA class, LVEF, peak $\dot{V}O_2$, Ex-T, VE-VCO₂, and the presence of EOV (all $p<0.01$), but not CHF aetiology, sex (both $p>0.2$). In a multivariate forward stepwise model, the presence of EOV (HR: 1.67, 95%CI: 1.03-2.70, $p<0.05$) remained an independent predictor of poor outcome, as well as age ($p<0.05$), LVEF ($p<0.05$), peak $\dot{V}O_2$ ($p<0.05$) and VE-VCO₂ slope ($p<0.001$). The 3-year survival rate was 58% (95%CI: 49-67%) vs. 80% (95%CI: 72-88%) for CHF patients with vs. without EOV ($p<0.001$).

Conclusions: Oscillatory ventilation during exercise is prevalent in more than 70% of patients with stable CHF. Its presence is not directly related to either disease severity or exercise capacity, but is accompanied by augmented ventilation both at rest and in response to exercise. The presence of EOV identifies CHF patients of high long-term mortality, independently of clinical variables and other parameters measured during CPX.

1187 The prognostic role of anemia in acute heart failure. Data from the Italian survey on acute heart failure



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Background: Recent clinical studies evaluated the impact of the anemic state on symptoms and prognosis in patients (pts) with chronic heart failure. The prognostic role of anemia in acute heart failure (AHF) is not yet established.

Aim: Evaluate the power of anemia as marker of severity and outcome in AHF.

Methods: We analyzed a cohort of 2807 pts with AHF referred to 206 Cardiology Units in a nationwide prospective observational study. To the purpose of the reported analysis, pts with history of neoplasia and/or gastro-enteric disease were excluded. The study population was of 2318 pts with mean age 72.4 ± 11.2 years, 60% were male, anemia (Hb < 12 gr/dl) was found in 31%. In 46% of pts AHF was the first evidence of disease, the underlying etiology was ischemic in 46% of pts. At hospital admission 12% of pts had creatinine > 2.5 mg/dl and 34% had creatinine > 1.5 mg/dl and < 2.5 mg/dl.

Results: Anemic pts (719 pts; =31% of study population), were older ($p=0.0002$)

than non anemic pts, with a prevalence of females ($p<0.0001$). In the anemic group more cases of vascular disease ($p<0.0001$), diabetes ($p=0.002$) and chronic renal insufficiency ($p<0.001$) were found. Lower Hb was associated with an impaired hemodynamic profile ($p=0.0001$), lower sodium ($p=0.001$), higher blood creatinine and urea nitrogen (creatinine > 2.5 mg/dl; $p=0.001$). The anemic pts needed a stronger therapy ($p=0.0001$) and a longer hospitalization ($p=0.04$) to compensate clinical status. Clinical events (arrhythmia, embolism, renal acute failure, ischemic cardiovascular events) were similar in the two groups ($p=0.26$), but the in-hospital mortality was higher in the anemic group (12% vs 5%; $p<0.0001$). In multivariate analysis low Hb (< 12 gr/dl) resulted to be an independent predictor of mortality ($p=0.013$; OR 1.6 e CI 95% 1.10-2.35).

Conclusions: Anemia (Hb < 12 gr/dl) is associated with worse prognosis in pts with AHF.

1188 The impact of a restrictive filling pattern on mortality in chronic heart failure is independent of ejection fraction: results from an individual patient meta-analysis (MeRGE)

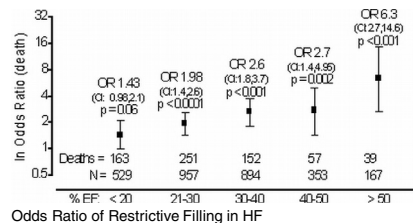


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Patients with heart failure (HF) have poor prognosis and both clinical and echo parameters are used to identify patients at especially high risk. The left ventricular (LV) restrictive filling pattern (RFP) is related to higher LV filling pressure and is a strong prognostic indicator in HF patients. However, it remains unclear whether this risk is independent or additive to LV ejection fraction (EF). Thus, we formed an international collaborative group (MeRGE) to investigate this further.

Methods: The individual patient data (demographic, clinical, echo and outcome) of 16 prospective studies (8 countries) relating RFP with outcome in HF patients was merged into a single database. The group was stratified based on EF: 50% and then each strata divided by the presence of RFP (deceleration time < 140 ms, or pattern defined). The odds ratio (OR) for all-cause death was compared between the patients with and without RFP. Kaplan Meier survival analysis and Cox proportional hazards multivariate analysis were performed to determine the combined and individual effects upon survival.

Results: 2900 patients were included: 24% female, mean age 60 ± 12 yrs, mean EF $28 \pm 10\%$ and 1142 (39%) had RFP at baseline. Average length of follow-up was 689 ± 425 days (median 599, max. 1464) and 662 patients died (22%). 329 deaths occurred in the RFP group and 189 deaths in the non-RFP group (odds ratio 2.31 (CI: 1.94, 2.76) χ^2 $p<0.0001$). RFP, EF and age were independent predictors of mortality in multivariate analysis.



Odds Ratio of Restrictive Filling in HF

Conclusion: This large collaborative individual patient meta-analysis has confirmed that RFP is an important and independent prognostic indicator in all patients with HF, and that the shorter survival associated with RFP is seen across all strata of EF, including those with preserved LV function.

1189 Outcome of patients with ischemic cardiomyopathy after coronary revascularization: does improvement in LVEF play a role?



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Background: In patients with ischemic cardiomyopathy and viable myocardium, left ventricular ejection fraction (LVEF) not always improves after coronary revascularization. Whether failure to improve in LVEF may affect prognosis is unclear and was evaluated in the present study.

Methods: Before revascularization, radionuclide ventriculography (RVN) and dobutamine stress echocardiography (DSE) were performed to assess LVEF and myocardial viability, respectively. Nine to 12 months after revascularization, LVEF improvement was assessed by RVN. According to the presence of a substantial amount of viable myocardium (major or equal 25% of the LV) and improvement in LVEF (defined as 5% or more increase in LVEF), patients were divided into 3 groups: Group 1, viable patients with LVEF improvement (n=27); Group 2, viable patients without LVEF improvement (n=15); Group 3, nonviable patients (n=48).

Cardiac events (cardiac death, myocardial infarction and hospitalization for heart failure) were evaluated during a 4 years follow-up.

Results: After revascularization, the LVEF improved from $32 \pm 9\%$ to $42 \pm 10\%$ in Group 1, but did not change significantly in Group 2 and in Group 3, $P < 0.001$ by ANOVA. LVEF improved of 5% or more in 27/42 viable patients (64%) as compared to 5/48 nonviable patients (10%, $P < 0.001$). Heart failure symptoms improved both in Groups 1 (NYHA class from 3.1 ± 0.9 to 1.7 ± 0.7) and 2 (from 3.2 ± 0.7 to 1.7 ± 0.9), but did not in Group 3 (from 2.8 ± 1.0 to 2.7 ± 0.5), $P < 0.001$ by ANOVA. During the follow-up, the cardiac event rate was low (4%) in Group 1, intermediate (21%) in Group 2 and high (33%) in Group 3 ($P = 0.01$).

Conclusion: Among patients with viable myocardium the best outcome after revascularization may be expected in those patients who improve in LVEF. Conversely, viable patients without functional improvement have a relatively high event rate. Patients without a substantial amount of viable myocardium rarely improve in LVEF and have the worst outcome.

1190 A practical, validated model for prediction of risk in chronic heart failure



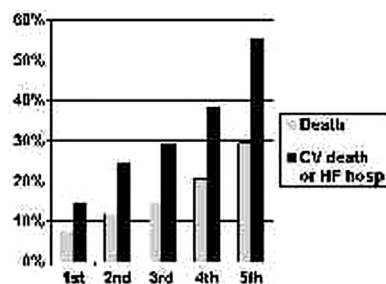
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Background: There is interest in tailoring the intensity of monitoring and treatment according to risk in patients with heart failure. Using large clinical trial databases for model development and validation, we sought to produce a simple user-friendly risk model.

Methods: We developed a simplified multivariable logistic regression model to predict i) death and ii) cardiovascular (CV) mortality or HF hospitalization using the 7 variables with the most independent prognostic information in the 7599 patients with chronic HF in CHARM (median follow-up 36 months), namely age (continuous over age 60), ejection fraction (beginning EF $< 45\%$), diabetes, prior CHF hospitalization (within 6 months or longer ago), NYHA class, cardiomegaly, and low body weight (male $< 71\text{kg}$ or female $< 59\text{kg}$). We tested this model (with minor modifications to match available data) in the COMET database of 3029 patients with chronic HF and LVEF $\leq 35\%$ with mean duration of follow-up of 58 months.

Results: The simplified models performed well in the CHARM database, with c-indices of 0.73 and excellent internal validation. When applied to the COMET database, all variables were significant independent predictors of death, and of CV death and HF hospitalization and calibration was good. When categorized into equal sized quintiles of risk, the COMET population's 2-year event rates are as shown in Figure.



2 year rates according to risk quintile

Conclusions: Based on the broad HF population in CHARM, a simple model is able to reliably estimate risk of death and CV morbidity. This model has now been validated in the low LVEF patients in the COMET database.

1191 Treatment according to current guidelines improves prognosis in patients with chronic heart failure: results of a prospective cohort study



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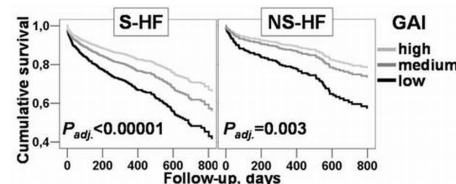
Background: Little is known about the effectiveness of guideline-adjusted pharmacotherapy in unselected chronic systolic heart failure (S-HF) patients outside therapeutic trials. It is unknown, whether symptomatic patients with preserved systolic function (NS-HF) benefit accordingly if they are treated along guidelines designed for S-HF.

Objective: To compare the effects of NYHA-adjusted pharmacological guideline

adherence on mortality in S-HF and NS-HF.

Method: Prospective cohort study; median follow-up 505d (IQR 213-680). 1054 consecutive patients with chronic HF of any etiology and severity were included and characterized in detail at baseline. Pharmacological care was assessed by calculating a global adherence indicator (GAI, 0-100%) as in the MAHLER study (Komajda, EHJ 2005). Predictors of all-cause death were sought by multivariable Cox regression. GAI entered Cox analyses in tertiles of "low adherence": GAI $\leq 50\%$; "medium": 50-79%; "high": $\geq 80-100\%$.

Results: Mean GAI in S-HF (n=699) was 72% (ACEi/ARB: 72%; Betablocker: 62%; Diuretics: 80%; Digitalis: 43%; Ald-Antagonists: 25%). Mean GAI in NS-HF (n=355) was 71% (ACEi/ARB: 70%; Betablocker: 60%; Diuretics: 79%; Digitalis: 36%; Ald-Antagonists: 17%). Mortality in GAI categories low-medium-high was 17-26-54% for S-HF and 17-23-61% for NS-HF. After adjustment for predictors of mortality risk (sex, age, NYHA, CRP, anemia, renal failure, BMI) GAI remained independently predictive for all-cause death in both S-HF and NS-HF (figure; P-values for comparison of high vs low tertile).



All-cause mortality according to GAI

Conclusions: In a 'real-world' setting, S-HF and NS-HF patients seem to receive comparable chronic HF treatment from their physicians. NYHA-adjusted therapy according to guidelines predicts prognosis irrespective of the degree of LV systolic impairment.

NOVEL PLAYERS AFFECTING CARDIAC HYPERTROPHY AND PERFORMANCE

1192 Smad3 deficiency restores cardiac function after myocardial infarction



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Background: TGF β s transduce their signal via a specific complex of type I and type II serine/threonine kinase receptors. Upon ligand binding, the TGF β type II receptor recruits and phosphorylates the TGF β type I receptor, which in turn phosphorylates downstream Smad proteins. These activated Smad complexes translocate to the nucleus where they regulate the transcription of TGF β target genes. Both Smad2 and Smad3 transduce signals of TGF β from the cell surface to the nucleus, but Smad3 was shown to be an essential mediator of TGF β responses, directly activating genes encoding for TGF β early targets, while Smad2 was not critical to the majority of gene responses. Interestingly, the TGF β /Smad3 pathway was shown to play a central role in specific pathological fibrosis in which TGF β has previously been implicated. Therefore, we hypothesized that Smad3 might prevent scarring after myocardial infarction and improve cardiac function.

Methods and Results: We induced myocardial infarction by permanent ligation of the LAD in Smad3 KO mice and WT controls. Our first observation was that Smad3 deficiency resulted in myocardial rupture in all null mice 4-5 days post MI. Analyzing RNA/Protein samples, isolated prior to myocardial rupture, showed that Smad3 deficiency results in a decrease in TIMP1 expression (KO 0.4 ± 0.2 vs WT 0.8 ± 0.3 $p < 0.05$) after myocardial infarction resulting in more active Matrix Metalloproteinases (MMP) and subsequent collagen degradation. Next, we pre-treated the Smad3 deficient and WT mice with doxycycline, a broad-spectrum MMP inhibitor, prior to LAD ligation. Doxycycline treatment rescued the Smad3 null mice from dying of cardiac rupture. More striking was that although the WT ligated animals (n=5) show a clear infarct and dilated left ventricle 28 days post MI and impaired function, as determined by MRI (Fractional shortening 23.6 ± 7.3), Smad3-null mice (n=5), showed almost complete restoration of ventricular damage, wall thickness, and function (Fractional shortening 62.6 ± 9.5 $p < 0.05$ compared to WT).

Conclusions: Our results show that Smad3 is extremely important in the response of the ventricle to MI damage and that Smad3 inhibition might be very beneficial for myocardial repair if applied within a certain temporary window after MI.

1193 Cardiac dysfunction in adults following conditional expression of cardiac-specific ErbB-1 (EGFR) mutant receptors



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Purpose: Decline in cardiac function may be associated with a variety of factors.

The ErbB tyrosine kinase receptors are essential for cardiac development and as gene knockouts are embryonically lethal. Moreover, they have been implicated in maintaining cardiac function during adulthood. However, the extent to which the cardiac ErbB signaling system controls cardiac function remains unresolved. Using the cardiac cell-specific and time-controlled ecdysone inducible gene expression system, we examined the hypothesis that a cardiac-specific ErbB-1 (EGFR) mutation would contribute to cardiac dysfunction in the adult population.

Methods: To study the role of ErbB-1 receptors in the adult heart, we produced bi-transgenic (TG) mice that express intracellularly truncated ErbB-1 receptors selectively in cardiomyocytes. The conditionally expressed ErbB-1 mutant receptors (ErbB-1-mut) dimerize with normal endogenous counterparts, leading to blockade of ErbB-1 receptor-mediated signaling in cardiomyocytes. Established procedures, including Western blot analysis and double immunohistochemistry, were performed and the TG mice were characterized. Morphological and echocardiographic analyses were used to study phenotypic changes. Survival rate of stress-induced TG mice was studied using Transverse Aortic Constriction (TAC). Wild type mice and TG mice without expressing the ErbB-1-mut were used as controls.

Results: ErbB-1-mut was expressed only in cardiomyocytes. Upon expression of mutant receptors in young adult mice, blockade of endogenous ErbB-1 and ErbB-2 phosphorylation was observed in a dose-dependent manner. Histologically, numerous cardiac lesions were observed and both the ventricles were dilated. mRNA levels of ANF (Atrial Natriuretic Factor) were increased indicating cardiac hypertrophy and dilation. Echocardiography following 6-weeks of induction revealed significant increase in left ventricular end-systolic dimension (2.12 ± 0.08 vs. 1.02 ± 0.13 mm, $p < 0.01$) and left ventricular end-diastolic dimension (3.36 ± 0.08 vs. 2.45 ± 0.24 mm, $p < 0.05$), and significant decrease in fractional shortening (FS) ($p < 0.01$) and ejection fraction (EF) ($p < 0.01$) ($n = 3$) in TG mice expressing ErbB-1-mut. Survival rate of TAC transgenic mice ($n = 5$) expressing the ErbB-1-mut was 20% at four days post-TAC, as compared to 100% survival in the controls.

Conclusions: These observations indicate that conditional expression of cardiac-specific ErbB-1 mutant receptors contribute to cardiac dysfunction in adult population. Alterations of cardiac ErbB-1 may have pathophysiological implications in adulthood.

1194 Inhibition of nuclear import of calcineurin prevents myocardial hypertrophy



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The formation of complexes between transcription factors and DNA is crucial for the transcriptional process. Therefore, the time that transcription factors remain nuclear is a major determinant for transcriptional activity. In recent years it has been demonstrated, that not only the transcription factor NF-ATc but also the phosphatase calcineurin is translocated to the nucleus. Here we identified a nuclear localization sequence (NLS) and a nuclear export signal (NES) in the sequence of calcineurin. Using different deletion mutants of calcineurin we were able to demonstrate the crucial role of calcineurin in the nucleus. We further identified the nuclear cargo protein importin β 1 as responsible for nuclear translocation of calcineurin. Inhibition of the calcineurin/importin interaction by a competitive peptide (KQECKIKYSEK) mimicking the calcineurin NLS prevented nuclear import of calcineurin and therefore the development of myocardial hypertrophy in neonatal cardiomyocytes. H3-Leucin incorporation and cell size were suppressed significantly (234 ± 13 vs. 112 ± 13 , $p < 0.01$). The NLS peptide inhibited calcineurin/NF-ATc transcriptional activity (234 ± 13 vs. 112 ± 13 , $p < 0.01$), whereas calcineurin phosphatase activity was not affected (234 ± 13 vs. 112 ± 13 , $p < 0.01$). A non-inhibitory control peptide did not interfere with the calcineurin/importin binding. We conclude that calcineurin is not only capable of dephosphorylating NF-ATc and thereby enabling its nuclear import but the presence of calcineurin in the nucleus is also important for NF-ATc to develop the full transcriptional activity. We propose that suppression of calcineurin nuclear import is a new tool to prevent myocardial hypertrophy.

1195 Cardiomyocyte-specific conditional over-expression of Plasma Membrane Ca²⁺ ATPase 4-C-I increased cardiac mass and performance



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Background: To examine the role of different isoforms of the plasmalemmal Ca²⁺ ATPase (PMCA) pump in cardiac myocytes (CM), we over-expressed the caveolin-1 and nNOS-associating PMCA4-C-I isoform (P4b) in transgenic mice with an mMHC promoter-driven Doxycycline (Dox)-responsive transcriptional activator (tTA) and a tTA-responsive transgene for human P4b.

Methods & Results: All genotypes appeared with expected frequencies, and none altered mouse survival. RT-PCR, Western blot and immunohistochemistry confirmed Dox-regulated, CM-restricted, caveolin-localized expression of P4b in binary transgenic (BT: tTA+/P4b+) but not non-binary transgenic (NBT: tTA-/P4b+, tTA+/P4b-, tTA-/P4b-) littermates. In CM microsomes, Western blot and coupled enzyme assays revealed 5- and 6-fold higher PMCA protein and activity levels

respectively in BT vs. NBT mice. Trans-carotid Millar catheterization of adult mice revealed elevated systolic BP in BT vs. NBT and Dox-treated BT mice (117 ± 1 , $n = 8$ vs. 101 ± 2 , $n = 12$; and 98 ± 1 , $n = 5$; mmHg; $p < 0.001$). While HR did not vary (420 ± 12 vs. 406 ± 5 , min⁻¹, $p = \text{NS}$), BT mice showed increased LV contractility and lusitropy (+dP/dTmax: 6003 ± 86 vs. 4597 ± 246 ; -dP/dTmax: 5477 ± 296 vs. 4713 ± 254 ; mmHg/s; $p < 0.05$). Although body weight (BW) did not vary ($P = \text{NS}$), wet heart-to-BW ratios were higher in BT mice vs. controls (5.3 ± 0.3 vs. 4.8 ± 0.07 ; mg/g; $p < 0.05$), and morphometry revealed increased posterior wall and inter-ventricular septal thickness ($p < 0.05$). 2D-guided M-mode echocardiography confirmed smaller end-systolic LV diameters and improved LV fractional shortening in BT mice. Freshly isolated CM confirmed hypertrophy of BT vs. NBT cells, but electrical field stimulation of Indo-loaded CM revealed no significant differences in Ca²⁺-transients or diastolic Ca²⁺ concentrations. Real-time RT-PCR confirmed adaptive changes in expression levels of other Ca²⁺-regulatory genes SERCA2a/2b, IP3R1 and PMCA1. By contrast, total and neuronal nitric oxide synthase (NOS) activities, as determined by L-[3H] arginine to L-[3H] citrulline conversion assays ($n = 6$), were reduced in BT vs. NBT littermates (2.3 ± 0.13 vs. 4.3 ± 0.14 ; 0.32 ± 0.19 vs. 1.3 ± 0.25 pmol/min/mg).

Conclusion: Forced 5-fold higher P4b expression levels in CM of transgenic mice increased cardiac mass and improved ventricular performance. In the absence of detectable changes in Ca²⁺-handling, this phenotype may be related to observed reductions in cardiac NOS activity. P4b over-expression could be explored as a potential therapy for heart failure.

1196 Therapeutic delivery of cyclin A2 induces myocardial regeneration and enhances cardiac function in ischemic heart failure



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Background: Heart failure is a global health concern with limited effective therapies. As a novel therapeutic strategy, the induction of endogenous myocardial regeneration was investigated by initiating cardiomyocyte mitosis by expressing the cell cycle regulator cyclin A2.

Methods and Results: Lewis rats underwent LAD ligation followed by peri-infarct intramyocardial delivery of adenoviral vector expressing cyclin A2 ($n = 32$) or empty adenovirus as control ($n = 32$). Cyclin A2 transgene expression was characterized by western blot and immunohistochemistry. Six weeks after surgery, while in heart failure, in vivo myocardial function was analyzed utilizing an ascending aortic flow probe and pressure-volume catheter. DNA synthesis was analyzed by proliferating cell nuclear antigen (PCNA), Ki-67, and BrdU expression. Mitosis was analyzed by phosphohistone H3 expression. Myofibrillar density and left ventricular geometry were assessed.

Cyclin A2 expression peaked at 2 weeks and tapered off by 4 weeks. Borderzone cardiomyocyte cell cycle activation was demonstrated by increased PCNA (40.1 ± 2.6 vs. 9.3 ± 1.1 , $p < 0.0001$), Ki-67 (46.3 ± 7.2 vs. 20.4 ± 6.0 , $p < 0.0001$), and phosphohistone-H3 (12.7 ± 1.4 vs. 0.0 ± 0.0 , $p < 0.0001$) expression. Cyclin A2 hearts demonstrated increased borderzone myofibrillar density (39.8 ± 1.1 vs. 31.8 ± 1.0 cells/hpf, $p = 0.0011$). Borderzone wall thickness was greater in cyclin A2 hearts (1.7 ± 0.4 vs. 1.4 ± 0.04 mm, $p < 0.0001$). Cyclin A2 animals manifested improved hemodynamics. Pmax (65.1 ± 1.0 vs. 59.4 ± 1.0 mmHg, $p = 0.0003$), max dP/dt (2689 ± 25.1 vs. 2406 ± 28.6 mmHg/sec, $p < 0.0001$), stroke volume (80.9 ± 2.9 vs. 67.8 ± 2.0 μ L, $p = 0.0007$), and cardiac output (26.4 ± 0.6 vs. 22.7 ± 0.6 mL/min, $p = 0.0002$).

Conclusions: A therapeutic strategy of cyclin A2 expression via gene transfer induced cardiomyocyte cell cycle activation and yielded increased borderzone myofibrillar density and improved myocardial function. This approach of inducing endogenous myocardial regeneration provides proof-of-concept evidence that cyclin A2 may ultimately serve as an efficient, alternative therapy for heart failure.

1197 Effect of Rho kinase inhibition in a model of pressure-overload hypertrophy



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Background: Studies suggest Rho kinase is involved in the pathogenesis of left ventricular (LV) remodelling. Inhibition of Rho kinase improves cardiac function which is associated with reduced levels of pro-inflammatory cytokine expression and fibrosis. Increased fibrosis is an important determinant in the development of diastolic dysfunction. We have previously reported the effect of Rho kinase inhibitors in reducing cytokine- and angiotensin II-induced collagen synthesis in rat cardiac fibroblasts.

Aim: In this study we examined the effect of a specific Rho kinase inhibitor (GSK 576371 - GSK) on measures of cardiac function using a model of pressure-overload hypertrophy (POH) in the rat.

Methods: POH was induced by suprarenal constriction of the abdominal aorta. Treatment commenced the next day with the POH + GSK group receiving 1mg/kg b.d. for 4 weeks. Echocardiographic images were obtained before and 4 weeks

after surgery, at which time haemodynamic parameters were measured. Trans-stenotic pressure gradients were used to group animals with similar constriction. **Results:** Wall thickness (IVSD 56%; PWTD 65%), relative wall thickness (RWT 67%) and deceleration time (DT 78%) were significantly increased in POH compared to sham animals. Similarly increases in systolic blood pressure (SBP 34%) and LV end diastolic pressure (LVEDP 95%) were observed. GSK treatment reduced all parameters except SBP (Table).

Echocardiography and haemodynamic data

Parameters	Sham (n=8)	POH (n=6)	POH + GSK (n=9)	% Decrease with GSK
IVSD (mm)	0.93 ± 0.04	1.45 ± 0.06 *	1.31 ± 0.06 #	10%, P=0.024
PWTD (mm)	1.00 ± 0.02	1.65 ± 0.09 *	1.34 ± 0.07 #	23%, P=0.005
RWT	0.22 ± 0.01	0.37 ± 0.03 *	0.28 ± 0.02 #	23%, P=0.003
DT (msec)	37.2 ± 2.2	66.1 ± 9.5 *	44.3 ± 2.5 #	33%, P=0.025
SBP (mmHg)	116.4 ± 7.1	155.0 ± 8.5 *	150.6 ± 10.3	NS
LVEDP (mmHg)	3.7 ± 0.6	7.1 ± 0.6 *	4.6 ± 0.7 #	35%, P=0.010
Press Grad (mmHg)	—	70.5 ± 7.4	65.3 ± 2.3 #	NS

Improved parameters were observed following GSK treatment. *P<0.004 compared to sham, #P<0.05 compared to POH.

Conclusion: Diastolic parameters, DT and LVEDP, are improved with GSK treatment. This suggests that Rho kinase inhibition is beneficial in the prevention of diastolic dysfunction in the pressure-overload setting and the mechanism may be due to a reduction in fibrosis as previously determined from our in vitro studies.

NUCLEAR IMAGING TO ASSESS THERAPY

1202 Viability predicts response to cardiac resynchronization therapy in ischemic cardiomyopathy



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Background: The response to cardiac resynchronization therapy (CRT) varies significantly among individuals. Preliminary data suggest that the presence of myocardial viability may be important for response to CRT. The aim of the present study was to evaluate whether the extent of viability could predict response to CRT after 6 months.

Methods: Sixty-one consecutive patients with advanced heart failure, left ventricular ejection fraction (LVEF) <35%, QRS duration >120 ms and chronic coronary artery disease were included. To determine the extent of viability all patients underwent nuclear imaging with F18-fluorodeoxyglucose SPECT before implantation. Clinical and echocardiographic parameters were assessed at baseline and after 6 months of follow-up.

Results: The presence of myocardial viability was directly related to an increase in LVEF after 6 months of CRT. Furthermore, the extent of viability in responders (n=38) was significantly larger compared to non-responders (n=23, 12±3 vs. 7±3 viable segments, P<0.01). Moreover, the optimal cut-off value to predict clinical response to CRT was identified at an extent of 11 viable segments or more (in a 17-segment model), yielding a sensitivity of 74% and a specificity of 87%.

Conclusion: The presence of myocardial viability is directly related to response to CRT in patients with ischemic heart failure. Interestingly, using a cut-off level of 11 viable segments or more, the extent of viability could be used to predict response. Evaluation for myocardial viability may therefore be considered in the selection process for CRT.

1203 Interaction of caffeine with Regadenoson-induced hyperemic myocardial blood flow as measured by PET



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Background: Pharmacologically induced increase in myocardial blood flow (MBF) by adenosine or dipyridamole for myocardial perfusion imaging (MPI) can be attenuated by caffeine, which is a competitive antagonist of adenosine A2A receptors. Regadenoson is a new selective adenosine A2A receptor agonist developed as a pharmacological stress agent with a higher receptor affinity than adenosine or dipyridamole.

Aim: To assess whether regadenoson-induced hyperemic MBF is blunted by caffeine.

Methods: The study was a randomized, double-blinded, placebo-controlled cross-over design. 45 healthy volunteers (age 27±6.1 years, 35% females) were enrolled; 4 had to be excluded for technical (3) reasons or were lost to follow-up (1). MBF (ml/min/g) was assessed by Positron Emission Tomography (PET) and 15O-labeled water at rest and after administration of an iv-bolus of 400 µg Regadenoson. 100 minutes prior to baseline MBF-measurement all individuals ingested a blinded capsule containing either 200 mg of caffeine or placebo. Measurements were repeated between 24 hours and 14 days later with each individual receiving the other capsule than on day 1. Hemodynamic parameters and ECGs were assessed at fixed intervals throughout the study and tolerability was

questioned. Coronary flow reserve (CFR) was calculated as hyperemic over resting MBF.

Results: The study did not show a significant effect of caffeine on MBF at rest (1.1±0.2 placebo vs. 1.1±0.3 caffeine, p=ns), or on regadenoson-induced hyperemic MBF (3.0±0.8 placebo vs. 3.0±0.9 caffeine, p=ns) and CFR (figure below). While, a less than 10% reduction in CFR can not be ruled out, the data suggest with 95% confidence that the CFR reduction associated with caffeine intake would not be greater than 20%. With the exception of attenuated heart rate increase during regadenoson-induced hyperemia after caffeine, hemodynamic parameters were not affected by caffeine and no significant ECG changes occurred. Side-effects were similar (90% caffeine vs. 95% placebo) but subjects felt more comfortable during the test with prior caffeine. No serious adverse events were reported.

Conclusion: Regadenoson causes coronary hyperemia without any serious side effects independent of prior caffeine intake. The heart rate increase induced by regadenoson is blunted by prior caffeine intake.

1204 Scintigraphic assessment of left ventricle in patients with AMI treated with intracoronary infusion of autologous bone marrow stem cells



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Aim of the study: Myocardial perfusion in pts with first anterior AMI treated with primary or rescue PCI of LAD was evaluated with Tc-99m-MIBI SPECT rest/dipyridamole at 4-6 days, after 3,6 and 12 months. Patient were randomized either to i.c. infusion of autologous BMSC at 4-6 days after AMI or to control group. Radionuclide ventriculography (RVN) was performed at 10 day, after 6 and 12 months in both groups.

Material and methods: Of 24 pts randomized to BMSC group, 14 have finished 12 month follow-up, of 13 pts from control group, 10 pts have finished 12 month follow-up so far. Perfusion index was calculated for left ventricle (PI) and for segments supplied with blood by LAD (PI-IRA). Results of BMSC vs control group; rest study PI did not differ; 2,22±0,48 vs 2,46±0,61 at 4-6 day and 2,15±0,39 vs 2,37±0,44 after 12 months, resp. PI-IRA did not differ at 4-6 day: 2,79 ±0,66 vs 3,07±0,86, resp., but differed after 12 months: 2,57±0,42 vs 2,96±0,34, p=0,03. PI at dipyridamole study (PId) did not differ at 3 months (2,21±0,34 vs 2,48±0,40, resp.) and after 12 months (2,20±0,46 vs 2,56±0,43, resp.) PI-IRAd did not differ at 3 months (2,77±0,62 vs 2,86±0,57, resp.), but differed significantly in favour of BMSC group after 12 months (2,57±0,53 vs 3,23±0,46, resp., p=0,005). Results of EF-RVN are given in table.

Group		EF 10 day	EF 12 months	EF 10 day vs EF 12 months
BMSC	mean	45,83	49,87	0,08
	SD	7,30	8,40	
Control	mean	42,69	38,33	NS
	SD	7,46	9,97	
BMSC vs Control		NS	0,005	

Conclusion: after 12 months follow-up of patients with AMI treated with BMSC we observed maintenance of EF in BMSC group and its gradual deterioration in control group. BMSC group presented with better perfusion at dipyridamole study, particularly in segments supplied with blood by patent IRA, while in control group perfusion of that segments worsened. Therefore the results confirm possible role of BMSC in encouraging of growth of new vessels and rebuilding of cardiomyocytes.

1205 Can the location of reversible hypoperfusion on myocardial perfusion scintigraphy be used to guide percutaneous coronary intervention?



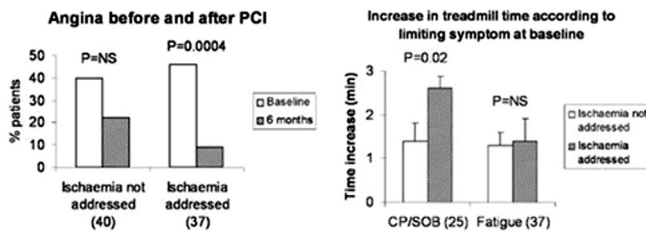
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Introduction: Myocardial perfusion scintigraphy (MPS) is often used to target percutaneous coronary intervention (PCI). However there has been no prospective blinded study demonstrating that PCI which targets ischaemia produces a particularly favourable symptomatic outcome.

Methods: 85 consecutive patients (age 65±10y, male 60) awaiting elective PCI underwent MPS using a 1-day stress-rest Tc-99m-tetrofosmin SPECT protocol. Reversible hypoperfusion was assigned to one or more coronary territories. All patients subsequently underwent the planned PCI, with the interventionalist blinded to the results of MPS. 81 patients underwent technically successful PCI and survived to follow-up at 6 months, both clinically and with treadmill exercise where possible (62 patients). Staff were blinded to MPS and angiographic findings.

Results: 37 patients had reversible hypoperfusion located entirely or mainly within the territory of the PCI vessel(s) ("ischaemia addressed"). 40 patients either had no reversibility, or reversibility located entirely or mainly outside the territory of the PCI vessel(s) ("ischaemia not addressed"). Only patients in whom ischaemia

was addressed exhibited a significant decrease in the prevalence of angina (Fig). All patient groups exhibited an increase in treadmill exercise time, but the increase was most striking in those with limiting angina at baseline in whom ischaemia was addressed (2.6 ± 1.4 min; Fig).



Figure

Conclusions: Patients in whom reversible ischaemia is targeted by PCI demonstrate good resolution of angina. Treadmill exercise time increases in all groups of patients following PCI, perhaps as a placebo effect, but the improvement is greatest in those in whom ischaemia has been addressed. We conclude that MPS can be used to target PCI.

1206 Significantly reduced clinical restenosis rate after drug eluting compared to third generation bare metal stenting in a real world setting



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Background: Drug-eluting stents (DES) have emerged as an effective solution to the problem of angiographic restenosis. However, data about clinical restenosis is lacking regarding the comparison of DES versus third generation bare metal stents (BMS) in a real world setting. The aim of this study was to prospectively assess clinical restenosis rates defined as target vessel (TV) ischemia (TVI) as assessed by myocardial perfusion SPECT, revascularization (TVR), or target vessel failure (TVF) including TVI, TVR, cardiac death or myocardial infarction within 6 months after stenting in consecutive non-selected patients randomized to DES versus third generation BMS (ratio 2:1) in the Basel Stent Kosten Effektivitäts Trial (BASKET).

Methods: All patients treated with PCI and stenting at the University Hospital of Basel, Switzerland, between May 05, 2003 and May 31, 2004 were included in BASKET, irrespective of indication for PCI. Patients were randomized to one of two DES (Cypher or Taxus) or to a cobalt-chromium-based BMS (Vision). Of these pts, pts who suffered TVR or underwent MPS within 6 months after intervention were evaluated.

Results: The study comprised 533 pts, age 64 ± 12 y, 111 female (21%), 57% with acute CAD, and 35% with triple vessel disease. Pts with DES had significantly less TVI (6.2% vs. 12.1%, $p=0.027$) TVI or TVR (10.8% vs. 19.5%, $p=0.008$), TVF (13.5% vs. 23.6%, $p=0.004$) than pts with BMS. If data of DES were considered separately there was a trend to better outcome in pts with Cypher stents: Cypher vs. Taxus: TVI or TVR (7.8% vs. 13.8%, $p=0.08$), TVF (10.1% vs. 16.8%, $p=0.07$).

Conclusions: Compared to a third generation BMS, DES proved effective in reducing TVI, TVI or TVR and TVF in a real world setting and there was a trend towards a more favorable result after Cypher compared to Taxus stents.

1207(W) The Effect of Verapamil on the Restoration of Myocardial Perfusion and Functional Recovery in Patients with Angiographic No-Reflow After Primary Percutaneous Coronary Intervention



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Objective Angiographic Thrombolysis in Myocardial Infarction (TIMI) flow grade ≤ 2 after primary percutaneous coronary intervention (PCI), defined as angiographic no-reflow, predicts poor functional recovery in patients with acute myocardial infarction (MI). We investigated the effect of verapamil on the restoration of myocardial perfusion and functional recovery in patients with angiographic no-reflow after PCI.

Methods Technetium-99m (99mTc) tetrofosmin single-photon emission computed tomographic (SPECT) imaging was performed (before, immediately after and 1 month after PCI) in 101 consecutive patients with acute MI. The defect score was calculated as the sum of perfusion defect in a 13-segment model (scores of 3, complete defect to 0, normal perfusion). The asynergic score, defined as the number of asynergic segments, was assessed by echocardiography before and 1 month later. Multiple logistic regression analysis was performed to elucidate the effect of verapamil administration.

Results Of 101 patients, 32 patients (31%) had angiographic no-reflow and were divided into 2 groups: 18 patients with verapamil (Group 1) and 14 patients without verapamil (Group 2). Sixty-nine patients had TIMI grade 3 reflow after PCI (Group 3). The change in the defect score 1 month after PCI in Group 1 was significantly

larger than that in Group 2 ($p=0.003$). The asynergic score improved more at 1 month in Group 1 compared to that in Group 2 ($p=0.007$). Moreover, logistic regression analysis revealed that TIMI flow grade ≤ 2 after PCI ($P=0.04$, OR=5.51), the defect score before PCI ($P=0.03$, OR=1.15), the asynergic score before PCI ($P=0.01$, OR=0.64) and the administration of verapamil ($P=0.002$, OR=22.4) were independently associated with successful myocardial reperfusion immediately after PCI. **CONCLUSIONS** Intracoronary verapamil restored myocardial perfusion in patients with angiographic no-reflow after PCI and lead to better functional recovery after acute MI.

MECHANISMS AND OUTCOME IN CARDIAC RESYNCHRONISATION THERAPY

1217 Effects of CRT on cellular and molecular mechanism in patients with advanced cardiac heart failure (preliminary reports)



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Aims: Recent data from the COMPANION trial have documented that cardiac resynchronization therapy (CRT) with biventricular (BiV) pacing reduces mortality and hospitalization in patients with advanced CHF, and only recently has been investigated about the cellular and molecular mechanisms of CRT. Our aim is to evaluate if the reverse interstitial remodelling obtained with CRT is permanent or exclusively related to effects of resynchronization with biventricular pacing.

Methods: We performed endomyocardial biopsies in 12 patients, medium age 63, with dilated cardiomyopathy in three different times (before, six and twelve month after the implant of BiV). Patients were randomized in two groups A and B. Group A was implanted with BiV without CRT function activation for the first six months, then this function was activated for next six months of follow-up time (CRT OFF-ON). In contrast Group B patients' the CRT was activated for the first six months, then was deactivated for the next six months (CRT ON-OFF).

Results: Clinical status and left ventricular (LV) architecture and function were assessed as well as myocardial histology, TNF- expression, and apoptotic index. The improving of clinical status reverse LV remodelling substantiated by significant reductions of LV volumes and end-systolic circumferential wall stress was evidenced during CRT ON period. Examination of myocardial tissue revealed a significant decrease of collagen volume fraction (CVF) (from 26.5 to 18.5%), TNF- expression (from 10 to 3.8 pixel x 103), and apoptotic index (from 2010 to 1390 apoptotic nuclei/106), with increased capillary density (from 1750 to 2050 capillary/mm²) after 6 months of CRT (all $P < 0.05$ vs. baseline). Moreover those changes in molecular and cellular mechanism were not observed during the CRT OFF period and regressed at the suspension of CRT as well as clinical benefits.

Conclusions: Our preliminary data confirm that CRT reduces the interstitial remodelling, TNF- expression, and apoptosis that may explain the beneficial effects of CRT on CHF progression and survival and confirm that reverse remodelling depends exclusively by CRT.

1218 Limitation of excessive collagen type I synthesis and deposition may contribute to long-term benefits of cardiac resynchronization therapy in patients with Heart Failure



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We have investigated whether the serum level of the carboxy-terminal propeptide of procollagen type I (PICP), a marker of cardiac collagen type I (CTI) synthesis and deposition, is related to the long-term response to cardiac resynchronization therapy (CRT).

The study was performed in 38 HF patients with classical indication for CRT and successfully implanted. Clinical and echo evaluation, as well as determination of serum PICP, were performed at baseline and at 1-year of follow-up.

Twenty-six (68%) patients were responders to CRT and 12 (32%) nonresponders. At baseline serum PICP was higher ($P < 0.001$) in responders (101 ± 34 μ g/L) than in nonresponders (57 ± 18 μ g/L) and controls (67 ± 9 μ g/L). Nonresponders exhibited higher ($P < 0.05$) left ventricular end-diastolic diameter (LVEDD) and lower ($P < 0.05$) septal-to-lateral wall motion delay than responders. At 1-year of follow-up, serum PICP decreased ($P < 0.005$) in responders (82 ± 21 μ g/L), while increased ($P < 0.005$) in nonresponders (91 ± 34 μ g/L).

Significant associations were observed between a positive response to CRT and high baseline values of PICP (> 73 μ g/L) ($\chi^2 = 16.29$, $P < 0.001$) and low baseline values of LVEDD (< 67.5 mm) ($\Delta = 5.37$, $P < 0.05$) in all patients. However, logistic regression analysis showed that the only independent predictor of a positive response to CRT was PICP (OR: 13.9, 95% CI: 7 to 97; $P < 0.001$). The accuracy

of the model was confirmed by the non-significant Hosmer-Lemeshow goodness of the fit test ($P=0.796$).

Using receiver operating characteristic curves, we observed that a cut off of 73 $\mu\text{g/L}$ for PICP provided 83% specificity and 85% sensitivity for predicting a positive response to CRT with an OR of 27.5 (95% CI 4.3 to 175.7, $P<0.001$).

Conclusions: (1) An association exists between abnormally high baseline serum PICP levels and a positive long-term response to CRT in HF patients; (2) Whereas the beneficial effects of CRT in HF patients are associated with its ability to normalize serum PICP, the lack of benefit is associated with enhancement of serum PICP. (3) Serum PICP is more accurate than some echo parameters and NT-proBNP in the prediction of a positive long-term response to CRT in HF patients. The findings of this pilot study suggest that limitation of the excessive cardiac synthesis and deposition of CTI I fibrils may be one of the mechanisms contributing to the long-term beneficial effects of CRT in HF patients. In addition, serum PICP may be an accurate predictor of long-term response to CRT in these patients.

1219 Effect of cardiac resynchronization on morbidity and mortality of diabetic patients with severe heart failure



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Background: Diabetes mellitus (Dm) and heart failure often coexist. Diabetic patients seem to benefit equally to non-diabetics from current standard heart failure medication. The effect of cardiac resynchronization therapy (CRT) on the outcome of patients with Dm remains undefined.

Methods: In CARE-HF 813 patients with moderate or severe heart failure were randomly assigned to pharmacological therapy alone or with the addition of CRT. For the present analysis, we studied the impact of diabetes mellitus on outcome by stratifying patients into those with and without a history of Dm or medication for Dm at baseline.

Results: Of the participants 207 (25.5%) had Dm. These patients were equally distributed between the CRT group (106 patients, 25.9%) and medical therapy group (101 patients, 25.1%). A total of 94 (11.7%) and 121 (15.0%) diabetic patients had received insulin and oral hypoglycaemic agents, respectively, 62 (7.1%) diabetic patients were on diet only. Patients with Dm more often had a history of hypertension (P0.1). By the end of the study extension period 181 non-diabetic patients had died as compared with 74 diabetic patients (29.9% vs. 35.9%; hazard ratio, 1.30; 95% CI 0.99 to 1.70; $p=0.06$). More diabetics on insulin (46 of 94 patients, 48.9%) than on oral hypoglycaemics (36 of 121 patients, 29.8%) or on diet only (21 of 62 patients, 33.9%; $p=0.0002$ for the interaction term of insulin versus diabetes) died. CRT reduced all cause mortality to a similar extent in diabetic and non-diabetic patients. There was no evidence of an interaction between CRT and Dm (hazard ratio for interaction 1.026; 95% CI 0.59 to 1.78; $P=0.93$). In patients with Dm, CRT also reduced the risk for all predefined combined endpoints (i.e. death or unplanned hospitalization for a cardiovascular event; death from any cause or unplanned hospitalization with worsening heart failure), and improved NYHA class and quality of life. No interaction between Dm and CRT was observed for any outcome (all $P>0.1$).

Conclusions: A history of Dm was associated with an increased risk of mortality. The relative benefits of CRT were similar in patients with and without Dm for a number of outcomes. Accordingly, somewhat greater absolute benefits from CRT may be expected in patients with Dm.

1220 The effect of classification of arrhythmic sudden cardiac death on the efficacy of cardiac resynchronization therapy in the CARE-HF study



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The definition of arrhythmic sudden cardiac death (SCD) differs widely among studies, which will affect the frequency with which it is ascribed as the cause of death. Cardiac resynchronization therapy (CRT) was reported to reduce SCD in the CARE-HF study. This could reflect a real effect of CRT on malignant arrhythmias or the methodology used to classify death. Accordingly, we investigated whether the way in which SCD was classified altered the conclusions of the study with respect to SCD.

Methods: All patients classified as dying suddenly and unexpectedly as the mode of death without other cause were classified as SCD with the following levels of certainty: definite: witnessed SCD with documented arrhythmia; probable (witnessed) and possible (unwitnessed) SCD without documented arrhythmia.

Results: The mode of death was sudden in 86 patients, of whom 71 were considered SCD: 10 definite, 29 probable, 32 possible. CRT decreased SCD in the overall cohort: Hazard ratio (HR) 0.53 [95% confidence interval (CI) 0.35 to 0.84;

$p=0.001$]. CRT decreased SCD in definite plus probable SCD: HR 0.58 (0.31 to 1.10; $p=0.09$) and possible: HR 0.35 (0.16 to 0.76); $p=0.008$. The HR for reduction in the definite plus probable SCD group and the possible SCD group were not significantly different.

Conclusion: CRT reduces SCD in patients with heart failure and markers of dyssynchrony. The observed effect is not dependent on the definition of SCD used.

1221 Predicting the long-term effects of cardiac resynchronisation therapy from baseline variables and the early response. A report from CARE-HF (Cardiac Resynchronisation in Heart Failure)



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Background: In some patients for whom cardiac resynchronisation therapy (CRT) appears appropriate, CRT fails to improve symptoms and may not improve prognosis. Prediction of response from baseline variables has met with limited success. Lack of response may reflect failure of the device to deliver effective CRT or failure of the patient to respond to technically successful CRT. If lack of short-term response predicts long-term outcome, then it might be used to alert clinicians to the need for further action. These complex issues can only readily be addressed in the context of a randomised trial.

Methods: In the CARE-HF study, 813 patients with moderate or severe heart failure and cardiac dyssynchrony were randomised to CRT or not in addition to standard therapy and followed for up to 53 months. Patients were assessed at baseline and 3 months. The main outcome of interest was all-cause mortality. Twelve pre-specified baseline variables, including age, NYHA class, aetiology, use of beta-blockers*, systolic blood pressure*, QRS duration*, interventricular mechanical delay (IVMD)*, severity of mitral regurgitation (MR)*, left ventricular (LV) end systolic volume*, LV ejection fraction*, glomerular filtration rate*, NT-proBNP* were included in the model. Values measured at 3 months for items marked with * were then included to see if they could improve predictive accuracy using a Cox Proportional Hazards model, including 3 month values as time dependent covariates. Forward stepwise elimination methods were used to identify the final model.

Results: On univariate analysis all variables except QRS predicted outcome either at baseline or at 3 months or both. In the multi-variable model, baseline variables that independently predicted longer survival were absence of ischaemic heart disease ($p=0.007$), less severe IVMD ($p=0.0029$) and more severe NYHA class ($p=0.002$). At 3 months, NT-proBNP ($p<0.0001$) and severity of MR ($p<0.0001$) provided further independent prognostic information. Indeed, NTproBNP at 3 months was the most powerful prognostic marker in the model. However, even after entering all of the above variables into the model, assignment to CRT was still associated with longer survival (HR 0.67 95%CI 0.49 to 0.91; $p=0.0113$).

Conclusion: Patients who have a persistently elevated NTproBNP or moderate to severe mitral regurgitation 3 months after implantation of a CRT device should be re-evaluated to ensure that CRT is functioning optimally and/or the need for alternative treatments. However, factors in addition to those used in this analysis appear to account for much of the benefit of CRT.

1222 Functional mitral regurgitation, left ventricular remodeling, cardiopulmonary performance early and late after cardiac resynchronization therapy: an exercise echocardiography study



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Background: Exercise-induced mitral regurgitation (MR) bears a poor prognosis in patients (pts) with congestive heart failure (CHF). Cardiac resynchronization therapy (CRT) is associated with improved clinical outcome but its effects on exercise-induced MR in relation to LV remodeling and cardiopulmonary performance are not known. Aim. To investigate serial changes in exercise-induced MR in relation to LV remodeling and cardiopulmonary performance before and after CRT.

Methods: Twenty-one pts with CHF, broad QRS complex ($171\pm27\text{msec}$), and at least mild MR were studied simultaneously with quantitative exercise echocardiography and cardiopulmonary exercise testing prior, within one week, and 3 months after CRT.

Results: Early after CRT, a decrease in LV asynchrony and MR at rest was associated with an increase in LV ejection fraction (EF). However, CRT did not attenuate exercise-induced increase in MR. At 3 months after CRT, a decrease in the mitral valve tenting area (TA) and increase in systolic sphericity index of the

LV (SSI) was noted in parallel with attenuation of exercise-induced MR. This was associated with a further increase in LV EF, increase peak VO₂, and a reduction in pro-BNP levels (2777 ± 1681 to 1963 ± 1361 pg/ml, $p < 0.05$), (Table).

	Prior CRT		Early CRT		Late CRT	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
ERO (cm ²)	0.25±0.12	0.34±0.12	0.20±0.09*	0.31±0.15	0.13±0.06***	0.19±0.06***
LV EF (%)	25±7	30±8	28±8**	31±8	35±9***	40±11***
LV dyssynchrony (ms)	54±20	44±19	19±7***	30±16	23±9***	24±11**
TA (cm ²)	3.3±1.2	4.0±1.2	3.2±1.6	3.5±1.5	2.0±0.6***	2.7±0.7***
SSI	1.5±0.3	1.7±0.5	1.5±0.4	1.6±0.4	1.8±0.5***	1.9±0.5*
Peak VO ₂ (ml/kg/min)		11.7±2.3		12±3.2		13.3±3.6*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; all vs prior to CRT

Conclusions: Though CRT is associated with an instant reduction in resting MR, it does not attenuate immediately exercise-induced MR. In contrast, reversed LV remodeling and improved mitral valve coaptation late after CRT is associated with a reduction of both resting and exercise-induced MR in parallel with improved cardiopulmonary performance. Thus, reduction in exercise-induced MR could contribute to beneficial effect of CRT in pts with CHF.

ANTIBRADYCARDIA PACING – CLINICAL ASPECTS

1223 Implications of national guidance on pacing mode in the UK

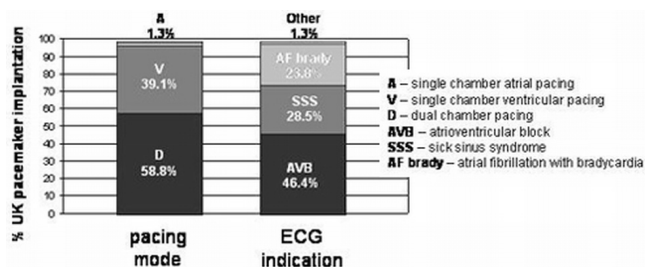


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Introduction: UK guidance on pacing mode for patients with sick sinus syndrome (SSS) and/or atrioventricular block (AVB) was published in February 2005. This states that dual chamber pacing is recommended for symptomatic bradycardia due to SSS, AVB or a combination, except in the management of SSS in patients in whom, after full evaluation, there is no evidence of impaired AV conduction, when single chamber atrial pacing is appropriate. We have audited UK practice, and considered the implications of its implementation.

Methods We interrogated the UK pacemaker and ICD database for pacemaker indications and modes in 2003 and 2004, and reviewed published data on the incidence and prevalence of AVB in SSS.

Results 40,284 new pacemakers were implanted, giving an annual rate of 411 per million. Pacing was for AVB in 46.4%, SSS in 28.5% and AF with bradycardia in 23.8%. The pacing mode was dual chamber (DDD±R) in 58.8%, single chamber ventricular (VVI±R) in 39.1% and single chamber atrial (AAI±R) in 1.3%. The number of VVI±R implants exceeds the number for AF by 15.3%, suggesting that these patients are receiving an inappropriate mode. Published evidence suggests that 49% of SSS patients have normal AV conduction, suggesting that 12.7% of patients paced for SSS are also receiving a mode not recommended.



Conclusions: 27.8% of patients receive a pacing mode other than that recommended. Full implementation of UK guidance would result in a 15.3% reduction in VVI±R pacing and an increase of 12.7% in AAI±R pacing. This means that the numbers of dual and single chamber pacemakers currently implanted and recommended are similar, so there would be little financial impact of guidance implementation, even allowing for an annual pacemaker upgrade rate from AAI to DDD for new AVB in SSS patients of 1.5%

1224 Prevalence and clinical predictors for new-onset heart failure after permanent Right Ventricular Apical pacing in patients with acquired high-grade atrioventricular block



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Background: Previous studies have demonstrated that long-term right ventricular apical pacing (RVA) lead to left ventricular (LV) dyssynchrony, worsening of LV function, and development of heart failure (HF). However, permanent RVA pacing

is required in patients (pts) with high-degree atrioventricular (AVB). There is limited data on the prevalence and clinical predictors for the development of HF after RVA pacing in pts with acquired AVB.

Methods and Results: We studied the clinical outcomes after long-term RVA pacing in 304 pts suffered from acquired high-grade AVB without prior history of HF. All pts had >90% RVA pacing as determined by device diagnostic data. At a mean of 99 mths, 77 pts (25%) developed HF after a mean of 77 mths of (2-332 mths) RVA pacing. As compared to pts without HF, pts developed HF were older at the time of implant (72 ± 11 vs. 67 ± 15 yrs, $p < 0.01$), had a higher incidence of diabetes (38 vs. 23%, $p < 0.01$), new onset of myocardial infarction (MI, 16 vs. 3%, $p = 0.014$) and atrial fibrillation (19 vs. 7%, $p < 0.01$), wider pacing QRS duration (170 ± 18 vs. 159 ± 16 ms, $p < 0.01$), and more likely to receive VVI pacemaker (34 vs. 14%, $p < 0.01$). However, there were no significance in male gender (47 vs. 44%), duration of pacing (72 ± 11 vs. 67 ± 15 mths) and baseline LV ejection fraction (62 ± 9 vs. $66 \pm 12\%$) between pts with or without HF ($p < 0.05$). Furthermore, pts with HF had significantly higher mortality than pts without HF (62 vs. 23%, $p < 0.01$). Cox-regression analysis demonstrated that elderly age at implant (Odds ratio [OR] 1.07, $p < 0.01$), wider pacing QRS duration (OR 1.03, $p < 0.01$), new onset of MI (OR 3.06, $p = 0.01$) and VVI pacemaker (OR 1.99, $p = 0.027$) predict the development of new-onset HF.

Conclusions: A significant proportion (1/4) of pts with AVB developed new-onset HF after RVA pacing. The age at the time of implant, wider pacing QRS duration, the onset of MI and VVI pacing, but not the duration of pacing and their coexisting condition, predict the development of HF after RVA pacing. More importantly, the development of HF after RVA pacing is associated with a high mortality on long-term follow-up. Whether alternative ventricular site or biventricular pacing can prevent new-onset of HF in pts with AVB requiring long-term pacing remain unclear.

1225 DDD(R) Pacing versus Biventricular Pacing in Patients with high-grade AV-block. One Year Results from a Randomized Clinical Controlled Trial



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Objectives: Single site right ventricular pacing is supposed to cause ventricular desynchronization and impaired left ventricular function. The aim of the study was to evaluate if biventricular (BiV) pacing is superior to conventional DDD(R) pacing in patients with high grade AV-block.

Methods: Thirty consecutive patients (pts.) with high-grade AV-block were randomized to permanent DDD(R) ($n=15$) or BiV pacing ($n=15$). All pts. had bipolar active fixation leads implanted in the right atrium and in the right ventricular septum connected to an Insync III (Medtronic) BiV pacemaker. In the BiV-group, a dedicated LV-lead was implanted in a lateral coronary sinus tributary. Endpoints were: LVEF measured by 3-D echocardiography, intraventricular dyssynchrony measured by tissue-Doppler-imaging, BNP in blood samples, patient daily activity (hours/day) recorded from the pacemaker telemetry and 6-Minutes Hall Walk test (6 MHW), all estimated the day after pacemaker implantation (baseline) and after 12 months of follow-up. Mean $\pm$ SD are reported.

Results: Mean age was 75 (range 25-90) years. At 12 months of follow-up, LVEF increased in the BiV-group from $49 \pm 13\%$ at baseline to $54 \pm 9\%$ ($p=0.10$), and decreased in the DDD(R) group $62 \pm 6\%$ and $54 \pm 11\%$ ($p=0.05$), respectively. Intraventricular dyssynchrony were more common in the DDD(R)-group compared to the BiV-group at 12 months of follow-up ($p=0.03$). At baseline the 6 MHW test was 433 ± 85 m in the DDD(R)-group versus 401 ± 104 m in the BiV-group ($p=0.38$). After 12 months, 6 MHW increased more in the BiV-group (34 ± 49 m) compared to the DDD(R)-group (27 ± 29 m) ($p=0.72$). There were no difference between groups at 12 months of follow-up concerning patient daily activity ($p=0.96$). BNP measurements decreased in both groups after 12 months of pacing (172 ± 610 vs. 24 ± 231 pmol/l, BiV- and DDD(R)-group respectively) but with no significant difference between groups ($p=0.43$).

Conclusions: In patients with high-grade AV-block, BiV-pacing increases LVEF, minimizes intra left ventricular dyssynchrony, decreases BNP and increases walking distance. These results indicate that BiV-pacing may prevent left ventricular desynchronization.

1226 Ventricular dyssynchrony induced by right apical, Hisian and para Hisian ventricular pacing: comparison between different pacing sites



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Aim of the study: to compare the degree of ventricular dyssynchrony induced by pacing from different ventricular sites: right ventricular apical pacing (RVAP), direct His Bundle Pacing (DHBP), para His Bundle Pacing (PHBP).

Methods: we studied 25 pts (18 male, mean age 74 ± 10) with normal QRS duration and LV ejection fraction who underwent permanent ventricular pacing at direct his bundle (DHBP=13 pts) and in the para-hisian area (PHBP=12 pts). In all pts a back-up pacing lead was added in the apical of RV. Echocardiographic examination and Tissue Doppler Imaging was performed at baseline and after DHBP, PHBP and RVAP to evaluate: 1) the mean interval time between the ear-

liest and the latest basal LV wall motion (I-LV delay); 2) the standard deviation of the basal segment activation time intervals (modified Yu index) 3) the electromechanical latency (EML) defined as mean interval time between onset QRS and LV basal segments movement; 4) Tei index; 5) dP/dT.

Results: the table summarizes the values at baseline after DHBP, PHBP and RVAP:

	DHBP		PHBP		RVAP		Base vs DHBP p	Base vs PHBP p	Base vs RVAP p
	base	pacing	base	pacing	base	pacing			
QRS ms	90±12	92±14	88±15	129±22	89±13	156±18	NS	<0.05	<0.05
I-LV ms	27±10	24±12	34±15	43±11	30±12	54±23	NS	NS	<0.05
Yu In. ms	14±7	13±10	13±6	17±8	14±7	23±11	NS	NS	<0.05
EML ms	164±25	176±32	171±35	225±41	167±30	227±43	NS	<0.05	<0.05
Tei In	0.48	0.50	0.49	0.57	0.48	0.59	NS	<0.05	<0.05
	±0.12	±0.16	±0.14	±0.20	±0.13	±0.18			
dP/dT	698	756	655	600	680	475	NS	NS	<0.05
	±240	±197	±179	±201	±200	±245			

Conclusions: Only the DHBP maintained the normal electrical and mechanical activation of the left ventricle preserving systolic parameters. The PHBP did not significantly increase the I-LV delay however it produced a similar increase of EML and deterioration of Tei index compared with RVAP. The RVAP induced a major degree of ventricular dyssynchrony worsening the cardiac function.

1227 Impacts of antibioprophylaxis practices on infectious complications after cardiac devices implantation. From the prospective evaluation of pacemaker lead endocarditis

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Introduction: There is an increasing number of cardiac devices implantations but there are not clear recommendations for complications prevention. The antibiotics are prescribed to prevent infection occurrence. But their effectiveness is still discussed. Through PEOPLE study (a multicenter prospective study designed to assess the incidence and the risks factors of PM and ICD related infections) we assessed the efficacy of the antibioprophylaxis practices on the infection occurrence.

Method: 44 centres practising implantation of PM and ICD have included their consecutive patients from 01-01-2000 to 12-31-2000. These patients were followed during 12 months. The use of antibioprophylaxis was left to the discretion of each implanting centre. The methods of antibioprophylaxis indicated (molecule, dose, time, duration, duct and number of administrations). In statistical analysis, the role of antibioprophylaxis is adjusted on the roles of the other risks factors of infectious complication.

Results: 6134 patients were included and followed. 5427 patients (88.5%) had antibioprophylaxis and 707 had not. 2294 (42.3%) antibiotic prescriptions were in accordance with the guidelines. At 12 month follow-up, infections were reported in 42 patients. 33 in the group with antibioprophylaxis (incidence = 0.61%; 95CI = [0.40-0.81]) and 9 in the group without antibioprophylaxis (incidence = 1.29%; 95CI = [0.44-2.09]). The adjusted RR of antibioprophylaxis was 0.35 (95CI = [0.14 - 0.88]; p = 0.03). If antibioprophylaxis was prescribed, the other factors related to antibioprophylaxis practice had not influence on the incidence of infections (table).

Table 1. Practices and risk of infection

	Incidence (yes/no)	p	RR	95%CI
Antibioprophylaxis	0.6/1.3	.04	.47	0.22-1.08
Systematic protocol in the center	0.6/0.6	.84	1.07	0.51-2.15
Protocol according to the guidelines	0.6/0.6	.98	1.01	0.48-2.14
Single versus multiple injections	0.7/0.5	.38	1.39	0.66-2.91

Conclusion: In this large cohort, we highlight the protective role of antibioprophylaxis on the risk of infection. We showed that when antibiotics were prescribed, the risk of infections is divided by 3. The molecule prescribed, the duration and the number of antibiotic administrations or the respect of the guidelines had not effect on the benefit of antibioprophylaxis on infection prevention.

1228 Transvenous removal of pacing and defibrillating leads: a single Center results and complications in about 2000 consecutive leads

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Purpose: The increasing number of implanted devices rises today the importance of transvenous extraction of Pacing (PL) and Defibrillating Leads (DL). Results and complications of these complex procedures are strongly affected by the experience of the operators and by the availability of different approaches for difficult cases. Aim of this paper is to analyse the longstanding experience performed in a single Italian Center in transvenous removal of about 2000 PL and DL.

Methods: Since December 1989, we managed 1179 patients (859 men, mean age 66.4 years, range 6-93) with 1984 leads (mean pacing period 65.8 months, range 0.1-336). PL were 1796 (1137 ventricular, 620 atrial and 39 coronary sinus leads), DL were 188 (175 ventricular, 5 atrial and 8 SVC leads). Indications to lead removal were class I in 53.4% and class II in 46.6% of the leads. We always performed mechanical dilation using the Cook Vascular (Leachburg PA, USA) extraction kit and, if necessary, other intravascular tools (Catchers and Lassos, Osypka, Grentzig-Whylen, G). Since 1997 a Jugular Approach (JA) through the internal jugular vein was performed in presence of free-floating or in cases of unsuccessful of the standard approach.

Results: Removal was attempted in 1984 leads; 1950 leads (1762 PL, all the 188 DL) were removed (98.3%). The success rate increased over the time. Since the introduction of the JA, 1775 leads were submitted to removal. The JA was performed in 203 leads, allowing to remove 201 (99%) leads. Totally, combining the standard approach and the JA, 1761/1775 (99.2%) leads were removed in this period. In our overall experience serious complications occurred in 8 cases (0.67 of the patients): cardiac tamponade (7 cases, 1 death), hemothorax (1 death).

Conclusions: Our experience shows that transvenous lead removal using mechanical dilation is an effective and acceptably safe technique. The experience of the staff and the use of alternative approaches, as the JA, allow a very high success rate and safe procedures.

MULTI MODALITY IMAGING TO ASSESS PERFUSION AND FUNCTION

1229 Assessment of correlation between myocardial perfusion abnormality detected by positron emission tomography and coronary artery calcification in asymptomatic subjects

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Background: Most of the acute coronary syndrome (ACS) occurs by the plaque rupture where coronary stenosis is less than 50%. Thereby, identifying mild to moderate stenosis in asymptomatic subjects is important for the prevention of ACS. Although detecting coronary calcification using X-ray computed tomography is widely used for the evaluation of coronary atherosclerosis, correlation between coronary calcification and luminal narrowing has not been well evaluated. Thus, we assess the correlation between stress induced myocardial perfusion and coronary calcification in asymptomatic subjects who underwent positron emission tomography (PET) using N-13 ammonia and electron beam computed tomography (EBT).

Methods: N-13 ammonia PET and ECG-gated EBT were performed for 108 asymptomatic subjects (82 males and 26 females, mean age 56.6 years) for cardiac screening and the relationship between stress induced myocardial perfusion defect and Agatston calcium score (CS) were compared.

Results: Out of 108 subjects, 27 showed mild to severe PET perfusion defect, suggesting focal or diffuse coronary narrowing. Mean CS of the subjects with perfusion defect was greater than that of those with normal perfusion (215.2 vs 84.0, p=0.02). Calcium deposition was not observed in 55 subjects, 10 of whom perfusion defect was observed. On the other hand, out of remaining 53 subjects with coronary calcification, 36 demonstrated normal perfusion.

Myocardial Perfusion vs Calcification

	PET Normal	PET Abnormal
EBCT Calc. Negative	45	10
EBCT Calc. Positive	36	17
	81	27

Correlation between PET myocardial perfusion and existence of coronary calcification. Fifty-five demonstrated non-calcified coronary artery, 10 of whom showed abnormal stress induced myocardial perfusion.

Conclusions: Absence of coronary calcification does not guarantee absence of coronary narrowing, and presence of calcification is not always associated with coronary narrowing as well. Additional information may be needed for EBT test for the better estimation of plaque development.

1230 Comparison of cardiac MRI and SPECT for the detection of hemodynamically significant coronary stenoses using angiography and fractional flow reserve as reference standard

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Cardiac magnetic resonance imaging (CMRI) is a rapid evolving method for the noninvasive assessment of symptomatic coronary artery disease (CAD). Single Photon Emission Computed Tomography (SPECT) is the widely used for the non-invasive assessment of CAD. Beneath morphological assessment by quantitative coronary angiography (CA) the pressure derived fractional flow reserve (FFR)

is the well established gold standard to invasively evaluate the functional severity of coronary lesions. The aim of our study was to compare CMRI and SPECT for detection of flow limiting coronary stenoses compared to the invasive reference standard FFR.

Methods: 43 Patients with suspected CAD received a CMRI (Siemens Sonata, Erlangen, GE; IPAT) and SPECT (Philips Prism 3000 XP, Cleveland, Ohio; 700MBq) within two weeks of the scheduled CA. Signal intensity curves of the first pass of a Gadolinium-DTPA bolus at rest and during hyperemia (Adenosine 140 µg/kg/min i.v.) were investigated and input function corrected signal intensity curve's upslope (US) was determined for each myocardial perfusion area using an 18 segment model. The myocardial perfusion reserve (MPR) was calculated as US stress and US rest ratio. A MPR1 50% was registered a FFR measurement (Pressure Wire, Radi, SE) was performed. If FFR was <0.75 the lesion was defined as hemodynamically significant. All other lesions were defined as normal. **Results:** 129 perfusion areas (43 LAD; 43 LCx and 43 RCA) were evaluated. 105 (81%) areas were normal by FFR and 24 (19%) areas showed hemodynamically significant stenoses. Mean MPR was 1.7 (range 1.0-3.5). Mean MPR was significantly different between the regions supplied by a normal coronary vessel (2.1 ± 0.5) and significant stenosis (1.2 ± 0.31) ($p < .001$). Using the cut-off value of 1.5 a sensitivity of 88% (CI: 0.69-0.96) and a specificity of 90% (CI: 0.82-0.94) was calculated. SPECT revealed a sensitivity of 71% (CI: 0.50-0.86) and a specificity of 91% (CI: 0.84-0.95).

Conclusion: This study could demonstrate the ability of CMRI and SPECT to identify perfusion territories with hemodynamically significant coronary stenoses with high sensitivity and specificity. The overall accuracy of CMRI was comparable to SPECT without the disadvantage of radiation exposure.

1231 Incidence of right ventricular wall motion abnormalities and fat infiltration in patient with frequent premature ventricular complexes with LBBB morphology and inferior axis: a MRI study

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Background: Frequent premature ventricular complexes (PVC) with LBBB morphology and inferior axis are often associated to arrhythmogenic right ventricular cardiomyopathy (ARVC). Magnetic resonance (MRI) can identify abnormalities of right ventricular wall.

Aim: to evaluate incidence of right ventricular wall abnormalities in patient with frequent PVC of LBBB morphology.

Method: Three hundred ninety six patients (258 male, mean age 35 years) with frequent PVC (>2000/die) of LBBB morphology with inferior axis, normal echocardiogram and negative exercise test underwent MRI examination. Study protocol included evaluation of right ventricular end-diastolic volume index (REDVi) and end-systolic volume index (RESVi), and left ventricular end-diastolic volume index (LEDVi) and end-systolic volume index (LESVi), with short axis cine images (30 phases for slice) from mitral valve plane to the apex (thickness 8 mm, no gap between slices). Regional left and right wall motion (WM) was also evaluated in axial cine images acquired from diaphragm to right ventricular outflow tract (thickness 5 mm, no gap between slices). Cine image were acquired using a SSFP pulse sequence (FIESTA). T1-weighted Fast Spin Echo images in the same short axis and axial slices were also acquired. Right ventricle WM was classified as normal, hypokinetic, akinetic, and bulging. Signal from right ventricular wall was classified: no alteration (grade 0), minor alteration (grade 1), alteration compatible with fat infiltration (grade 2).

Result: All patients completed MRI protocol. 97 patients (24%) showed WM abnormalities consisting of hypokinesia in 30 (7.2%), akinesia in 32 (8%) and bulging in 35 (8.8%) patients; 36 (9.1%) patients had WM abnormalities without signal alteration; 71 (17.9%) patients had signal alteration consisting of grade 1 in 27 (6.8%) and grade 2 in 44 (11.1%); 20 (5.1%) patients had signal alteration with normal WM. In 27 patients (6.8%) major WM abnormalities (akinesia or bulging) and signal grade 2 were combined; this subgroup of patient showed higher REDVi (102.6 ± 63.7 vs 82.4 ± 21.9 ml $p < 0.001$) and higher RESVi (47.6 ± 62.7 vs 33.9 ± 16 ml $p < 0.009$). In 46 patient (11.6%) every grade of WM abnormalities and every grade of signal alteration were combined. In 2 patients (0.51%) fat infiltration was also documented in the left ventricular wall.

Conclusion: Patients with frequent PVC with LBBB morphology showed high incidence of right ventricular abnormalities but less than 7% showed combined abnormalities associated to enlargement of right ventricle providing diagnosis of ARVC.

1232 Role of Multidetector Computed Tomography (MDCT) in the management of patients with chest pain

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Background: for patients (pts) who present with chest pain, the current AHA/ACC guidelines recommend use of the exercise-ECG (ex-ECG) as the first test to determine whether they should undergo coronary angiography (CA). However while exercise capacity and ST segment changes are useful prognostically, they

are less accurate than other imaging technologies, often leading to inconsistent results. The aim of this study was to propose a decision-analytic model to identify which pts with chest pain benefit from MDCT.

Methods: we enrolled 160 consecutive pts (110 males, average age 64 ± 12) admitted to our hospital for chest pain undergoing to ex-ECG. According to AHA/ACC guidelines for the management of chronic stable angina the patients were divided into four groups: 54 pts with atypical angina and negative ex-ECG (Group 1), 48 pts with typical angina and negative ex-ECG (Group 2), 39 pts with atypical angina and positive ex-ECG (Group 3) and 19 pts with typical angina and positive ex-ECG (Group 4). Each patient underwent to MDCT (GE Medical System Ligth Speed Pro 16x0.625 mm, 400 msec time rotation, 100 ± 15 cc Iomeron 400 mg/ml at 4.5 ml/sec) before CA. MDCT data sets was evaluated with multiple approaches including volume rendering, multiplanar reconstruction and vessel analysis by three observers. The accuracy [sensitivity (Se), specificity (Sp), negative predictive (NPV) and positive predictive values (PPV)] in detection significant stenoses ($\geq 50\%$ diameter reduction) in comparison with CA were measured and compared among groups.

Results: the prevalence of CAD was respectively: Group 1: 46%; Group 2: 70%; Group 3: 68%; Group 4: 90% (*: $p < 0.01$ Group 1 vs Group 2-3-4; #: $p < 0.01$ Group 2-3 vs Group 4). The Se, Sp, NPV, and PPV were respectively: Group 1 100%, 87%, 87%# and 100%; Group 2: 100%, 87%*, 92%#, 100%; Group 3: 100%, 85%*, 93%# and 100%; Group 4: 100% for all parameters.

*: $p < 0.01$ Group 1-2-3 vs Group 4, #: $p < 0.01$ Group 1 vs Group 4, @: $p < 0.05$ Group 2-3 vs Group 4

Conclusions: usefulness of MDCT in the detection of CAD is markedly influenced by clinical and non-invasive characteristics of the study population. In pts with typical angina and positive ex-ECG, MDCT seems unnecessary due to the very high prevalence of CAD. In pts with only atypical angina and negative ex-ECG, MDCT may potentially lead to unnecessary CA due to its sub-optimal PPV. In pts with inconsistent or equivocal clinical symptom and non-invasive tests, MDCT may have an important clinical role in the detection of CAD due to its very high NPV and good PPV.

1233 High-dose adenosine overcomes the attenuation of myocardial perfusion reserve caused by caffeine

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Purpose: Adenosine is a purine nucleotide that mediates coronary vasodilation by activation of arteriolar adenosine A2a receptors. This effect is antagonised competitively by caffeine. This study investigated the effect of caffeine on adenosine myocardial perfusion scintigraphy (MPS) and whether an increase in adenosine dose overcomes the antagonism.

Methods: Caffeine-free patients with inducible perfusion abnormalities on adenosine MPS underwent a second study on a separate day after consumption of 2 cups of coffee (200 mg of caffeine) up to 12 hours before the test. For the second study, patients were randomly assigned to either conventional adenosine infusion (140 µg/kg/min) or high-dose adenosine (210 µg/kg/min) after serum caffeine measurement (serum caffeine threshold = 2mg/L). Perfusion variables (summed stress (SSS) and summed difference (SDS) scores based on a 20-segment model of the left ventricular myocardium) and test tolerance were compared between the caffeine-free and caffeine-loaded studies.

Results: 10 patients received the conventional adenosine dose and 12 patients the high-dose (age mean $\pm$ SD, 65 ± 5.4 years). At baseline, there were no differences in serum caffeine levels between the two groups (0.89 vs. 1.02 mg/L, $P = NS$). After caffeine ingestion, there was significant reduction in the extent and severity of inducible perfusion abnormalities compared with the caffeine-free state in the conventional adenosine group ($SDS = 4.3$ vs. $SDS = 12.0$, $P < 0.001$), whereas there was no change after high-dose adenosine (table). The incidence of adenosine-induced side effects was comparable between the groups (65% conventional vs. 67% high-dose adenosine, $P = NS$). All side effects were mild and well tolerated.

Summed scores and high-dose adenosine

Summed scores (mean $\pm$ SD)	Caffeine-free/ conventional adenosine	Caffeine-loaded/ high-dose adenosine	P value
SSS	12.8 ± 10.0	12.1 ± 10.0	0.6
SDS*	8.4 ± 4.8	8.1 ± 5.6	0.5

(*)SDS defines the magnitude of reversible perfusion abnormalities.

Conclusion: Caffeine reduces the extent and severity of adenosine-induced myocardial perfusion abnormalities and this effect can be prevented by increasing the adenosine dose without affecting test tolerance.

1234 Global and regional left ventricular function: a comparison between gated SPECT, 2D echocardiography and MSCT



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Background: Global and regional left ventricular (LV) function are important indicators of the cardiac status in patients with coronary artery disease (CAD). Therapy and prognosis are to a large extent dependent on LV function. MSCT has already earned its place as an imaging modality for non-invasive assessment of the coronary arteries, but since retrospective gating to the patient's ECG is performed, information on LV function can be derived.

Purpose: To evaluate the performance of MSCT for the assessment of global and regional LV function and LV volumes, and to compare the MSCT findings with measurements on gated SPECT and 2D echocardiography.

Methods: In 49 patients with known or suspected CAD, coronary angiography with MSCT imaging was performed, in addition to gated SPECT and 2D echocardiography. LV end-diastolic and LV end-systolic volumes and LV ejection fraction was analyzed with dedicated software (Mass, Medis, Leiden, The Netherlands for MSCT; gated SPECT by QGS, Cedars-Sinai Medical Center, Los Angeles, California), and by the biplane Simpson's rule for 2D echocardiography. Regional wall motion was evaluated according to a 17-segment model and a 3-point score system.

Results: Correlations were fairly good between gated SPECT and MSCT (LVEDV: $r = 0.65$; LVESV: $r = 0.63$; LVEF: $r = 0.60$), and excellent between 2D echocardiography and MSCT (LVEDV: $r = 0.92$; LVESV: $r = 0.93$; LVEF: $r = 0.80$). Agreement for regional wall motion was 95% ($\kappa = 0.66$) between gated SPECT and MSCT; Agreements for the individual gradings for the regional wall motion (normokinesia, hypokinesia, and a -or dyskinesia) were 98%, 60%, and 54%, respectively. Between 2D echocardiography and MSCT, agreement for regional wall motion was 96% ($\kappa = 0.73$). Agreements for the individual gradings for the regional wall motion were 98% (normokinesia), 71% (hypokinesia), and 62% (a -or dyskinesia).

Conclusions: Global and regional LV function and LV volumes can adequately be assessed with MSCT. Correlations with 2D echocardiography are stronger than with gated SPECT.

CARDIAC CT: ARTERIES, VEINS AND VALVES

1235 Noninvasive coronary computed tomographic angiography for patients with an intermediate Pre-Test probability for having coronary artery disease



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Background: Non-invasive coronary angiography by multislice spiral computed tomography (MSCT) is a promising method for the diagnosis of coronary artery disease (CAD). Previous studies comparing MSCT with invasive angiography have yielded high values for diagnostic accuracy in selected patients. However, the clinical role of this method has not been established for specific patient cohorts. Therefore, we sought to investigate in this prospective, blinded trial the diagnostic value of coronary MSCT angiography in patients with an intermediate pre-test probability for having CAD when compared with invasive angiography.

Methods: Consecutive patients with an intermediate pre-test probability for having CAD were asked to undergo coronary MSCT angiography before planned invasive angiography. CAD was defined as significant stenoses ($\geq 50\%$ lumen diameter reduction) in coronary arteries with a diameter of ≥ 2.0 mm. Assuming a CAD prevalence of 33%, the sample size calculation indicated that 240 patients had to be enrolled to obtain sensitivity, negative predictive and specificity values with their lower 95%-confidence levels of at least 90%, 90% and 66%, respectively. The primary endpoint analysis was assessed on an "intention-to-image" and on a per patient basis (without exclusion of non-evaluable patients or coronary segments).

Results: A total of 243 patients were enrolled, 129 and 114 patients were studied by 16- and 64-slice CT angiography, respectively. The overall sensitivity, negative predictive value and specificity for CAD detection by MSCT were 99% (95%-CI: 94-99%), 99% (95%-CI: 94-99%) and 75% (95%-CI: 66-81%), respectively. On a per-segment basis, the use of 64-slice CT was associated with significantly less non-evaluable segments (11.4 vs. 7.4%, $p < 0.01$) resulting in a higher specificity (88 vs. 92%, $p < 0.01$).

Conclusions: In patients with an intermediate pre-test probability for having CAD this large, prospective blinded trial demonstrates that noninvasive coronary CT angiography is a very sensitive method for CAD detection. Furthermore, this method allows ruling out CAD very reliably and safely. Finally, 64-slice CT is superior due to its improved spatial and temporal resolution when compared with 16-slice CT.

1236 Coronary artery stent geometry, in-stent contrast attenuation, and stent patency with 64-slice computed tomography



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Purpose: To prospectively assess stent geometry, in-stent attenuation, and stent patency with 64-slice CT in patients with various coronary artery stents. **MATERIALS AND METHODS:** Twenty-nine patients (mean age, 60years $\pm$ 11) with 50 stents underwent 64-slice CT and quantitative coronary angiography (QCA) at a mean interval of 8 $\pm$ 16 days after stent implantation. Mean in-stent luminal diameter, stent length, and reference vessel diameter proximal and distal to the stent were compared between CT, QCA, and with manufacturer values. In-stent attenuation was compared with values in the reference vessels and between the medium-smooth (B30f) and sharp (B46f) reconstruction kernel. Stent patency was qualitatively graded with CT and QCA on a 4-point scale.

Results: Mean in-stent luminal diameter was systematically underestimated with CT compared to QCA (1.60mm $\pm$ 0.39 vs 2.49mm $\pm$ 0.45; $P < .0001$) resulting in a modest correlation of QCA versus CT ($R = 0.49$, $P < .0001$). Stent length as given by the manufacturer was 18.2mm $\pm$ 6.2, correlating well with CT (18.5mm $\pm$ 5.7, $R = 0.95$, $P < .0001$) and QCA (17.4mm $\pm$ 5.6, $R = 0.87$, $P < .0001$). Proximal and distal reference vessel diameters were similar with CT and QCA ($P = 0.06$ and $P = 0.03$). B46f kernel images showed higher image noise ($P < .05$) and lower in-stent luminal CT attenuation values than images reconstructed with the B30f kernel ($P < .001$). In-stent luminal CT attenuation was higher than attenuation in proximal and distal reference vessels ($P < .001$). CT correctly identified 1 stent with $\geq 50\%$ stenosis and 2 stents with non-significant in-stent stenosis.

Conclusion: 64-slice CT allows evaluation of coronary artery stents with regard to in-stent attenuation but systematically underestimates in-stent luminal diameter compared to QCA.

1237 Relationship between non-invasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging



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Purpose: Multi-slice computed tomography (MSCT) and myocardial perfusion imaging (MPI) are different techniques in the evaluation of coronary artery disease (CAD); how these 2 techniques compare in patients with an intermediate likelihood of CAD is currently unknown. The purpose of the study was to perform a head-to-head comparison between MSCT and MPI in patients with an intermediate likelihood of coronary artery disease (CAD), and to compare non-invasive findings to invasive coronary angiography in a subset of patients.

Methods: 114 patients, mainly with intermediate likelihood of CAD, underwent both MSCT and MPI. MSCT studies were classified as having no CAD, non-obstructive ($< 50\%$ luminal narrowing) CAD or obstructive CAD. MPI examinations were classified as showing normal or abnormal (reversible and/or fixed defects). In a subset of 51 patients, invasive coronary angiography was performed.

Results: Based on the MSCT data, 41 (36%) patients were classified as having no CAD. A total of 33 (29%) patients showed non-obstructive CAD, whereas at least 1 significant ($\geq 50\%$ luminal narrowing) lesion was observed in the remaining 40 (35%) patients. Only 45% of patients with an abnormal MSCT had abnormal MPI; even in patients with obstructive CAD on MSCT, 50% still had a normal MPI. In the subset of patients undergoing invasive angiography, the agreement with MSCT was excellent (88%).

Conclusions: MPI and MSCT provide different and complementary information on CAD, namely detection of atherosclerosis versus detection of ischemia. As compared to invasive angiography, MSCT has a high accuracy for detecting CAD in patients with an intermediate likelihood of CAD.

1238 Preoperative Computed Tomography coronary angiography to detect significant coronary artery stenosis in patients referred for valve surgery



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Conventional coronary angiography (CCA) is recommended in patients scheduled for valve surgery. The diagnostic performance of the latest 64-slice Computed Tomography scanner to rule out or detect significant coronary lesions in this clinical relevant patient population is unknown.

During a 6-month period, 145 patients were prospectively identified from a consecutive patient population scheduled for valve surgery. After CCA patients were asked to undergo CT coronary angiography (CTCA). 48 patients were excluded: atrial fibrillation (n:26), impaired renal function (n=5), previous allergic reaction to

contrast (n= 4), hospitalization in peripheral hospital (n=4), no CCA (n=4), previous coronary bypass surgery (n=1) and percutaneous coronary intervention (n=4). Of the remaining 97 patients 27 denied informed consent. Thus, the study population comprised 70 patients (49 male, 21 female; mean age 63 ± 11 years. Aortic valve stenosis was seen in 31 patients, mitralic valve insufficiency in 25 and other valve pathology in 8. Six patients had redo valve surgery. Prevalence of significant lesions per patient was 25.7%. Mean scan-time was 12.8 ± 1.3 seconds. 71% of patients received β -blockers and 64% lorazepam resulting in a mean heart rate of 59.5 ± 7.5 b.p.m. All patients with a significant lesion were detected. Sensitivity, specificity, positive and negative predictive value of CTCA for the detection of significant stenoses on a per-patient, per-vessel and per-segment basis is depicted in the attached table.

Diagnostic Accuracy of CTCA

	Sensitivity	Specificity	PPV	NPV
Patient	100% (18/18)	92% (48/52)	82% (18/22)	100% (48/48)
Vessel	100% (26/26)	97% (246/254)	76% (26/34)	100% (246/246)
Segment	94% (34/36)	98% (949/967)	65% (34/52)	100% (949/951)

PPV: positive predictive value NPV: negative predictive value

The diagnostic accuracy of 64 slice CTCA for ruling out the presence of significant coronary lesions in patients undergoing valve surgery is excellent and allows CTCA implementation as a gatekeeper in these patients.

1239 Diagnosis of aortic valvular stenosis by multislice cardiac computed tomography

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Hypothesis: Because of improvement in spatial, temporal and contrast resolution, ECG-gated 16-slice Computerized Tomography (CT) could be useful in the examination of cardiac valvular anomalies. We evaluated the diagnostic accuracy of CT analysis for the identification and quantification of aortic valvular stenosis (AS) and compared it to echocardiography.

Methods: 107 consecutive patients (63 $\pm$ 13 years; 65 males) referred for coronary-CT (16x0.625 mm), before cardiac surgery, were evaluated for the presence of AS, using the standard cardiac scan protocol. Multiplane reformat was applied to systolic phases of the cardiac cycle, using both Maximal Intensity Projection and Minimal Intensity Projection on thick slices (>5 mm) to measure the aortic valve area (AVA). Mean heart rate was 71 ± 16 bpm. The echocardiographic examination was independently performed and the AVA was estimated using Doppler continuity equation.

Results: The CT analysis of the AVA was impossible in 4 patients because of noise, breath or motion artefacts. Optimal phase for the analysis was 20% of the R-R cycle in 67 patients. The mean CT AVA was 244 ± 133 mm². Among the 30 patients with AS, area on CT and echocardiography were closely related ($r = 0.87$, $p < 0.0001$); T-test revealed a bias of 7.4 mm² and a standard deviation of 16.5 mm². For the diagnosis of severe stenosis (< 100 mm²), sensitivity, specificity, negative and positive predictive values of the CT were 81%, 98%, 94% and 95% respectively, compared to echocardiography. For the CT AVA, intra-observer and inter-observer correlation coefficients were both 0.99.

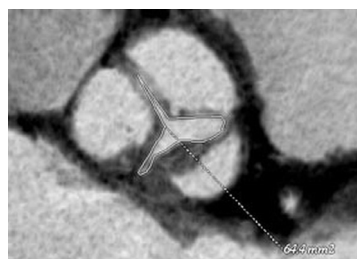


Fig. 1. Planimetry of aortic valve stenosis.

Conclusion: CT analysis of the aortic valve is feasible in most cases and allows for reliable diagnosis and quantification of aortic valvular stenosis.

1240 Noninvasive visualization of the cardiac venous system in coronary artery disease patients using 64-slice computed tomography

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Background Cardiac Resynchronization Therapy is an attractive treatment for highly symptomatic heart failure patients. Knowledge on the anatomy of the coro-

nary sinus (CS) and its tributaries could help identifying potential candidates for successful left ventricular lead implantation.

Aim To evaluate the value of 64-slice computed tomography (CT) to depict the cardiac venous anatomy in patients with coronary artery disease (CAD).

Methods The 64-slice cardiac CT data of 50 individuals (age 59 ± 11 years, 76% men) were evaluated. Subjects were divided in 3 groups: 15 controls (without CAD), 18 patients with significant CAD and 17 CAD patients with a history of myocardial infarction. The presence of the following CS tributaries was evaluated: posterior interventricular vein (PIV), posterior vein of the left ventricle (PVLV) and left marginal vein (LMV). Diameters of the proximal part of these veins and in-between distances were measured.

Results Anatomic variations are depicted in Figure 1. The CS diameter was 11.4 ± 3.5 mm in the antero-posterior direction and 11.5 ± 3.2 mm in the supero-inferior direction. Diameters of the PIV, PVLV and LMV were 5.2 ± 1.3 , 3.8 ± 1.1 and 3.5 ± 1 mm respectively. Mean distance from the PIV to the PVLV was 35 ± 21 mm and mean distance from the PVLV to LMV was 38 ± 16 mm.

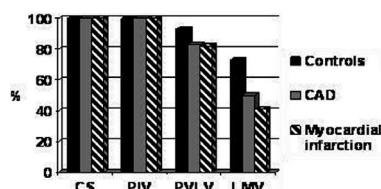


Figure 1: Coronary sinus and tributaries

Conclusion The anatomy of the coronary sinus and its tributaries can be evaluated with 64-slice CT. There is considerable variation in cardiac venous anatomy. Patients with a history of myocardial infarction were less likely to have a left marginal vein thus limiting optimal left ventricular lead positioning in case of CRT implantation.

MANAGEMENT STRATEGIES IN NON-STEMI – TO INTERVENE OR NOT

1262 Effects of revascularization within 14 days of hospital admission due to acute coronary syndrome on 1-year mortality in patients with previous coronary artery by-pass graft surgery

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Background: Current recommendations from European and American guidelines for patients with the acute coronary syndrome (ACS), includes early revascularization, in addition to pharmacological therapy. The evidence is derived from randomized studies, in which patients with a previous coronary artery bypass graft surgery (CABG) most often were excluded. Furthermore, coronary interventions of vein grafts are associated with decreased success rates, increased complications and higher restenosis rates. Thus, available evidence is insufficient to support a similar strategy also for this patient group.

Purpose: To determine whether revascularization within 14 days reduces 1-year mortality in patients admitted for ACS.

Methods, setting and patients: We studied a cohort of 8766 patients from a national registry, all with a previous CABG, and admitted to coronary care units in Sweden between 1991 and 2003, with a discharge diagnosis of non-ST elevation myocardial infarction or unstable angina pectoris. Patients <80 years old and alive at day 14 were included. We obtained 1-year mortality data from the Swedish National Cause of Death Registry. Relative risk of 1-year mortality in patients undergoing revascularization within 14 days (n=2644) of admission compared to those who did not (n=6122) was calculated by using Cox regression analyses, with multiple adjustments for baseline differences and by using propensity scores for the likelihood of early revascularization. Main outcome measure was 1-year mortality.

Results: At 1-year, unadjusted mortality was 6.0% in the revascularized group and 15.8% in the conservatively treated group. After multiple regression analyses revascularization was associated with a reduction of 1-year mortality (relative risk, 0.69; 95% CI, 0.56-0.85; $p = 0.001$).

Conclusion: Despite expected higher procedural complication rates in patients with a previous CABG, revascularization within 14 days of admission in patients with ACS was associated with a marked reduction in 1-year mortality. An invasive approach seems to be favorable also in this subset of patients.

1263 New ESC/ACC definition of myocardial infarction and long-term mortality in patients undergoing early invasive treatment



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Background: Data about the prognostic impact of new European Society of Cardiology/American College of Cardiology (ESC/ACC) guidelines for definition of myocardial infarction (MI) on clinical outcome are inconsistent. Our study evaluated the long-term mortality in patients with acute non-ST segment elevation myocardial infarction (NSTEMI) according to current ESC/ACC guidelines that are not meeting World Health Organization (WHO) criteria for MI.

Methods: This historical cohort study included 1,024 consecutive patients with acute coronary syndrome classified into unstable angina (UA), "classic NSTEMI" according to WHO definition and "new NSTEMI" according to new ESC/ACC definition but not meeting WHO criteria for MI. All patients underwent coronary angiography and, if appropriate, subsequent stenting of the culprit lesion as the primary revascularization strategy within 24 hours of admission. The primary endpoint was all-cause mortality during long-term follow-up of up to 48 months.

Results: During follow-up (median 16 months, interquartile range 6 to 29 month) 67 deaths and 42 non-fatal myocardial infarctions occurred. Kaplan-Meier survival analysis showed cumulative four-year mortality rates of 8.5% in patients with UA, 9.1% in patients with "classic NSTEMI", and 26.7% in patients with "new NSTEMI" not meeting WHO criteria for MI ($p<0.001$). Cox regression analysis confirmed "new NSTEMI" as predictor of mortality (hazard ratio, 3.067 [95% CI, 1.894 to 4.975]; $p<0.001$) whereas "classic NSTEMI" failed to demonstrate a predictive value ($p=0.814$).

Conclusion: Current ESC/ACC definitions of MI have a major impact on long-term mortality in patients with NSTEMI that are not meeting WHO criteria for MI.

1264 Contraindications to cardiac catheterization in Non-ST-elevation Acute Coronary Syndromes: Insights from the CRUSADE national quality improvement initiative



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Purpose: The European Society of Cardiology and American College of Cardiology/American Heart Association guidelines recommend invasive management of non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) for pts with high-risk features. Although contraindications are not specified in the guidelines, many pts do not receive invasive care due to a range of contraindications.

Methods: We describe baseline characteristics and outcomes for a range of investigator-listed contraindications for cardiac catheterization in NSTEMI ACS pts (positive cardiac markers and/or ischemic ST-segment changes) admitted to 282 U.S. hospitals with full revascularization services. Only one contraindication was listed per pt.

Results: Among 62,943 patients treated from February 2003 to September 2005, the majority 47,711 (75.8%) received cardiac catheterization. Reasons for contraindication to catheterization were listed in another 9,861 (15.7%) patients. The clinical features and outcomes are shown by specific contraindication (Table 1). The most common listed reasons for contraindication to catheterization were medical comorbidities, patient refusal, and not a candidate for revascularization. In-hospital mortality was highest for patients with medical comorbidities and those with do not resuscitate status.

Conclusions: Reasons for non-use of invasive procedures appear to be broad, yet insights from this analysis may help to identify "ideal" populations of patients for determining quality metrics for the use of invasive management strategies.

Conclusions: Reasons for non-use of invasive procedures appear to be broad, yet insights from this analysis may help to identify "ideal" populations of patients for determining quality metrics for the use of invasive management strategies.

Abstract 1264 – Table 1. Characteristics of Contraindications

Variable	Medical Comorbidities	Patient Refusal	Not a Revascularization Candidate	Do Not Resuscitate Status	Other	Advanced Age	Active Bleeding
N (%)	2003	1785	1640	1556	1350	1100	427
Age, yrs, median (25th, 75th percentile)	77 (68, 83)	81 (71, 86)	78 (69, 85)	85 (80, 90)	70 (58, 79)	90 (87, 92)	77 (70, 84)
Female	44%	56%	46%	61%	61%	63%	44%
Prior MI	38.5%	43.7%	51.3%	33.8%	40.9%	32.4%	36.3%
Prior CABG	27.1%	22.5%	35.7%	17.4%	24.8%	12.6%	28.3%
Renal insufficiency	42.1%	26.1%	34.7%	28.8%	20.8%	21.9%	30.0%
Signs of CHF on presentation	51.6%	43.5%	45.1%	54.6%	32.9%	46.6%	38.6%
In-hospital mortality	15.5%	4.2%	6.2%	24.6%	5.7%	5.1%	10.4%

MI indicates myocardial infarction; CABG, coronary artery bypass grafting; CHF, congestive heart failure.

1265 Compliance with contemporary guidelines for non-ST-elevation acute coronary syndromes: influence on outcome and interaction with risk stratification



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Background: Several risk markers have been proposed to guide clinical decision making, predict prognosis, and direct appropriate management strategies for patients (pts) with non-ST-elevation acute coronary syndromes (NSTEMI-ACS). The purpose of this study is to evaluate the impact of compliance with treatment guidelines on outcome of unselected NSTEMI-ACS pts, and whether current risk stratification markers interact with the effect of guideline compliance on pt outcomes.

Methods: Pts with NSTEMI-ACS enrolled in a nationwide prospective registry since 2002 were eligible. Compliance with guidelines was assessed with a 6-point scale based on the aggregate use of aspirin, clopidogrel, heparin, beta-blockers, ACE inhibitors, and statins. Study endpoint is in-hospital all-cause mortality.

Results: Study population consisted of 7577 pts, in whom average guideline compliance score was 4.6 ± 1.2 points. Compliance was better for aspirin (96%) and heparin (97%), than for statins (81%), beta-blockers (72%), ACE inhibitors (69%) or clopidogrel (49%). Overall in-hospital mortality was 2.5%. Compliance score was significantly lower among pts who died (3.9 ± 1.2 vs 4.7 ± 1.1 points; $p<0.001$), and independently predicted the risk for in-hospital death (adjusted odds ratio for each point increase = 0.68; 95% CI, 0.60-0.78; $p<0.001$). The effect of the guideline compliance score on the study endpoint was not significantly influenced by any of the following (p -ns for all interaction tests): gender, diabetes, prior history of multiple territory atherothrombotic disease, TIMI risk score, Killip class on admission, troponin elevation, and in-hospital revascularization. A compliance score of 6 independently predicted in-hospital mortality (adjusted odds ratio compared to score $\leq 6 = 0.30$; 95% CI, 0.17-0.56; $p<0.001$). Pts who received a GP 2b/3a inhibitor in addition to all other 6 therapies did not derive significant additional prognostic benefit when compared to those receiving the 6 therapies only (odds ratio for in-hospital death = 0.30; 95% CI, 0.08-1.49).

Conclusions: Compliance with recommended guidelines for the management of pts with NSTEMI-ACS results in lower hospital mortality, independently of risk stratification markers.

1266 Myocardial revascularization reverses the adverse outcome in non-ST-elevation acute coronary syndromes complicated by heart failure

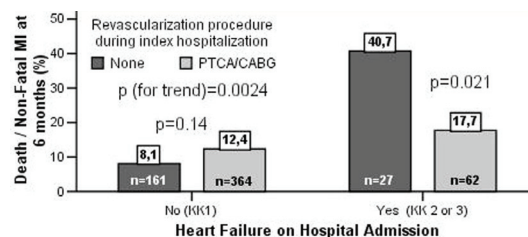


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Background: Heart failure has been shown to hold a strong negative prognostic impact in patients (pts) with non-ST-elevation acute coronary syndromes (NSTEMI-ACS). The purpose of this study is to establish the prognostic impact of myocardial revascularization in NSTEMI-ACS pts presenting heart failure on admission.

Methods: We retrospectively studied 648 pts (mean age 65 ± 10.6 years, 81.1% male) admitted with a NSTEMI-ACS and not presenting cardiogenic shock. Heart failure (HF) was defined as a Killip class 2 or 3 on admission.

Results: Thirty four pts (5.2%) were excluded from this analysis on the basis of a normal coronary angiogram. HF was present in 89 (14.5%) patients. During the index hospitalization, 426 patients received myocardial revascularization therapy (Rev), through percutaneous coronary intervention (PCI) in 321, and coronary surgery (CABG) in 105. By 6 months follow up, 38 (6.2%) patients had died, and 57 (9.3%) had experienced a non-fatal (re)MI. HF was an independent predictor



of both 6-month mortality (adjusted HR 3.33; 95% CI, 1.73-6.44; $p < 0.001$), and the 6-month rate of death/(re)MI (adjusted HR 1.88; 95% CI, 1.12-3.09; $p = 0.012$). Rev significantly influenced the prognosis of pts presenting HF (adjusted HR 0.36; 95% CI, 0.15-0.84; $p = 0.019$), but not of those without HF (adjusted HR 1.4; 95% CI, 0.75-2.7). We detected a significant interaction between Rev and the prognostic impact of HF at admission ($p = 0.021$ for the interaction test).

Conclusion: In pts with NSTEMI-ACS, clinical manifestations of HF constitute a strong predictor of adverse intermediate-term outcome that may be significantly modified by myocardial revascularization.

POSTER SESSION 2

MODERATED POSTERS

HEART FAILURE, LEFT VENTRICULAR FUNCTION, VALVULAR DISEASE AND PULMONARY CIRCULATION

P1287 The impact of right ventricular involvement on long term mortality following acute inferior ST elevation myocardial infarction



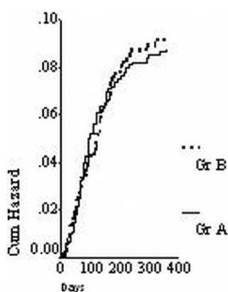
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Background: It is well known that right ventricular (RV) myocardial involvement carries an increased risk of early fatal on non-fatal complications in patients who hospitalized due to an acute inferior ST elevation myocardial infarction. However, there is scant data concerning the long term impact of RV myocardial involvement in this setting.

Methods: The study cohort comprised 1208 consecutive pts (mean age=64.5±10.3 yrs, 79.2% males) who survived to hospital discharge after hospitalization for acute inferior ST elevation myocardial infarction. The cohort was divided into two groups according to the presence (Group A, 459 pts) or no (Group B, 749 pts) of RV involvement, defined as ST-segment elevation ≥ 1 mm in V4R, in admission ECG. Cardiac death by the first year was the prespecified primary study endpoint.

Results: There were not significant differences in baseline characteristics, medical history and medical therapy during the study period between the 2 groups. By 1-year the incidence of the primary endpoint was similar in both groups (8.7% and 8.4% for Groups A and B, respectively; $RR=1.03$, 95%CI=0.69-1.53; $p=0.87$) (figure).



Conclusions: In patients who survived to hospital discharge following hospitalization for acute inferior ST elevation myocardial infarction, right ventricular involvement does not portend any increased risk for long term mortality.

P1288 Right ventricular reverse remodelling in patients with chronic thromboembolic pulmonary hypertension undergoing pulmonary endarterectomy



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Aim: Rapid hemodynamic improvement and satisfactory long-term clinical outcome have been reported in patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH) undergoing Pulmonary Endarterectomy (PEA). However, the degree and the time course of recovery of Right Ventricular (RV) function after PEA have not yet been fully clarified. The present study was set to evaluate the long-term reverse remodelling of the right ventricle with the pre-specified aims of differentiating short-term and long-term changes induced by PEA and of clarifying whether severe RV dysfunction at baseline impairs recovery of RV function after surgery.

Patients and methods. We studied 128 patients who underwent PEA between April 1994 and May 2005. A complete echocardiographic examination including a thorough evaluation of RV geometry and function was performed at baseline and serially during follow-up (pre-discharge, 3 and 36 months).

Results: The RV End Diastolic Diameter (RVEDD), RV Fractional Area Change (RVFAC), Tricuspid Annular Plane Systolic Excursion (TAPSE), % of significant Tricuspid Regurgitation (TR) and % of abnormal flow patterns in Superior Vena Cava (SVC) during follow-up are shown in table below (* = $p < 0.01$ as compared to previous control).

Table of results

	Baseline	Pre-discharge	3 months	36 months
RVEDD (mm)	38.7±7.6	31.5±6.4*	29.4±5.8	28.9±5.6
RVFAC (%)	22.6±10.0	30.2±11.7*	31.6±11.5*	36.4±7.6*
TAPSE (mm)	14.8±4.6	11.4±2.5*	13.8±3.4*	15.3±3.0
TR ++/+++ (%)	69.4	24.1*	14.1	18.6
Abnormal SVC flow pattern (%)	30*	22	13*	4

RVEDD= Right Ventricular End Diastolic Volume; RVFAC= Right Ventricular Fractional Area Change; TAPSE= Tricuspid Annular Plane Excursion; TR= Tricuspid Regurgitation; SVC= Superior Vena Cava

Importantly, RV function improved after successful PEA regardless of the degree of RV dysfunction at baseline.

Conclusions: Marked improvements in RV geometry and function can be obtained immediately after PEA in patients with CTEPH. Full recovery of RV geometry occurs rapidly after surgery whereas recovery of RV function progresses over a longer period. Importantly, RV function improves after successful surgery whatever the degree of RV dysfunction at baseline.

P1289 A decrease in plasma N-terminal pro-B-type natriuretic peptide level after mitral valve repair is associated with improved left ventricular function and improved functional status



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Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been demonstrated to have diagnostic and prognostic value in patients with heart failure and coronary artery disease. This prospective study assessed whether a reduction in NT-proBNP level after mitral valve repair was associated with improved left ventricular function and functional status.

Methods: The study population consisted of 22 patients (mean age 62.8 ± 14.2 years, 68% male) undergoing mitral valve repair. Serial NT-proBNP measurement, transthoracic echocardiography and NYHA class assessment was performed prior to surgery and 6 months after. The change in NT-proBNP level and the % change of left atrial dimension, left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD) and fractional shortening (FS) was calculated. Patients were divided into three groups according to the change in NT-proBNP (see Table).

Results: All patients underwent successful mitral valve repair; no patients died during follow-up. The Table summarizes the association between changes in NT-proBNP and changes in echocardiography and functional status during the 6-month follow-up period after mitral valve repair. Higher decreases in NT-proBNP were associated with larger reductions in left atrial dimension ($r=0.67$, $p=0.001$), LVESD ($r=0.71$, $p<0.001$) and LVEDD ($r=0.51$, $p=0.016$). Higher decreases in NT-proBNP were also associated with improved left ventricular FS ($r=-0.74$, $p<0.001$). Finally, the largest improvement in functional status was noted in patients with decreasing NT-proBNP levels ($p=0.015$).

NT-proBNP change and follow-up results

	Decrease in NT-proBNP level >100 pg/ml (n=9)	Similar NT-proBNP level, changes between -100 and 100 pg/ml (n=6)	Increase in NT-proBNP level of >100 pg/ml (n=7)	P-value
Change in NYHA class (grade)	-2.1 ± 1.1	-0.8 ± 1.0	-0.7 ± 0.8	0.015
Change in mitral regurgitation (grade)	-3.7 ± 0.7	-3.7 ± 0.5	-3.1 ± 0.9	0.32
Change in left atrial dimension (%)	-19.1 ± 4.9	-4.2 ± 10.4	+1.2 ± 16.6	0.001
Change in LVESD (%)	-21.6 ± 9.4	-0.1 ± 19.3	+14.0 ± 21.3	<0.001
Change in LVEDD (%)	-10.7 ± 9.1	-3.6 ± 13.0	+5.2 ± 10.1	0.016
Change in FS (%)	+47.0 ± 31.4	-1.5 ± 40.3	-24.7 ± 32.5	<0.001

Values are expressed in mean ± SD

Conclusion: During a 6-month follow-up period after mitral valve repair, higher decreases in NT-proBNP level were associated with larger reductions in left atrial and ventricular dimensions, improved left ventricular fractional shortening and a better functional outcome.

P1290 NT-proBNP and aortic valve replacement



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Background: Plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) reflect left ventricular wall stress and are elevated in patients

with aortic stenosis (AS) closely linked to disease severity and clinical symptoms. This prospective study sought to evaluate the association of NT-proBNP-levels with clinical symptoms and echocardiographic measures prior to and post surgical aortic valve replacement (AVR).

Methods: In 44 patients with severe AS (Mean $\pm$ SD; age, 67 ± 10 years; mean gradient, 55 ± 21 mm Hg; EF $56 \pm 16\%$), NT-proBNP was correlated to clinical and echocardiographic findings from 1d prior to 1d, 3d, 8d and 3 month post AVR.

Results: Before AVR, all patients expressed markedly elevated NT-proBNP (Median $\pm$ SEM; 1021 ± 589 pg/ml). Postoperatively, there was further and significant increase in NT-proBNP in all patients with a maximum after 72 hours (3388 ± 1035 pg/ml; $p < 0.001$). After three months, NT-proBNP was still above physiological average but significantly declined when compared to corresponding preoperative levels (461 ± 137 pg/ml; $p < 0.001$). A significant relationship was observed between plasma NT-proBNP and transaortic pressure gradient (PG mean) preoperatively and 3 month after AVR ($p < 0.001$). Concomitantly, with declining NT-proBNP, NYHA class was improved from 2.4 to 1.4 ($p < 0.01$).

Conclusions: NT-proBNP is elevated in patients with aortic stenosis and increased significantly in the early period after AVR and decreases significantly 3 months after AVR. Decreasing of NT-proBNP level was closely linked to an improvement in clinical symptoms and reduction of transaortic pressure gradient. NT-proBNP analysis provide a surrogate method for comprehensive assessment of transaortic valve gradient and clinical symptoms after AVR.

P1291

mRNA expression and protein levels for granulocyte colony stimulating factor are increased in left ventricular myocardium of patients with heart failure



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Background: Granulocyte colony stimulating factor (G-CSF) is a cytokine that stimulates the survival, proliferation, and differentiation of primitive bone marrow stem cells. In mice with acute myocardial infarction, G-CSF-mediated translocation of bone marrow stem cells was shown to result in significant myocardial tissue regeneration. G-CSF also plays a role in the proliferation, differentiation and survival of primitive progenitor cells present in the myocardium since birth. In this study, we tested the hypothesis that mRNA and protein expression of G-CSF is increased in the failing left ventricular (LV) myocardium as a possible response to ongoing injury, degeneration and loss of cardiomyocytes.

Methods: mRNA and protein expression of G-CSF were measured in LV myocardium of explanted failed human hearts due to ischemic cardiomyopathy (ICM, n=6), idiopathic dilated cardiomyopathy (IDC, n=6), and normal donor human hearts which were deemed not suitable for transplantation (NL-Human, n=6). Tissue samples from all three groups were used to extract RNA. mRNA gene expression for G-CSF was measured using reverse transcriptase polymerase chain reaction (RT-PCR). Protein expression was determined in SDS-extract of LV tissue homogenate using specific antibodies. Bands obtained after RT-PCR and Western blots were quantified in densitometric units (du).

Results: Data are shown in the table. mRNA expression for G-CSF was significantly increased in LV myocardium of patients with ICM and IDC compared to LV myocardium from NL-Human donor hearts. Similarly, protein expression of G-CSF was significantly increased in LV myocardium of patients with ICM and IDC compared to LV myocardium from NL-Human donor hearts.

mRNA and Protein Expression of G-CSF

	NL-Human	ICM	IDC
G-CSF mRNA (du)	1235 $\pm$ 34	2140 $\pm$ 43*	2243 $\pm$ 115*
G-CSF Protein (du)	36 $\pm$ 2	48 $\pm$ 3*	63 $\pm$ 2*

* $p < 0.05$ vs. NL-Human

Conclusions: The results of this study indicate that in LV myocardium of explanted failed human hearts, regardless of etiology, mRNA and protein expression of G-CSF is upregulated. This finding may represent an intrinsic adaptation aimed at stimulating the proliferation, differentiation and survival of resident myocardial progenitor cells into cardiomyocytes in an attempt to compensate for the ongoing loss of these essential cardiac functional units.

P1292

Pharmacogenetic interactions between Arg389Gly beta-1 adrenoceptor polymorphism and beta-blocker treatment in the patients with heart failure



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Background: Beta-blockers improve survival in the patients with heart failure. There are possible pharmacogenetic interactions in the treatment with beta-blockers, since beta-adrenergic receptors are highly polymorphic. The beta-1 Arg389 polymorphism is associated with a 3- fold higher agonist-promoted activity compared to the beta-1 Gly389 allele, as a result of a greater coupling to the Gs protein. In this study was to assess whether patients with different beta-1 Arg389Gly genotypes require different beta-blocker doses to achieve the same

degree of beta-blockade. With this aim, we compared peak exercise heart rate (HR), a widely accepted index of cardiac response to sympathetic drive, and beta-blocker dose amongst a large group of patients with heart failure (HF).

Methods: Genotyping was performed in 316 patients with HF due to idiopathic (51%) or ischemic (49%) dilated cardiomyopathy, LVEF $31 \pm 11\%$, peak VO2 15.5 ± 5.09 ml/kg/min, NYHA class 2.33 ± 0.33 . 95% of the patients were on ace-inhibitors and 85% on beta-blockers (carvedilol).

Results: The degree of beta-blockade was equal among all the different subgroups, since resting and peak exercise HR were evenly distributed among all the subgroups. Resting HR was 70 ± 14 beats/min for Arg389Arg patients (n=148), 68 ± 17 for Gly389Gly (n=27), 70 ± 13 for Arg389Arg+Arg389Gly (n=289) carriers (p= ns). Peak exercise HR was 124 ± 24 beats/min for Arg389Arg patients, 118 ± 39 for Gly389Gly, 123 ± 24 for Arg389Arg+Arg389Gly carriers (p= ns for comparisons between groups). Carvedilol dose was 22 ± 17.9 mg/die for Arg389Arg patients, 14.6 ± 14.6 for Gly389Gly, 23.8 ± 19.6 for Arg389Arg+Arg389Gly carriers (p=0.05 for Arg389Arg vs Gly389Gly and p=0.02 for Arg389Arg+Arg389Gly vs Gly389Gly).

Conclusions: Arg389Arg homozygous and heterozygous carriers, characterized by increased response towards sympathetic drive, need and receive higher doses of beta-blocker in order to achieve the same degree of beta-blockade.

P1293

Telomere length of circulating leukocytes is decreased in patients with chronic heart failure



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Background - Telomere length is considered to be a marker of biological aging. Since some of the mechanisms associated with telomere shortening also appear to play a role in chronic heart failure (CHF) we studied telomere length in patients with this condition.

Methods - DNA was extracted from leukocytes of 620 patients (aged 40-80 years) with CHF New York Heart Association (NYHA) functional class II-IV and an ejection fraction of 0.40 or less. Mean telomere length was determined by a quantitative polymerase-chain-reaction-based method and was compared to 183 age and gender matched healthy controls.

Results - The median telomere length was 0.64 (interquartile range, 0.47 to 0.88) in CHF patients compared to 1.05 (interquartile range, 0.86 to 1.29) in controls ($P < 0.001$). Telomere length in CHF patients was related to severity of disease (median value [interquartile range] of patients with NYHA II, III and IV was 0.67 [0.48-0.92], 0.63 [0.46-0.86] and 0.55 [0.46-0.75], respectively; P for trend < 0.05). Telomeres were shorter in patients with ischemic, compared to non-ischemic etiology of CHF. Patients with none, one (coronary, cerebral, or peripheral vascular disease), two (any combination of the previous) or three atherosclerotic manifestation had a median (interquartile range) telomere length of 0.72 (0.51-1.01), 0.65 (0.48-0.87), 0.48 (0.39-0.72), and 0.43 (0.27-0.67), respectively (P for trend < 0.001).

Conclusions - Telomere length is shorter in patients with CHF compared to age- and sex-matched controls, and relates to the severity of disease. In addition, telomere length was incrementally shorter according to the presence and extent of atherosclerotic disease manifestations.

P1294

Long-term therapy with non-excitatory cardiac contractility modulation electrical signals normalizes expression of maladaptive cardiac genes in patients with chronic heart failure



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Background: Heart failure (HF) is associated with maladaptive up-regulation of fetal genes and down-regulation of sarcoplasmic reticulum (SR) calcium cycling genes. Therapy with non-excitatory cardiac contractility modulation (CCM) electrical signals delivered to LV muscle during the absolute refractory period improves LV systolic function in patients with HF. We examined the effects of 3 months CCM therapy on mRNA expression of cardiac fetal and SR genes in 7 patients with advanced HF.

Methods: Right sided endomyocardial biopsies were obtained at baseline, prior to activating CCM therapy, and at 3 and 6 months thereafter. CCM therapy was delivered in random order of ON for 3 months and OFF for 3 months. mRNA expression was performed in a blinded fashion as to the ON/OFF order of therapy. Expression of the housekeeping gene GAPDH, the fetal A-type (ANP) and B-type (BNP) natriuretic peptides and α -myosin heavy chain (MHC) genes, and the SR genes SERCA-2a, phospholamban (PLB) and ryanodine receptor (RyR) was measured using RT-PCR and bands quantified in densitometric units (du). The percent change in du between baseline and the ON and OFF 3 months phases was calculated.

Results: The 3 months therapy OFF phase was associated with increased expression of ANP and BNP and decreased expression of α -MHC, SERCA-2a, PLB and RyR (Table). In contrast, the 3 months ON therapy phase resulted in

decreased expression of ANP and BNP and increased expression of α -MHC, SERCA-2a, PLB and RYR (Table). GAPDH was unchanged with ON/OFF phases.

mRNA Expression (% Change from Baseline)

	OFF Phase	ON Phase	P-Value
GAPDH	0.22 $\pm$ 1.1	0.64 $\pm$ 1.1	0.816
ANP	83 $\pm$ 20	-55 $\pm$ 6	0.001
BNP	94 $\pm$ 25	-53 $\pm$ 7	0.003
α -MHC	-28 $\pm$ 6	68 $\pm$ 13	0.0001
SERCA-2a	-26 $\pm$ 8	85 $\pm$ 32	0.022
PLB	-5 $\pm$ 14	91 $\pm$ 31	0.013
RYR	-19 $\pm$ 4	39 $\pm$ 6	0.0001

Conclusions: In HF patients, CCM therapy reverses the cardiac maladaptive fetal gene program and normalizes expression of key SR calcium cycling genes. These observations are consistent with improvement in LV systolic function in HF patients following long-term CCM therapy.

VASOVAPAL SYNCOPE

P1295 Effect of music listening during head up tilt testing in neurocardiogenic syncope



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Purpose: The purpose of this study was to examine the effects of music on the outcome of head-up tilt tests (HUT) in patients (pts) with neurocardiogenic syncope (NCS).

Methods: Thirty pts with a clinical history highly suggestive of NCS and a positive HUT with clonidine challenge were studied. They all repeated the HUT two days after. Fifteen pts repeated the test while listening to relaxing music via headphones. Blood samples for the measurement of epinephrine, norepinephrine, prolactin and cortisol levels in the plasma were taken during both tests at baseline (1), peak-syncope or end of the test (2) and 10 min after the end of the test (3). **Results:** Ten (66.6%) from the music group and 3 pts (20%) from the group without music had a negative second HUT ($p < 0.05$). Epinephrine, norepinephrine, prolactin and cortisol levels during the negative HUT, with music, were compared to corresponding levels during the first positive HUT (Table). Music normalized the sympathoadrenal imbalance noticed during positive head-up tilt-tests. This was expressed through the increase in norepinephrine during negative HUTs while music listening. In addition, cortisol and prolactin which showed an approximate two fold increase during positive HUTs did not rise significantly when tests with music listening became negative.

Results

	1 st positive HUT (N=15)	2 nd negative HUT with music (N=10)
(1) Epinephrine (pg/ml)	14.0 $\pm$ 14.9	15.5 $\pm$ 15.7
(2) Epinephrine (pg/ml)	33.7 $\pm$ 16.3*	29.1 $\pm$ 13.0*
(3) Epinephrine (pg/ml)	20.1 $\pm$ 13.9	18.6 $\pm$ 14.4
(1) Norepinephrine (ng/ml)	2.2 $\pm$ 2.5	1.1 $\pm$ 0.8
(2) Norepinephrine (ng/ml)	1.5 $\pm$ 2.5	5.1 $\pm$ 3.4*
(3) Norepinephrine (ng/ml)	1.6 $\pm$ 2.5	2.6 $\pm$ 3.1
(1) Cortisol (pg/ml)	4897 $\pm$ 2912	3498 $\pm$ 1650
(2) Cortisol (pg/ml)	9227 $\pm$ 3377*	5543 $\pm$ 3354
(3) Cortisol (pg/ml)	5703 $\pm$ 3162	3682 $\pm$ 1486
(1) Prolactin (μ U/ml)	150 $\pm$ 131	131 $\pm$ 75
(2) Prolactin (μ U/ml)	300 $\pm$ 242*	193 $\pm$ 110
(3) Prolactin (μ U/ml)	228 $\pm$ 200	164 $\pm$ 86

Results are expressed as mean $\pm$ SD and statistical analysis was performed with ANOVA for repeated measurements. * $p < 0.05$ compared to baseline (1).

Conclusion: Music seems to modify the neuroendocrine profile related to NCS and it may also alter the response to tilt-testing.

P1296 The influence of respiratory instability during presyncope on cerebrovascular and cardiovascular dynamics



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Purpose: Cerebral autoregulation (CA) has been reported as altered or preserved before the onset of syncope, but the role of end-tidal carbon dioxide (CO₂-et) and, thus, the effect of breathing pattern on cardio- and cerebrovascular haemodynamics has not been fully clarified. We examined the effect of respiratory changes on cerebrovascular regulation, as a possible factor inducing syncope.

Methods: Right mid-cerebral artery blood flow velocity (MCAV, transcranial Doppler), continuous noninvasive blood pressure (BP), heart rate, CO₂-et, tidal volume, minute ventilation and breathing frequency (inductance plethysmography) were monitored during 45°, 60° tilting. Thirty-eight subjects developing neurogenic syncope (SYNC), were compared with 61 age-matched subjects with

negative tilt (C). Respiratory, cardiovascular and cerebrovascular variability indices (standard deviation and coefficient of variation), static CA (cerebrovascular resistance (CVR) = estimated mean cerebral BP/mean MCAV, absolute (CVR-abs) and corrected for CO₂-et at 40 mmHg, (CVR-40mmHg)) and dynamic CA (transfer function phase analysis), were obtained during supine rest, early (first 5 minutes) tilting, presyncope1 and presyncope2 (first and second half of 4 minutes preceding syncope in SYNC, and equivalent time in C).

Results: Tilting induced a larger BP drop ($p < 0.001$) in SYNC during presyncope1 and presyncope 2. CO₂-et decreased with tilting in both SYNC and C; the reduction became larger in SYNC during presyncope2 (SYNC: 27.8 $\pm$ 0.7 mmHg vs C: 32.3 $\pm$ 0.6 mmHg, $p < 0.001$), indicating higher degree of hyperventilation. CVR-abs decreased in C from supine till presyncope2 ($p < 0.05$), whereas it remained unchanged in SYNC, suggesting impaired static CA. Conversely, CVR-40mmHg decreased ($p < 0.05$) to the same extent in SYNC and C. Similarly, dynamic CA showed no differences between SYNC and C. Variability indices of tidal volume, minute ventilation and breathing frequency increased ($p < 0.05$ or better) from early tilting to presyncope2 in SYNC but not in C, and were significantly correlated ($p < 0.05$) to increases in MCAV variability indices.

Conclusions: When MCAV data were corrected for CO₂-et, CA resulted preserved and even prominent in SYNC. During presyncope, the increase in respiratory instability, by effect of the resulting hypocapnia, may impair CA, thus facilitating the onset of syncope. These results suggest that regularisation of breathing may thus be beneficial in the management of neuromediate syncope.

P1297 Involuntary upper limbs spasm is related to more pronounced cerebral hypoxia during vasovagal syncope



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Cerebral hypoperfusion and hypoxia resulting in syncope may lead to involuntary limbs movements and eyes deviations. Involuntary limbs movements could be divided into myoclonic jerks and tonic upper limbs spasm. Near infrared spectroscopy (NIRS) is a method of monitoring cerebral oxygenation. The duration of the decrease in cerebral oxygenation measured by NIRS before syncope could be used as a parameter of the severity of cerebral hypoperfusion and hypoxia. We aimed to establish the relation of involuntary movements to decrease in cerebral oxygenation measured by the NIRS.

The study group consisted of 40 pts (19 M, 21 F) aged 35.0 $\pm$ 17.0 years with the history of vasovagal syncope and the positive diagnostic tilt testing. The group was very symptomatic and the mean syncopal spells was 66 $\pm$ 83, range 6-300, median 30. The tilt testing was performed according to Westminster protocol with NTG provocation when necessary. During tilt testing hemodynamic parameters and cerebral oxygenation with the NIRS technique were monitored.

Nitroglycerine provocation was necessary in 4 pts. 8 pts had mixed type, 19 pts had cardioinhibitory type and 13 pts had vasodepressor type of the provoked vasovagal reaction. During tilt test induced syncope involuntary movements were observed in 31 pts: 18 pts had eye deviations, 17 pts had myoclonic jerks, 17 pts had tonic upper limbs spasm. 17 pts had two of the above considered movements, 2 pts had all three kinds of movements. After dividing pts into different groups according to presence or absence of each kind of involuntary movement it was shown that time of decreased cerebral oxygenation was longer in pts with tonic upper limbs spasm than in pts without tonic upper limbs spasm 292.3 $\pm$ 230.1s vs 161.1 $\pm$ 82.9s $p < 0.05$. Comparing the demographic data the patients with myoclonic jerks were significantly frequent women than men 82 vs 18% and without myoclonic jerks men than women 70 vs 30% $p < 0.05$. Logistic regression analysis revealed that younger age and female sex significantly positively predicted involuntary movements ($p < 0.05$).

Conclusions: The patients with tonic upper limbs spasm during tilt induced syncope have longer time of decreased cerebral oxygenation assessed by NIRS. The relationship between decreased cerebral oxygenation and presence of tonic upper limbs spasm may be a consequence of lack of the cortical inhibition of lower cerebral nuclei. Myoclonic jerks are not related to the time of decreased cerebral oxygenation but rather to female sex. Female sex and younger age are related to higher probability of involuntary movements.

P1298 Head-up tilt table testing in syncope: safety and efficiency of isosorbide versus isoproterenol in pediatric population



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Objective: To compare the diagnostic value and safety of sublingual isosorbide dinitrate (ISDN) with intravenous isoproterenol (ISOP) during head-up tilt table testing (HUTT) in pediatric patients with suspected neurocardiogenic syncope. Experiencing a severe response to ISDN in 14 years old boy was the drive to this study (Figure 1).

Patients and Methods: 136 consecutive pediatric patients complaining of presyncope or syncope were submitted to HUTT for the first time. Those who did

not develop symptoms during passive HUT for 20 min underwent repeated HUT with either 1.25-2.5 mg sublingual ISDN or intravenous ISOP (1-3mg/min) for 20 minutes. There were 54 boys and 82 girls, aged 10 to 18 years with an average of 15.5 ± 2.4 years and a median of 16 years. The severity of the positive response was scored 1 to 3 (symptoms relieves within 10 seconds, 10-20 seconds and >20 seconds while back to supine position, respectively).

Results: During the passive period 24 out of 136 (17.6%) patients had a positive response to HUTT. Syncope was observed in another 44 patients during either ISDN or ISOP period (14/58 (24.1%) and 30/54 (55.5%) with ISDN versus ISOP, respectively, $P < 0.05$). The time to symptoms was shorter with both ISDN and ISOP compared with passive period (6.5 ± 2.9 minutes, 6.3 ± 5.9 , 10.3 ± 4.4 , respectively ($P < 0.05$)). The severity score was significantly higher with ISDN compared with passive period and ISOP (2 ± 0.8 and 1.25 ± 0.45 and 1.26 ± 0.45 respectively $P < 0.01$)

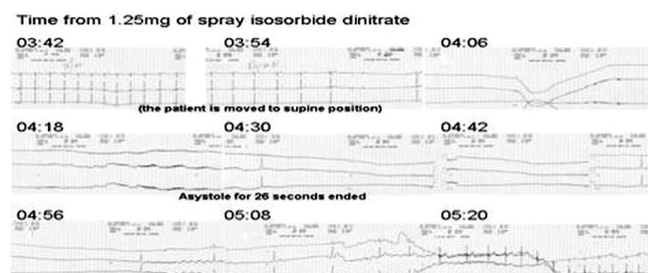


Figure 1

Conclusion: Sublingual ISDN is less sensitive and less safe compared to intravenous ISOP in assessing pediatric age patients with suspected neurocardiogenic syncope and with a negative tilt test without provocation. The simplicity of ISDN use should be waved against the risk of longer symptoms with ISDN.

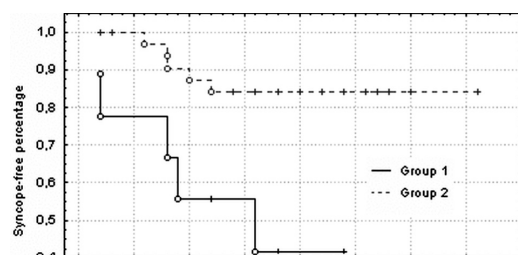
P1299 Prognostic value of RAAS assessment in patients with vasovagal syncope



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The inadequate reaction of renin-angiotensin-aldosterone system to upright posture may be a cause of susceptibility to the recurrence of vasovagal syncope. The aim of the study was to analyse syncope recurrence after positive diagnostic tilt testing. The examination was directed towards the meaning of the activation of the renin-angiotensin-aldosterone system.

Study group consisted of 52 pts (M, F) aged 37.4 ± 8.4 years with the history of vasovagal syncope, the median syncope spells was 3. The diagnostic tilt testing was performed according to Italian protocol with the NTG provocation when necessary. The blood to assess plasma aldosterone concentration was taken in the baseline conditions, immediately after syncope and 10 min after syncope. 20 pts had mixed, 32 pts cardiodepressive type of syncope. The NTG was used in 34 pts. The pts were divided into 2 groups: 13 pts included to group I had the increase of plasma aldosterone concentration immediately after syncope less than 20% from baseline values. 39 pts included to group II had the increase of plasma aldosterone concentration immediately after syncope more than 20%. The syncope occurred in 12 pts. 50 pts where treating with tilt training, 2 pts had implanted pacemaker, 2 pts received only general recommendations. The mean observation time was 14.0 ± 8.8 months. Survival curves analysis revealed that group I had significantly greater risk of the syncope recurrence - picture.



Kaplan-Meier syncope-free curves

Logistic regression analysis revealed that the higher number of syncope and slower pattern of aldosterone concentration were independently correlated with syncope recurrence. Slow response of RAAS activation is associated with syncope recurrence during follow-up. Neurohumoral assessment in patients with vasovagal syncope could be of prognostic value.

P1300 Holter monitoring in syncope: diagnostic yield in different patient groups



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Background Holter monitoring is routinely used in the evaluation of syncope, but its diagnostic value in different patient (pt) groups is often not taken into consideration. Aim of this analysis was to describe the pt population evaluated for syncope and to determine the diagnostic yield in different pt groups.

Methods All Holter studies performed due to syncope between 2000 and 2005 were reviewed. A study was considered diagnostic when an arrhythmia was found to explain syncope (AV block (at least Mobitz type II), sinus pauses >3 seconds, atrial fibrillation (AF) with severe bradycardia, or tachycardias >175 beats per minute).

Results 826 Holter studies were performed in pts with syncope. Female pts (n=445, age 75 ± 15 years) were significantly older than male pts (age 69 ± 16 years, $p < 0.0001$). 71 studies (8.6%) were considered to explain syncope (AV block (n=23), sick sinus syndrome (n=16), bradycardia in AF (n=19) and tachycardias (n=13)). Based on the results of Holter monitoring, 45 pts (5.4%) received a pacemaker, medication was changed in 13, ablation performed in three, and no action taken in ten pts, respectively. 33/755 (4.4%) pts with a Holter study not explaining syncope had a device implanted within the next 6 months (31 pacemakers, 2 ICD).

The numbers of Holter studies explaining syncope in different subgroups are shown table 1.

Table 1

	yes	no	P-value
SHD	43/375 (11.5%)	28/451 (6.2%)	0.007
Age > 60 years	67/675 (9.9%)	4/151 (2.6%)	0.001
Male sex	40/381 (10.5%)	31/445 (6.7%)	0.07
SHD/> 60 years	41/345 (11.9%)	30/481 (6.2%)	0.005
SHD/< 60 years	2/30 (6.6%)	69/796 (8.7%)	0.7
No SHD/< 60 years	2/119 (1.7%)	19/707 (9.8%)	0.0006
No SHD/> 60 years	26/332 (7.8%)	45/494 (9.1%)	0.5

Dependence of diagnostic Holter studies on presence or absence of different parameters. (SHD = structural heart disease)

Conclusion The overall diagnostic yield of Holter-ECG for the evaluation of syncope is low (8.6%). The probability of a positive test is especially low in pts younger than 60 years without structural heart disease suggesting that this pt group should not undergo Holter monitoring. In contrast, the yield is highest in pts older than 60 years with structural heart disease.

P1301 Interaction of catecholamines and hemodynamics during neurocardiogenic syncope



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Purpose: Vegetative imbalance is involved in causing neurocardiogenic syncope. However, vegetative status and hemodynamics before syncope are still incompletely understood. Study aim is to elucidate the pathophysiology of neurocardiogenic syncope by focusing on the interaction of catecholamine levels and hemodynamics.

Methods: 40 consecutive patients with a history of syncope or presyncope underwent standardized head-up tilt-table testing. Data of 33 patients were suitable for analysis. Continuous monitoring included invasive intra-arterial blood pressure measurement, ECG and non-invasive measurement of blood pressure by finger-plethysmography and of cardiac output (CO), total peripheral resistance (TPR) and contractility index (CI) by impedance cardiography. Epinephrine and norepinephrine plasma levels were measured in supine position and every 5min during tilting.

Results: In patients without syncope during tilting (n=7), the ratio of epinephrine and norepinephrine remained constant throughout the examination. In patients with syncope (n=26), small decreases of TPR (0.9 ± 0.3 times the baseline value), CO (0.9 ± 0.2 times baseline) and CI (0.8 ± 0.5 times baseline) were followed by distinct increases of epinephrine (15.6 ± 26.1 times baseline) and relatively small increases of norepinephrine (2.5 ± 1.2 times baseline). This disproportion of epinephrine and norepinephrine was associated with significant increases of CI (1.3 ± 1.0 times baseline), further vasodilatation (TPR 0.7 ± 0.2 times baseline) and significant decreases of heart rate.

Conclusions: In patients with neurocardiogenic syncope, a minor hemodynamic drop led to an excessive increase of adrenomedullary activity and an inadequate noradrenergic activation. The epinephrine surge, followed by parasympathetic activation and sympathetic inhibition, was shown to be a decisive factor in the pathophysiology of neurocardiogenic syncope.

P1302 A circadian rhythm of syncope in patients with vasovagal syncope

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Most of the cardiovascular physiological and pathophysiological events show a circadian rhythm. In this study we investigated the presence of circadian variation of syncopal episodes of patients with vasovagal syncope. A prospective consecutive series of 305 patients (pts, mean age: 32±8 years) with recurrent syncope and positive head-up tilt was included in this study. We used combined protocol with a passive and nitrate-stimulated phases. Patients who were receiving any drug therapies (such as beta blocker, serotonin reuptake inhibitors, vasodilators) and who had cardiac, psychiatric, neurological or metabolic disorders were not enrolled in the study. The time of syncope was determined in 605 episodes in 208 patients (124 women; mean age 30±6 years). The assessments of episodes were done according to the days of week and 3 time periods of day (06-12AM, 12-18 PM, 18-24PM). The relationship between the sex and age of pts with frequency of episodes were also evaluated.

Results: As the hemodynamic responses of positive tilt-table 79 pts (38%) had cardio-inhibitory, 24 pts (24%) had vasodepressor, 8 pts (4%) had postural orthostatic tachycardia and 71 pts (34%) had mixed type of classical vasovagal syncope. The mean of syncopal attacks was 2.8±1/month. There was not a significant correlation between sex and the age of pts with syncopal episodes ($p>0.05$). According to the 3 different time periods the frequency of episodes were 29%, 48% and 23% respectively. The peak of episodes was in the middle of the week (Thursday 32%, $p=0.003$) and during the 12-18 PM ($p<0.001$).

The frequency of syncopal attacks

	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Σn (%)
06-12AM	32	27	28	53	26	5	3	174 (29%)
12-18PM	29	19	44	106	46	28	21	293 (48%)
18-24PM	23	15	23	34	26	9	8	138 (23%)
Σn (%)	84 (14%)	61 (10%)	95 (16%)	193 (32%)	98 (16%)	42 (7%)	32 (5%)	605

Conclusion: In conclusion: The episodes of vasovagal syncope shown prominent circadian rhythm which was seen during the middle of week and 12-18 PM time period.

P1303 Algorithm for the evaluation of patients with syncope. Diagnostic yield

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Background: Capturing the cause of syncope is difficult. The causal origin is often presumptive. There is a need for specific criteria for choosing tests, time to perform them, diagnosis yield and the way to use their results in establishing their real cause.

Objective: To assess the diagnostic yield of an algorithm based in the initial evaluation (history, physical examination, blood pressure, ECG, carotid sinus massage), presence of structural heart disease and abnormal ECG and the selection of specific tests from these baseline information.

Methods: From march 2003 to November 2005, 233 pts (64 ± 19 years old) with syncope were prospectively evaluated. After the initial evaluation, pts were divided into: Group A (GA): Structural heart disease and/or abnormal ECG: Cardiac syncope causes were studied from the first stages in 161 pts. Group B (GB) without structural heart disease and normal ECG: Neurally mediated causes were studied from the beginning in 72 pts.

Results: GA: Out of 161 pts, 147 pts completed the algorithm. In 143 pts (97.3%) the etiology was: Cardiac syncope: 75 pts (52.5%); neurally mediated 49 pts (34.2%); orthostatic hypotension: 4 pts (2.8%); 2 or more causes: 9 pts (6.3%); pacemaker malfunction: 6 pts (4.2%). The diagnosis was met by: Initial evaluation: 50 pts (35%); Holter: 19 pts (13%); electrophysiologic study (EPS): 40 pts (28%); magnetic resonance image/EPS: 1 pt (0.7%); Adenosine test: 3 pts (2.1%); treadmill test: 1 pt (0.7%); Tilt test: 28 pts (20%); AICD control: 1 pt (0.7%). The etiology was unknown in 4 pts (2.7%).

GB: Out of 72 pts, 70 pts completed the algorithm. In 69 pts (98.6%) the etiology was: Neurally mediated 52 pts (75.4%); cardiac syncope: 8 pts (11.6%); orthostatic hypotension: 7 pts (10%); 2 or more causes: 2 pts (3%); The diagnosis was achieved by: Initial evaluation: 38 pts (55%); Holter: 4 pts (4%); Tilt test: 24 pts (35%); EPS: 1 pt (1.5%); Ajmalin test: 1 pt (1.5%); Adenosine Test: 1 pt (1.5%). The etiology was unknown in 1 p (1.4%).

Conclusions: In this study population, this strict algorithm allowed a high diagnostic yield.

It seems to be very important because the goal of the diagnosis and treatment is prevention of syncopal recurrences and reduction of mortality.

P1304 Cardiac autonomic function immediately preceding spontaneous vasovagal syncope: different patterns in cardio and non-cardio inhibitory syncope

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Very little data exists concerning the autonomic function at the time of spontaneous vasovagal (VV) syncope. Implantable loop recorder (ILR) would allow temporal analysis of the heart rate variability (HRV) in the minutes immediately preceding spontaneous Cardioinhibitory (CI) and Non-Cardioinhibitory (NCI) VV syncope.

Methods: in this prospective study, patients (pts) with at least 2 VV syncope within the previous 12 months were implanted with an ILR (Reveal Plus[®]). The ILR was interrogated after each syncope. A VV syncope was defined as CI when a ventricular rate < 40 bpm was observed during syncope. ILR recordings were considered for HRV analysis when they lasted more than 10 minutes before syncope and when the exact timestamp of the syncope could be clearly determined by characteristic notchings and fluctuations on the tracing. The ECG waveforms were analysed through a special R-wave sensing algorithm. Temporal analysis of HRV included SDNN and RMSSD. The 20 sec immediately preceding syncopes were excluded from analysis because of major artefacts. Three periods of 1 minute were studied: P1 for the last minute of analysis before syncope, P2 starting 3 minutes before P1 and P3 starting 3 minutes before P2.

Results: Twenty five pts (14 women, aged 60 ± 16 years) were included in the study and followed for a mean of 18.9 ± 6.7 months. Out of 42 syncopal episodes (15 pts) there were 21 (13 pts) which met the criteria for HRV analysis: 6 syncope were CI (3 pts) and 15 NCI (10 pts). In the 21 syncopal events, SDNN and RMSSD were significantly higher at P1 (10.2 ± 2 and 5.6 ± 0.1 ms respectively) than at P2 (3.5 ± 1.9 and 3.5 ± 2.3) and P3 (3.6 ± 2.8 and 3.5 ± 2.9) and there was no significant difference between P2 and P3. SDNN and RMSSD were significantly higher at P1 in CI than in NCI syncope (20.8 ± 3.6 and 10.4 ± 1.8 vs 5.8 ± 4.5 and 3.6 ± 1.7); there was no difference at P2 and P3 between the two forms of syncope.

Conclusion: during spontaneous VV syncope, HRV indexes significantly increase in the last minute before syncope. The indices of both the global autonomic function and the cardiac parasympathetic activity are higher in CI than in NCI syncope.

P1305 Predicting recurrence of syncope: a simplified risk score

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Background: Syncope is a very common clinical entity. In a significant proportion of patients the underlying cause can not be identified during standard neurologic and cardiovascular work-up and remains uncertain even after head up tilt table testing (HUT). In these patients, prediction of recurrence is of practical importance as syncope recurrence can result in injury. While some predictive factors for syncope recurrences (PFSR) have been already identified, a simple risk score was still not proposed. Aim of this study was to detect PFSR and prepare a risk score of easily use.

Methods: In the study were prospectively enclosed 276 patients with a history of syncope and negative workup until HUT. Head-up tilting test was performed after enrolment in all subjects and all were followed up for 24 months. Patients were randomly allocated at a 1:2 ratio to a derivation (n=176) and a validation cohort (n=100). In the validation cohort PFSR were identified by Cox regression analysis. Based on these factors, a risk score was calculated and applied to both cohorts.

Results: A high number of previous syncopal events, female gender and certain drugs predicted recurrence on syncope whereas the HUT result had not predictive power. Based on a risk score derived from these factors we identified patients in the derivation cohort with high (40%), intermediate (27%) and low (11%) risk for recurrence (log rank $p<0.005$, ROC 0,652, $p<0.01$). Recurrence rates in the validation cohort were 38% vs. 17% and 9% for patients with high, intermediate and low risk score (log rank $p<0.05$; ROC 0,681 und $p<0.05$), respectively.

Conclusions: The present risk score based in number of previous syncopes, presyncopes, gender and concomitant medication allowed to identify patients with low, intermediate and high risk for recurrence of syncope.

P1306 Ajmaline challenge in patients with syncope of unknown origin

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Intravenous ajmaline challenge is used to identify patients with Brugada syndrome if the diagnostic type I ECG pattern is not overt in the basal resting ECG. Patients with Brugada syndrome often present with a syncope of unknown origin. Purpose of this study was to evaluate the diagnostic value of intravenous ajmaline challenge in patients with a syncope of unknown origin.

Methods: Out of a total of 670 consecutive ajmaline challenges at the University hospital of Mannheim and the University of Nantes, 172 tests were performed due to syncope of unknown origin. Complete cardiological and neurological work-up was performed in advance and found to be without pathological findings. Ajmaline was administered intravenously following the recommendation of the Brugada consensus conference 2002 and 2005.

Results: Out of 172 patients (mean age 43 years; 107 males) ajmaline challenge was positive in 40 patients (24%). 27 out of these 40 patients were males (68%). In patients with positive response to ajmaline 37% had a type II baseline ECG, 29% a complete or incomplete right bundle branch block and 34% a normal ECG. In comparison to patients with negative response to ajmaline challenge, a type II baseline ECG was significantly more often found in patients with positive response to ajmaline ($p < 0.0001$). No serious side effects occurred during ajmaline challenge.

Conclusion: In 24% of patients with syncope of unknown origin, Brugada syndrome could be diagnosed by intravenous ajmaline challenge. Ajmaline challenge in patients with the history of syncope of unknown origin is a simple tool to diagnose or exclude Brugada syndrome and can be performed safely. Ajmaline challenge should be considered in patients with syncope of unknown origin, especially if the baseline ECG shows Brugada type II, incomplete or complete right bundle branch block pattern.

P1307 Lower limb and abdominal compression bandage in preventing orthostatic intolerance. A randomized placebo-controlled study



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Background: A progressive orthostatic hypotension can occur in elderly people after prolonged standing. The cerebral hypoperfusion caused by hypotension leads to clinical manifestation of Orthostatic Intolerance (OI) that have a strong negative impact on the quality of life of the patients.

Aim: The aim of the study was to assess the efficacy of compression bandage applied over the legs and abdomen with regard to the prevention of the orthostatic hypotension and reduction of the associated clinical manifestations.

Methods: Nineteen old patients (71 $\pm$ 10 years) affected by persistent symptoms of OI had a progressive orthostatic hypotension pattern during tilt testing which reproduced spontaneous symptoms. These patients underwent a randomised single-blind placebo-controlled tilting study of the hemodynamic effect of elastic bandage applied under standardized pressure over the legs (40-60 mmHg) and over the abdomen (20-30 mmHg). A 7-item Specific Symptom Score (SSS) was developed to assess the severity and relative contribution of OI symptoms before and after 1 month of therapy with elastic compression stocking of the legs.

Results: In the acute tilt study, leg bandage was administered for 10 minutes and was followed by leg plus abdominal bandage for further 10 minutes. In the placebo arm, systolic blood pressure decreased from 127 $\pm$ 18 mmHg immediately after tilting to 118 $\pm$ 20 mmHg after 10 minutes of placebo leg bandage and to 110 $\pm$ 20 mmHg after 20 minutes despite the addition of placebo abdominal bandage. The corresponding values with active therapy were 130 $\pm$ 19 mmHg, 128 $\pm$ 18 mmHg (+9 $\pm$ 16 mmHg vs placebo, $p=0.03$) and 127 $\pm$ 18 mmHg (+16 $\pm$ 20 mmHg vs placebo, $p=0.005$) respectively. In the active arm, 84% of patients remained asymptomatic, versus 53% in the control arm ($p=0.04$).

During the month before evaluation, the mean SSS score was 35 $\pm$ 10 (over a maximum value of 70) with dizziness, weakness and palpitations accounting for 63% of total score. This decreased to 22 $\pm$ 10 after 1 month of therapy ($p=0.002$).

Conclusion: Lower limb compression bandage is effective in avoiding orthostatic systolic blood fall in patients affected by OI. Abdominal bandage may have an additive effect. Elastic leg compression seems feasible and effective in reducing symptoms due to OI.

P1308 Cardiac-hemodynamic patterns during orthostatic stress in patients with postural orthostatic tachycardia



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Background: The pathophysiology postural orthostatic tachycardia syndrome (POTS) is poorly understood.

Objective: To assess the cardio-hemodynamic pattern (CHD) in patients with POTS during orthostatic stress. (OS)

Methods: 15 patients with previous clinical diagnosis of POTS [Mean age: 33 SD (13) years] and 13 subjects tolerant to head up tilt table test (HUT) referred for vasovagal syncope diagnosis [CON: 37(12) years] underwent passive OS test during 10 minutes at 70 degrees using a conventional tilt table. Task Force Monitor (CNSystems, Au) was used to compute CHD variables using impedance cardiography and beat-to-beat pletismography blood pressure monitoring. Heart rate (HR: beats per minute), mean arterial blood pressure (MAP: mmHg), EDV-preload (end diastolic volume in ml/m²), TPRI-afterload (Total peripheral resistance in dyne*s/m²/cm²) and (LVWI in mmHg*min/m²) were obtained during rest and

at 5 and 10 minutes during OS. Results are expressed as mean and (SD) as well as medians. T test and Kruskal-Wallis test, for normal and non-normal distribution respectively, were used to compare differences between groups (alpha level=0.05)

	Rest		5 min		10 min	
	CON	POTS	CON	POTS	CON	POTS
HR	70.7 (12.5)	87.4 (13.3)*	78.3 (15.3)	111.6 (111.6)*	80.3 (14.4)	105.6 (15.5)*
MAP	Median 100.1	Median 99.6	106.7 (12.5)	103.5 (10.9)	107.1 (14.4)	104 (8.7)
EDI	73.8 (15.5)	70.4 (18.6)	61.3 (10.4)	54.9 (10.2)	58.1 (11.0)	55.1 (15.0)
TPRI	258.5 (100.1)	2258 (966)	3136 (891)	2514 (611)*	3082 (869)	2535 (567)*
LVWI	4.5 (1.0)	4.7 (1.6)	3.9 (0.5)	4.6 (1.0)*	4.0 (0.6)	4.7 (1.1)

$p < 0.05$

Conclusion: HR was increased in patients with POTS at baseline and during OS. LVWI was increased during orthostatic stress in this group of patients. Decreased TPRI was documented in patients with POTS. Impaired vascular reactivity affecting TPRI during orthostatic stress may be associated with abnormal cardiac compensatory mechanisms that may trigger orthostatic intolerance symptoms in subjects with POTS.

P1309 New method of assessment of cardiac sympathetic innervations in patients with vasovagal syncope



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Objective: The aim of the study was to determine condition of sympathetic innervation performed by single - photon emission computed tomography (SPECT) and planner scintigraphy using 123I-metaiodobenzylguanidine (123I -MIBG) in patients with vasovagal syncope.

Methods and subjects: 23 patients with vasovagal syncope (VVS), mean age 34 $\pm$ 9, 11 female and 9 control subjects, mean age 29 $\pm$ 8, underwent SPECT imaging and planner scintigraphy after injection 123I -MIBG with activity 148 MBq. The global sympathetic activity was defined by heart/mediastinum ration (H/M) and washout rate. Images were obtained between 30 min and 4h after administration of 123I-MIBG. Regional sympathetic activity was defined by Extent of Defect (ED) and Severity of Defect (SD).

Results: VVS: ED,%: 20(15.5; 27)*, SD: 180(-260.5; 80.45)*; WR,%: -1.83(-4.96;-6.29); HRM_{30min}: 2.23 (1.92; 2.62); HRM_{4h}: 2.14 (1.87; 2.5); Control: ED,%: 1(1.0;4.0)*; SD:-2.8(-36;-1)*; WR,%: 2.08 (-7.73; -1.56); HRM_{30min}: 2.42 (2.08; 2.56); HRM_{4h}: 2.51 (2.34; 2.6); $p: 0.0001, 0.006, 0.643, 0.073, 0.107$ respectively.

Conclusion: There were not found abnormalities of global cardiac sympathetic innervations in patients with VVS as compared with control. Regional cardiac sympathetic innervations abnormalities are present in patients with VVS and can play the role in genesis of vasovagal syndrome.

P1310 Diagnostic yield of a short nitroglycerine tilt test without passive phase in patients with suspected vasovagal syncope: a randomized study



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Conventional tilt test protocols are time consuming and there is no consensus regarding the optimal duration and the clinical usefulness to maintain a previous drug-free phase. Several reports have shown that most of the positive responses observed during NTG-sensitized head-up tilt test (HUT) occurred early, during the first ten minutes of each phase, passive and mostly during drug-challenge. The aim of the study is to evaluate the diagnostic yield of a short NTG test without passive phase against a biphasic 20-minutes NTG tilt test protocol.

Methods and results: We assessed a series of 100 consecutive patients with unexplained syncope who underwent to HUT at our Institution, between February 2004 and September 2005. Patients were randomized to two different tilt protocols: G1 were 50 patients (22F/28M) who were tilted to 70° with 20 minutes test with a passive phase of 10 minutes and if this proved negative, 400 mg of sublingual NTG spray for a further 10 minutes. G2 included 50 patients (30F/20M) who were tilted to 70° with a 15 minutes NTG test without passive phase and a drug-challenge from the beginning. A control group was included consisting of 12 healthy volunteers without a history of syncope, who were tilted following G2 protocol. There were no differences between G1 and G2 in the presence of structural heart disease (14%, 12%, respectively $p = NS$) and duration of symptoms (46 $\pm$ 55, 39 $\pm$ 54 months, respectively $p = NS$). Patients from G1 were slightly younger than patients in G2 (48 $\pm$ 21, 57 $\pm$ 18 years, respectively $p < 0.03$). There were no differences in the rate of positive responses in the 2 groups (66%, 60%, $p = NS$). The most common type of response was vasodepressor (48%, 76%, $p = NS$); a mixed response was observed in 34%, 17%, respectively, $p = NS$. The mean time to syncope in G2 was shorter than biphasic protocol (14.8 $\pm$ 2 vs 7.1 $\pm$ 3 minutes, $p < 0.01$). Total test time was significant shorter in G2 than G1 (10.1 $\pm$ 4.7 vs 15.3 $\pm$ 5 minutes, $p < 0.01$). The positive responses rate in healthy subjects was 16%, so the specificity of the short protocol was 84%.

Conclusions: Suppression of drug-free phase did not affect the diagnostic yield of nitroglycerine-sensitized HUT with respect to longer protocols including passive phase in evaluating patients with suspect vasovagal syncope. A short nitroglycerine-sensitized tilt test protocol without passive phase has the same percentage of positive responses than longer protocols including passive phase.

P1311 Activation of sympathetic nervous system during syncope in passive and active phase of the head-up tilt test



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Syncope related to head-up tilt test (HUTT) is a consequence of inappropriate reflex response which may be triggered by different mechanisms. Overactivity of sympathetic nervous system and dysfunction of mechanism of venoconstriction potentialized by nitroglycerine (NTG) administration in response to orthostatic stress may be the two causes leading to such event. The aim of the study is to assess reactivity of sympathetic nervous system to HUTT in patients with positive response in the passive versus active (after NTG) phase of the test. Material and method: Plasma concentration of neuropeptide Y (NPY) was assessed in 18 patients (12F, 6M) mean age 40.9 ± 17.9 years with vasovagal syncope after 30 min rest before HUTT and 10 min after positive HUTT performed according to Italian protocol with provocation with nitroglycerin if necessary.

Results: The HUTT result according to VASIS classification was mixed in 7 cases and cardiodepressive in 11 cases. Faints occurred in 7 cases in passive phase and in 11 cases after NTG. The relationship between the phase of positive HUTT reaction and changes of concentration of NPY after HUTT was analyzed using Fisher's exact test.

Results: Plasma concentration of neuropeptide Y was higher 10 min after HUTT than in basal conditions in all 7 cases with positive HUTT in the passive phase and in 4 cases with positive HUTT in active phase, plasma concentration of neuropeptide Y was lesser 10 min after HUTT than in basal conditions in 7 cases with positive HUTT in active phase, so statistical analysis revealed categorical dependency between phase of HUTT and changes in the concentrations of neuropeptide Y ($p < 0.05$).

Conclusions: 1. In patients fainting in the passive phase of HUTT the probably primary cause of the vasovagal reaction is the excessive sympathetic activation assessed as elevation of the NPY concentration. 2. Different patterns of NPY concentration changes due to syncope in different phases of HUTT indicate on the heterogeneity of mechanisms leading to the vasovagal reaction.

P1312 Value of cardiac remote telemetry for syncope: what patients really benefit from it?



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Background Syncope is a common medical problem that often leads to hospitalization. Diagnosing arrhythmias as a cause of syncope is often difficult. Telemetry (TL) may benefit hospitalized patients (PP) in the diagnosis. We describe the outcomes of PP admitted to a TL unit with the diagnosis of syncope, examine the role of TL, and identify those PP that benefit most.

Methods We analyzed prospectively 102 consecutive PP, 52% men, 73 ± 14 years-old. A 16-channel TL was controlled 24-hours/day by trained nurses. Information included: age, gender, cardiovascular risk factors, historical information, clinical presentation, potentially arrhythmogenic drugs and ECG. Historical information included: coronary artery disease, hypertrophic or dilated cardiomyopathy, stroke or transient ischemic attacks, ejection fraction, chronic kidney disease or previous arrhythmias. Arrhythmias with clinical significance (guided therapy or use of diagnostic test), transfers to intensive care units (ICU) and mortality were documented. Arrhythmias considered were: supraventricular tachycardias (atrial fibrillation or flutter) of new diagnosis, ventricular fibrillation, sustained or non-sustained ventricular tachycardia, sick sinus syndrome, extreme bradycardia, asystole > 3 seconds, second and third degree AV-block. Chi-square test and multivariate analysis were performed.

Results: 30 PP (29.4%) presented events. ICU transfer occurred in 15 PP (14.7%), principally related with extreme bradycardia and third-degree AV-block. TL was diagnostic in 18 PP (17.6%) in which arrhythmias coincided with symptoms. No death was documented. Events were more frequent in older PP (77.6 vs 71.4, $p < 0.05$), those > 86 years-old presented a higher risk (OR 7.28 [IC 95% 2.03-26.03]). Those with heart failure and atrial fibrillation on admission showed a significant trend to develop events, OR 6.18 (IC 95% 1.69-22.5) and 2.9 (IC 95% 0.98-8.68) respectively. Although treatment with potentially arrhythmogenic drugs was not associated to higher risk, PP treated with digoxin developed more events (OR 8.75 [IC 95% 1.65-46.3]). A multivariate analysis was performed to control the effect of possible confusion factors. After analysis only the age over 86-years-old ($p < 0.01$) and the presence of heart failure ($p < 0.04$) remained as markers of high risk.

Conclusion TL utility for syncope is not defined. In our study 29% of the PP presented relevant events, 17% were diagnosed of cardiac syncope and near 15% were transferred to ICU. No death was documented. We conclude that TL is useful

and maybe lifesaving for PP with syncope, especially those older and with heart failure.

P1313 High incidence of tachyarrhythmias detected by an implantable loop recorder in patients with unexplained syncope

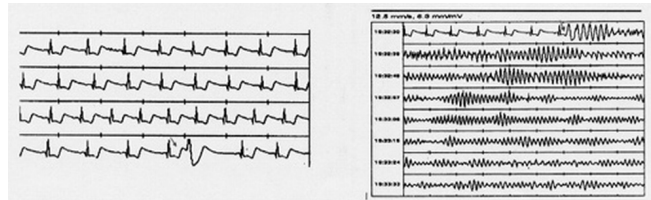


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Background: Syncope is a complex clinical syndrome that can be very challenging with respect to a definite diagnosis. The implantable loop recorder (ILR) is a useful tool to define but also to exclude an arrhythmic etiology.

Methods: Between April 1998 and September 2005 an ILR (Reveal[®], Medtronic) was implanted at our institution in 45 pts (30 m, 15 f; age 62 ± 20 y) with unexplained syncope (N=42) or palpitation (N=3). Prior to implantation all pts underwent detailed neurological and cardiac work-up including a tilt table test.

Results: 28 pts (61%) had a recurrence of syncope, near-syncope or dizziness. SHD was present in 13 pts (29%) and 4 pts (9%) had EF $\leq 35\%$. In 10 of the pts (22%) an arrhythmia has been excluded as explanation for the recurrent clinical event. However, in 17 pts (38%) the ILR revealed an underlying arrhythmia, such as sick sinus syndrome with bradycardia (N=2) or significant pauses (N=4), paroxysmal AV block (N=3), paroxysmal SVT (N=2), VT or TdP (N=6). The mean follow-up period from implantation to occurrence of the arrhythmias was 8.4 ± 7.9 months. Nine pts were treated with a dual-chamber pacemaker and 6 pts with an ICD. Four of the ICD recipients had non-ischemic CM (EF $27 \pm 3\%$), and 2 pts showed a preserved left ventricular function. Adjunctive RF-ablation was performed in 3 pts targeting Purkinje Extrasystole, bundle branch reentry tachycardia and focal VT.



Short coupled PVC triggering TdP

Conclusion: Significant brady- or tachyarrhythmias were diagnosed within the life-expectancy of the device in nearly two thirds of the pts. A relatively high proportion of ventricular tachyarrhythmias was diagnosed particularly in pts with non-ischemic CM. Consequently, the ILR helped efficaciously to determine the appropriate therapy in case of arrhythmogenic syncope.

P1314 Autonomic cardiovascular modulation after spaceflight during orthostatic stress



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Introduction: Changes in the cardiovascular control contribute to the occurrence of orthostatic intolerance after space flight. Long-term recovery of the autonomic nervous system has rarely been studied. Heart rate variability (HRV) and blood pressure variability (BPV) provide a non-invasive means to study the autonomic cardiovascular modulation.

Methods: ECG and continuous blood pressure was measured for at least 10 minutes in supine and standing position 45 days before launch; and at 1, 2, 4, 9, 15, 19 and 25 days after return to Earth. These measurements were performed in 5 cosmonauts during short term space missions (10 days).

Results: Measurements in supine position and sitting position did not show as high differences as the measurements in standing position. During standing after spaceflight HF was extremely depressed compared to the preflight conditions ($p < 0.005$). The recovery of the HF power was not completed at day 25. LF power of BPV was slightly increased up to 25 days after landing. Heart rate in standing position at landing day was significantly higher compared to preflight and remained higher up to 25 days after landing. The baroreflex mechanism was also extremely depressed immediately after landing and showed a gradual recovery ($p < 0.05$ compared to preflight values).

Conclusion: After return to Earth especially the vagal autonomic modulation is extremely depressed. This also affects the baroreflex feedback. The recovery of the autonomic nervous system takes several weeks and is not completed 25 days after return to Earth. The recovery period is characterised by a strong sympathetic dominance, which is particularly visible during orthostatic stress.

P1315 Heart rate accurately opposes respiratory arterial pressure fluctuations following short-term spaceflight



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In the autonomic intact state, mechanical effects of respiration on cardiac output and arterial blood pressure induce autonomic heart rate reflexes, including cardiac baroreflexes and respiratory sinus arrhythmia (RSA) that act in concert to attenuate respiratory induced variations in arterial blood pressure. The purpose of this study was to investigate offsetting effects of heart rate on short-term respiratory fluctuations in arterial blood pressure before and after a 10-day spaceflight. Five male cosmonauts who each took part in one of three different (10-11 days) Soyuz missions were studied (age: 40 yrs $\pm$ 3, height: 180 $\pm$ 4, weight: 76 $\pm$ 10). Data collection occurred at preflight (L - 25) and two postflight (R+1 and R+25) conditions. Subjects were supine and were instructed to pace their breathing at 6 and 12 breaths per minute, each within 3-minute periods. Subjects were then moved to the standing position and the breathing protocol was repeated. The ECG and continuous arterial blood pressure (Portapress) were recorded. Variations in stroke volume (SV) were estimated by modelling flow from the arterial pressure waveform (Modelflow). Spectral and cross-spectral indices were calculated in the respiratory (0.2Hz and 0.1Hz) and non-respiratory frequency bands (0.04 - 0.15 Hz). Compared to preflight, heart rate (HR) and diastolic pressure (DAP) increased and SV decreased at R + 1. Both respiratory and non-respiratory induced variations in HR were suppressed at R+1. The transfer gain and phase of systolic arterial pressure (SAP) and the RR-interval (RRI) were lower at R+1. Respiratory induced variations in mean arterial pressure (MAP) were similar between sessions. The amount of respiratory mediated variability in SV and CO was proportional before and after spaceflight. Differences between sessions were more pronounced when standing-up. Our data suggest that spaceflight decreases vagal cardiac neural outflow, and increases sympathetic influences on circulatory control. These changes are suggested to reflect normal baroreflex mediated adjustments to altered hemodynamic loading conditions after spaceflight. Observed alterations are disappeared after 25 days.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR AND SUDDEN DEATH

P1316 What are the mechanisms of inappropriate therapies in patients implanted with an ICD



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Introduction: Atrial tachyarrhythmia is the most common reported event leading to inappropriate (I) therapies (Tx) in implantable cardioverter defibrillator (ICDs) recipients. The aim of OPERA registry was to assess the occurrence of the first (F) ITx in patients (pts) implanted with an ICD and to determine the technical causes inducing ITx.

Methods and results: 665 pts (88% of males, 62 $\pm$ 13 years) were implanted with a single (SC) (n=273) or dual chamber (DC) (n=392) ICD. Mean tachycardia detection rate was 164 $\pm$ 19 bpm and 16% of devices were programmed with a low tachycardia detection zone at 143 $\pm$ 16 bpm. Based on investigators' interpretation, the number of FITx was 55 during a mean follow-up of 421 $\pm$ 239 days (d). The mean time occurrence of FITx was 180 $\pm$ 182 days. Two experts reviewed the stored EGMs to classify the intrinsic rhythm in 2 groups: atrial fibrillation (AF) or other atrial tachycardia (AT) including sinus tachycardia and to determine the causes leading ICD to deliver the Tx directly or after a period of inhibition in accordance with the programmed parameters. In total, 48 among 665 pts experienced a FITx (7.2%) as described in the table 1. 7 episodes were re-classified as VT

Table 1

Causes (n, %)	SC/DC (n)	AF/AT (n)
Direct therapy		
Algorithm of correlation (6,13)	3/3	1/5
Rate cut-off* (3,6)	2/1	1/2
Inhibition Tx not programmed* (3,6)	2/1	3/0
No algorithm in VT zone* (1,2)	1/0	1/0
Lead or noise (5,10)	2/3	0/5
Limit of the algorithm (6,13)	0/6	0/6
T: 24 (50%)	10/14	6/18
Therapy after first inhibition		
Modification of vector and algorithm of correlation (8,17)	3/5	2/6
Modification and stabilization of rhythm (3,6)	1/2	2/1
Nominal sustained rate duration* (SRD) (10,21)	4/6	2/8
Change of zone (1,2)	0/1	1/0
Limit of the algorithm (2,4)	1/1	0/2
TOTAL: 24 (60%)	9/15	7/17

*these programming could be improved and represent 37% of the described mechanisms.

(appropriate Tx). 42% of the ITX pts were on amiodarone which is significantly lower than in pts experiencing appropriate Tx (p<0.02).

Conclusion: During a mean follow-up of 14 months, the delivery of a FITx is very low, occurring in 7.2% of the overall population, equally distributed within single or dual chamber ICDs. AF is documented in about one third of the pts. In half of the cases, the Tx is first inhibited, then mainly delivered due to a change of the rhythm or because the SRD period has expired. Optimization of ICD programming may decrease by one third the rate of inappropriate therapies.

P1317 Prediction of ventricular tachycardia in ICD patients based on the multipole method



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Introduction: Heart rate variability (HRV) parameters are often used as prognostic markers and as predictors of onset of ventricular tachyarrhythmias (VT). The multipole method was recently developed as an alternative to the usual HRV parameters for this purpose. The method is based on the dynamic features as extracted from the beat-to-beat (RR) time series recurrence plot.

Methods: We applied the multipole method on 6000 stored RR intervals recorded prior to the onset of 84 VT episodes in 39 ICD patients enrolled in the Biotronik HAWAI study. We compared the data to 53 control recordings of the same duration obtained from the same patients on days without VT, with each patient serving as his own control.

Results: We found pathological multipole recordings prior to the onset of VT in 44 of the 84 recordings. The multipole parameters became typically pathological between 800 and 5000 RR intervals before the onset of VT, i.e. approximately 10 to 60 minutes before VT. In the control recordings there were 4 observations of pathological multipole parameters that were not followed by an arrhythmia. The method had sensitivity 52% and specificity 91% (p<0.0001), positive predictive accuracy of 90% and negative predictive accuracy of 55% for prediction of VT.

Conclusion: The multipole method can provide early warning of approaching VT in many ICD patients.

P1318 Home defibrillation in survivors of acute myocardial infarction at intermediate risk of sudden death: retention of BLS and AED use skills and impact on anxiety, depression and quality of life



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Background: Out-of-hospital cardiac arrest (OHCA) occurs at home in 65-80% of cases and is witnessed in 52%-81% of events. Ventricular fibrillation (VF) and ventricular tachycardia (VT) are the presenting rhythm in up to 70% of cases. The efficacy of automated external defibrillators (AEDs) on the outcome of OHCA caused by VF/VT is proved. Therefore a role for in-home AED use has been proposed but evidence is scanty.

Aims of the study: To assess the retention of BLS-AED use (BLSD) skills and the impact on anxiety, depression and quality of life of a home defibrillation (HD) program in families of survivors to myocardial infarction at intermediate risk of sudden death.

Methods: Families of patients surviving to acute myocardial infarction at intermediate risk of sudden death were trained to BLSD and received an AED. BLSD performance, quality of life (SF-36), anxiety and depression (Zung) were followed up for 12 months.

Results: Ninety-two persons have been enrolled in the study (33 patients and 59 relatives). Sixty-six persons (7/33 patients and 59/59 relatives) received a formal BLSD course. Quality of BLSD performance decreased over time: BLSD score was 26 (24-28) at baseline vs. 23.5 (17-26) at 3 mo (p<0.0001), 22.0 (16-25) at 6 mo (p<0.0001), 23.0 (17-25) at 9 mo (p<0.0001) and 24.0 (17-26) at 12 mo (p=0.004). BLSD performance was analyzed through the breakdown of the components: Evaluation of victims of suspected cardiac arrest (EVAL), Chain of survival activation (CHSA), Cardio-pulmonary resuscitation (CPR) and finally AED use (AEDu). EVAL score decreased from 4.8 $\pm$ 2.7 at baseline to 4.0 $\pm$ 2.5 at 3 mo (p<0.008), 4.0 $\pm$ 2.4 at 6 mo (p<0.041), 3.7 $\pm$ 2.4 at 9 mo (p=ns) and 3.8 $\pm$ 2.5 at 12 mo (p=0.026); CHSA score decreased from 5.3 $\pm$ 2.9 at baseline to 4.5 $\pm$ 2.8 at 3 mo (p=0.02), 4.2 $\pm$ 2.4 at 6 mo (p=0.028), 4.2 $\pm$ 2.3 at 9 mo (p=ns) and 5 (2-6) at 12 mo (p=0.007). CPR score decreased from 6.6 $\pm$ 3.7 at baseline to 5.6 $\pm$ 3.5 at 3 mo (p=0.021), 5.9 $\pm$ 2.9 at 6 mo (p=ns), 5.8 $\pm$ 3.0 at 9 mo (p=ns) and 6.3 $\pm$ 3.5 at 12 mo (p=ns). AEDu score was 6 (4-6) at baseline and remained stable over time: 5 (3-6) at 3 mo (p=ns), 5 (4-6) at 6 mo (p=ns), 5 (4-6) at 9 mo (p=ns) and 5.5 (4-6) at 12 mo (p=ns). SF-36 physical and mental health scores as like as Zung depression and anxiety scores remained stable in the study period.

Conclusion: BLSD performance declines over time in families enrolled in our HD

program but AED use is the least affected component. Our HD program had no detectable impact on quality of life, anxiety and depression in study population.

P1319 Neurologic outcome in mild hypothermia treatment for comatose survivors after cardiac arrest (ventricular fibrillation)



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Background: Mild hypothermia therapy after out-of-hospital cardiac arrest (CA) caused by ventricular fibrillation (VF) had been shown neurological benefit in recent clinical studies. However, it was not clarified in better neurologic outcomes whether acute coronary syndrome (ACS group) or not (non-ACS group).

Method: From June 2001 to April 2005, 28 eligible patients (pts) (age under 75, witnessed comatose survivors who had been resuscitated after out-of-hospital cardiac arrest due to ventricular fibrillation) were cooled to pulmonary artery blood temperature of 34° for 24-48 hours using external cooling blanket. In the case of acute coronary syndrome, coronary reperfusion therapy was subsequently performed after restoration of spontaneous circulation (ROSC).

Results: Baseline characteristics of the patients was as follows: ACS group in 15 pts vs non-ACS group in 13 pts; acute myocarditis in 4pts, old myocardial infarction in 6 pts or cardiomyopathy in 3 pts. Survival at hospital discharge was 19 pts (68%) and GR (Good recovery, cerebral performance category 1; able to care for self, discharged directly to home) was 16 pts (57%). Survival at hospital discharge was 77% in the non-ACS group, as compared with 60% ($p=0.339$) in the ACS group. Ten of the 13 pts (77%) in the non-ACS group had a GR, as compared with 6 of 15 (40%, $p=0.049$) in the ACS group.

Table 1

	ACS (N=15)	Non-ACS(N=13)	p value
age	62±7	57±14	$p=0.280$
Woman	33%	23%	$p=0.549$
by-stander CPR	40%	46%	$p=0.743$
CA-CPR	7±5	6±4	$p=0.450$
CA-ROSC	44±29	31±23	$p=0.197$
Survive	60%	77%	$p=0.335$
Good Recovery	40%	77%	$p=0.049$

HT; hypertension, DM; Diabetes, HLP; hyperlipidemia, SMK; smoking.

Conclusions: There were no significant statistical differences in survival rate between ACS group and non-ACS group. However, GR could be achieved in non-ACS group as compared with ACS group.

P1320 Reasons for reluctance to buy Automatic External Defibrillator(AED) for home use by cardiac patients



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Background: Sudden cardiac death (SCD) is an important cause of death in patients having heart disease. The commonest event leading to SCD is ventricular fibrillation. External defibrillation is a proven effective method to improve survival for SCD. Automated External Defibrillator (AED) is a simple and easy-to-use device that may be helpful for those patients who developed SCD. In our past experience, many patients were reluctant to buy AED for home use. This study aimed at exploring the reasons why those patients were reluctant to buy AED for home use.

Method: Consecutive patients who were admitted to our cardiac ward or visited our cardiac nurse assessment clinic were interviewed to explore their willingness and reluctance to buy the AED for home use. Both irreversible and reversible reasons for reluctance were assessed by questionnaire. For the reversible reasons, more than one choice were allowed, patients could rank at most three reasons. Only those who were reluctant to buy AED for home use were analysed.

Result: Totally 207 patients (58.5% male) with mean age of 68(range 31-91) years were analysed. The most common irreversible reason for reluctance to buy the AED for home use were the price of the AED(66.7%), followed by solitary living status of patient(14.6%). For those reversible factors, patient being left alone at day time was the most common reason(31.3%), followed by "Patient thought that the chance of SCD was low, it was not necessary to buy AED for home use"(25%). Education level and sex showed no significant effect on their reasons for reluctance to buy AED for home use.

Conclusion: Financial issue was the main concern for the patients when they made decision in buying the AED for home use. Sex or different education levels did not show any differences.

P1321 Sequential shock delivery using a single capacitor device and its effect on defibrillation thresholds



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Purpose: An iso-electric window (ISW) has been shown to follow both successful (SDF) and failed (FDF) defibrillations. The duration of the ISW is longer after a SDF than a FDF. We attempted to extend the ISW by delivering a definitive biphasic shock(BS) after a mono-phasic pre-shock (PS) to assess the effect on defibrillation thresholds (DFT) using a single capacitor prototype device.

Methods: The PS was delivered as a rectangular waveform, 1ms duration, constituting 0.33% of the total stored energy. The remainder was delivered as a truncated BS with tilt at 50% decay from the leading edge and/or 15ms duration for both phases. The distal electrode in the right ventricle (RV) was cathodal for PS and phase 1 of BS. Intershock intervals(ISIs) (measured between the leading edges of both waveforms) were programmable at 16, 31 and 47ms and were randomly selected for each DFT test. A standard ventricular coil electrode (2.7mm width) was inserted via the left internal jugular vein under fluoroscopy into the right ventricular apex in 6 anaesthetised pigs. An emulator Can was placed in a left pectoral subcutaneous pocket. DFTs were assessed using a binary search. Thresholds obtained using BS without a preceding PS formed the controls.

Results: Mean weight of the pigs was 38.7±7 kg. The median energies delivered were: PS=5.8 (range 3.3-9.0)J, BS= 11.8 (range 6.7-17.9)J and control =14.4 (range 9.8-23.3) J. No significant differences existed between the shock impedances and VF duration for both control and tests. Delivery of BS at the shortest ISI (16msec) was equivalent to control values ($p=0.9$) but DFTs rose incrementally with increasing ISIs.

Intershock intervals

Averages	Control	16ms	31ms	47ms
DFT (Joules)	17.8±5	18±3	22±5	23±5
Impedance (Ohms)	48.7±6	47.4±4	48.2±5	49.2±5
VF duration (seconds)	22±7	18±4	19±2	22±3

Summary of defibrillation characteristics.

Conclusion: Use of a single capacitor device to deliver a sequential waveform consisting of a nominal mono-phasic PS preceding a BS achieved equivalent DFTs to a standard truncated BS when delivered at a short ISI. Increasing DFTs at larger ISIs possibly reflect delivery of the BS after re-initiation of VF. A further reduction in overall DFTs should be possible by using a narrower ISI. This was not achievable in this study due to device limitations.

P1322 Pre-clinical evaluation of Tissue Ingrowth into defibrillation electrodes

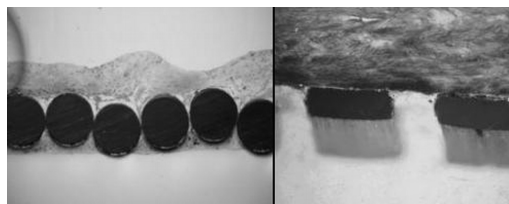


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Background: When ICD leads must be extracted, due to infection or malfunction, tissue attachment can cause complications. There are several strategies to reduce tissue attachment by limiting fibrotic ingrowth into the defibrillation coils. This study examined the efficacy of a non-tissue ingrowth (NTI) electrode design.

Methods: Two types of ICD leads were implanted in canine hearts for 3-6 months. The defib electrodes of the control leads were constructed with a round wire, similar to a majority of leads used clinically today. The control lead electrodes had a non-isodiametric profile and did not have any NTI features to limit tissue ingrowth. The defib electrodes of the test leads were constructed with a flat wire coil and silicone rubber filling the wire gaps, resulting in an isodiametric profile. The tissue was specially prepared using PMMA histological techniques, allowing the preparation of longitudinal cross sections of the defib electrodes. Samples were stained with H&E and Masson's Trichrome and the level of tissue ingrowth was assessed qualitatively.

Results: Control leads demonstrated significant fibrotic encapsulation of the coil. The tissue surrounded the individual wires, resulting in secure tissue attachment. The test leads with the NTI feature demonstrated minimal tissue penetration through the silicone filler and, therefore, no fibrotic encapsulation of the individual coil wires.



Conclusions: Defibrillation coils with NTI features, such as the silicone gap filler, can significantly reduce tissue attachment to defib electrodes, thereby having the potential to reduce complications during lead extractions.

NEW ASPECTS OF CARDIAC RESYNCHRONISATION THERAPY AND BRADYCARDIAC PACING

P1323 The Left Ventricular Capture Management algorithm is accurate and effective

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Purpose: Left Ventricular Capture Management (LVCM) automates LV stimulation threshold measurements using a capture detection algorithm based on the timing of an RV sense following an LV pace. Capture is determined when RV senses are due to interventricular conduction. This study's primary objective evaluated accuracy of the LVCM algorithm by comparing in-office LVCM thresholds to manual LV thresholds.

Methods: The LVCM algorithm was downloaded into 130 patients (pts) with Medtronic 7289 ICDs. A manual LV threshold test and an LVCM in-office test were performed at download, 2-week, 1-month and 3-month visits. Clinical equivalence was defined as LVCM being no more than one voltage step above or below the manual test result (one step = 0.5V for thresholds 0.5-3.5V and 1V for threshold >4V). A subset of LVCM strips from the initial clinic visits were reviewed for test pace capture determination accuracy.

Results: From 107 pts, 307 pairs of data were collected comparing in-office LVCM to manual thresholds: 99.7% met clinical equivalence criterion and support the accuracy of LVCM. The majority of the 23 pts not contributing could not run LVCM in-office due to rhythm or rate instability. Ambulatory LVCM thresholds within two days prior to clinic visits were available for 90% of follow-up visits. Of 306 comparisons 295 (96.4%) met clinical equivalence criterion. LVCM test paces from 113 in-office LVCM tests were reviewed for test pace accuracy; of 758 test paces evaluated, 417 (100%) of 417 capture beats and 336 (98.5%) of 341 loss of capture beats were classified correctly.

Conclusions: This automated Left Ventricular Capture Management algorithm was demonstrated to be both accurate and effective.

P1324 Long term effects of cardiac resynchronization therapy on atrial and ventricular anatomical remodeling in patients with advanced heart failure, permanent atrial fibrillation and AV node ablation

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Cardiac resynchronization therapy (CRT) has been shown to reverse left ventricular (LV) remodeling in sinus rhythm patients with conventional CRT indication according to the guidelines. The role of CRT remains however controversial in pts with permanent atrial fibrillation (AF). The aim of this prospective study was to assess the effect of CRT on left atrial and ventricular anatomical remodeling in heart failure AF pts with chronic left ventricular systolic dysfunction (LVSD) of any cause and who required radiofrequency AV node ablation for rate control. 49 pts (68.3±8.4 years) were included. All had advanced heart failure (NYHA class III: n=36, or IV: n=13) despite optimal pharmacological treatment and evidence of severe LVSD of ischemic origin in 20 and non ischemic in 29. Clinical (NYHA class, 6 minute walk test (WT), quality of life (QOL) and echocardiographic (LVEF, LV end-diastolic diameter (EDD), left atrial diameter (LAD) and mitral regurgitation (MR) assessment was performed at baseline and at 12 month follow-up. 15 pts died, 12 from progressive heart failure, 3 from sudden cardiac death

	Baseline	12 months FU	p
QRS intrinsic (ms)	191±28	155±20	≤0.01
NYHA class	3.2±0.5	2±0.4	≤0.01
6WT	290±10	415±71	≤0.01
QOL	46±14	24±10	≤0.01
LVEF (%)	22±7	31±8	≤0.01
LVEDD (mm)	70±8	64±9	≤0.01
LAD (mm)	57±9	52±8	≤0.01
MR	2.2±0.7	1±0.3	≤0.01

Conclusion: CRT significantly improved symptoms and quality of life of pts with permanent AF and wide QRS. CRT reversed left atrial and ventricular anatomical remodeling and significantly decreases MR at 1 year follow-up.

P1325 Optimisation of the atrioventricular delay of cardiac resynchronisation determined during exercise can be predicted by a resting pacing model

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Background Optimisation of atrioventricular (AV) delay of cardiac resynchronisation therapy would ideally be performed during exercise, as this is when patients

are most symptomatic. It may be possible to use fast pacing at rest to simulate exercise, however, account has been taken for the difference in optimal AV delay between atrial pacing and sensing. We test a pacing model for exercise, to determine whether it is possible at rest to predict the haemodynamic peak AV delay determined during exercise.

Method and Results: We performed AV delay optimisation, using non-invasive haemodynamics by Finometer, in 12 biventricular pacemaker patients, using our system for maximising signal-to-noise ratio. We calculated the difference between the haemodynamic optimal AV delay for atrial paced and atrial sensed AV delay at resting rates (the "sensed-paced optimum difference"). We subtracted this from the optimal AV delay found with atrial pacing at 100bpm, in order to create a "predicted exercise AV optimum". Patients separately underwent haemodynamic optimisation during actual treadmill exercise (~100bpm), to test the validity of the resting prediction. All patients showed a clear optimum. The actual exercise optimal AV delay was shorter than the 100 bpm pacing value and was closely predicted by our resting formula ($r=0.93$, $p<0.001$). The root-mean-square difference between predicted and actual was only 14ms.

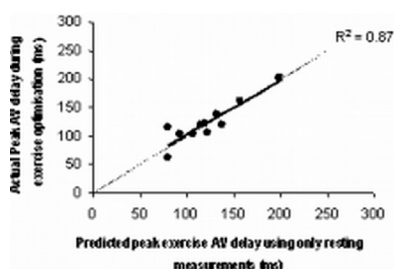


Fig. 1. Comparison of predicted optimal AV delay at rest and actual optimum determined during the exercise.

Conclusions: Actual exercise haemodynamic optimisation is possible, in patients able to exercise for several minutes. The exercise optimum for AV delay can be determined from resting optimisation, if the sensed-paced difference is also measured. This may allow appropriate exercise AV delays to be selected without the need for optimisation during exercise.

P1326 Cardiac resynchronization therapy in patients with a narrow QRS complex

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Objective To evaluate the effects of cardiac resynchronization therapy (CRT) in heart failure patients with a narrow QRS complex (≤ 120 ms) and evidence of severe left ventricular (LV) dyssynchrony on tissue Doppler imaging (TDI).

Background: CRT is beneficial in selected heart failure patients with a wide QRS complex (>120 ms). Patients with a QRS complex ≤ 120 ms are currently not eligible for CRT and the potential effects are not well studied.

Methods: Thirty-three consecutive patients with a QRS complex ≤ 120 ms and 33 consecutive patients with a QRS complex >120 ms (control group) were prospectively included. All patients had LV dyssynchrony ≥ 65 ms on TDI, New York Heart Association (NYHA) class III/IV heart failure and LV ejection fraction (EF) $\leq 35\%$.

Results: All baseline characteristics, in particular LV dyssynchrony, were comparable between patients with QRS duration ≤ 120 ms (mean 110 ± 8 ms) and patients with a QRS duration >120 ms (mean 175 ± 22 ms). No significant relationship was observed between baseline QRS duration and LV dyssynchrony ($r=0.21$, ns). The magnitude of improvement in clinical symptoms (e.g. NYHA class improved by 0.9 ± 0.6 vs. 1.1 ± 0.6 , respectively, ns) and improvement in LV function (e.g. LV end-systolic volume decreased by 39 ± 34 ml vs. 44 ± 46 ml, respectively, ns) were comparable in both groups.

Conclusion: CRT is beneficial in patients with a narrow QRS complex (≤ 120 ms) and severe LV dyssynchrony on TDI. The magnitude of improvement in LV dyssynchrony, clinical symptoms, LVEF and LV volumes was comparable to patients with a QRS complex >120 ms.

P1327 Device-based intrathoracic impedance measurements in patients after cardiac resynchronization therapy

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Purpose: Heart failure patients (P) frequently suffer from cardiac decompensation (D) due to volume overload despite to cardiac resynchronization therapy (CRP). An early warning system may allow an immediate initiation of heart failure treatment. Intrathoracic impedance (ITI) measurement has been integrated in a resynchronization device (InSync Sentry, Medtronic) to monitor intrathoracic fluid. The aim of this study was to evaluate the capacity of ITI to detect D in CRT patients.

Methods: The intrathoracic impedance (ITI) is measured between the shock coil and the device can 64 times a day providing an average daily impedance. A reference impedance is generated within the first 34 days after implantation. Fluid accumulation in the lung results in a decrease of ITI. The accumulated differences between the daily ITI and the reference ITI in relation to a programmable threshold triggers an acoustic alarm of the device. Inclusion criteria for consecutive CRT patients were: NYHA $\geq$ III, ejection fraction (EF) $\leq$ 35%, QRS $\geq$ 150 ms, LBBB, left ventricular enddiastolic diameter (LVEDD) $\geq$ 65 mm and VO2 max $\leq$ 18 ml/kg/min.

Results: Since 2004 the CRT device was implanted in 74 P (57 men, 39 DCM, 35 CAD, age 61.0 ± 11.6 years, EF $24.4 \pm 5.4\%$, QRS 168.7 ± 21.3 ms, NYHA 2.9 ± 0.2 , LVEDD 73.9 ± 11.2 mm, VO2 max 12.3 ± 3.6 ml/kg/min). During a mean follow-up of 5.1 ± 3.8 (1-15) months 18 acoustic alarms occurred, most of them prior to the onset of clinical symptoms. 15 P suffered from D and in 2 P without symptoms the diuretics had been reduced. A clinical deterioration without device alarm was found in 3 P, 2 of them had a new onset of atrial fibrillation. The device-based intrathoracic impedance measurement has a positive predictive value of 94% and a sensitivity of 85% for the detection of a cardiac D.

Conclusions: The intrathoracic impedance measurement is a sensitive method to detect pulmonary fluid overload in patients after CRT.

P1328 Time course of perfusion and wall motion changes after CRT in patients with heart failure



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Rationale: Cardiac resynchronization therapy (CRT) may induce significant changes in regional wall motion and perfusion in patients with heart failure. There are currently no data on the relationship between these variables and recovery of ventricular function at short and medium term follow-up.

Methods: To this purpose, 36 patients with idiopathic (22) or ischemic (14) cardiomyopathy (mean age 70 ± 8 yrs, 24 male), were studied by Gated SPECT before (T0), within 2 months (T1) and 6 months (T2) after CRT.

Results: NYHA Class improved in all but 4 patients at T1 and did not change at T2. SPECT showed significant reperfusion at T1 in 92% of patients without significant changes at T2. Baseline end-diastolic volume index obtained by gated SPECT modulated at T1 the increase of EF, ($p < .001$), the reduction of end systolic volume index ($p < .01$), the improvement of regional wall motion ($p < .001$) and ventricular wall thickening ($p < .002$). Beyond T1, these variables showed only minor changes at T2. Finally, despite CRT induced significant reperfusion at T1 in the majority of patients, extension of perfusion defects at T0 correlated well with EF improvement after CRT ($p < .05$ at T1; T1 vs T2 = ns).

Conclusions: in responders, the main effects of CRT on regional myocardial perfusion and wall motion are obtained within 2 months and are stable over a period of 6 months. Volume overload modulates recovery of regional and global ventricular function independently of reperfusion both at short and medium term follow-up. In patients undergoing CRT the extension of perfusion defects contributes to the identification of responders.

P1329 Interventricular delay less than 20 milliseconds on body surface potential mapping identifies cardiac resynchronisation therapy responders



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Background: Clinical/functional parameters currently identify patients who benefit from the cardiac resynchronisation therapy (CRT). Electrical and mechanical alterations in both ventricles have not been well evaluated yet.

Objective: To establish ventricular electrical activation criteria that can distinguish patients whose clinical-functional parameters improved after CRT, using a non-invasive method, the body surface potential mapping (BSPM).

Methods: Twenty-two patients with heart failure and left bundle-branch block (LBBB) undergoing CRT, mean age 64 ± 10 years, left ventricle ejection fraction (LVEF) $30\% \pm 8\%$, QRS 169 ± 19 ms, NYHA class III - 86%, IV - 14%, underwent 87-lead BSPM assessment (58 leads on the anterior chest and 29 on the back), before and after CRT. BSPM isochronal maps were used to analyse the ventricular activation time (VAT) in the right (RV) and left ventricles (LV) in three situations, (1) native LBBB, (2) single-site RV pacing, and (3) biventricular pacing. CRT clinical/functional improvement was measured by LVEF on echocardiography, and NYHA functional class. VAT's were compared using the Mann-Whitney's non-parametric method. The groups with and without clinical/functional improvement who showed RV/LV difference of VAT less than or equal to 20ms, and >20 ms were compared by the Fisher's test. Significance level was $P < 0.05$.

Results: Although only a trend towards a shorter VAT RV/LV difference during biventricular pacing was found among patients who improved (12.9 ± 10.9 ms vs 23.1 ± 12.9 ms, respectively; $P = 0.08$), the majority of the patients with clinical/functional improvement had a VAT RV/LV difference shorter than or equal to

20ms during biventricular pacing, $P = 0.026$ (79% vs 25%, RR 2.5, CI=95% 0.09-6.58). Baseline characteristics were not significant.

Conclusion: BSPM could distinguish patients who improved clinically/functionally after CRT when VAT difference between the ventricles was shorter than 20ms.

P1330 Coronary sinus lead extraction: usefulness of mechanical transvenous dilation in patients underwent ineffective manual traction



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Purpose: Few data are currently reported about outcome of coronary sinus (CS) lead removal, particularly using mechanical dilation (MD). We aimed to evaluate feasibility, safety and effectiveness of CS lead extraction, focusing on usefulness of MD, in the event that manual traction (MT) was ineffective.

Methods: We studied 41 consecutive patients (34 male, mean age 67.9 , range 52-80); the indication to extraction was a local infection in 19 patients (46.3%), sepsis in 14 patients (34.1%) and a lead malfunction in 8 patients (19.6%). The procedure was first attempted by MT, followed, if unsuccessfully, by MD using polypropylene sheaths.

Results: All CS leads (time from the implant 27.9 ± 36.8 months, range 2-168) were successfully removed; MT was effective (MT group) in 29 patients (70.7%) and ineffective in 11 patients (26.8%), whereas MD was necessary (MD group). One patient (2.5%) with three large vegetations along the catheter was submitted successfully to MD during on-pump heart surgery. There were 4 no serious complications. No differences between MT and MD group about the data analyzed was noted; particularly, the time from the implant was not significantly longer in MD group than in MT group (28.9 ± 31.8 months vs 23.6 ± 32.7 months; $p = ns$).

Conclusions: - Our study suggests that pacing leads implanted in the CS and its branches could be effectively and safely removed using MD with polypropylene sheaths, when MT was unsuccessful; we didn't found preoperative predictive factors identifying CS leads in whom MT was ineffective.

P1331 Chronic performance of a new bipolar far-field signal (fsr) reduction pacing lead in the right atrium



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Objectives: Far Field (FF) R wave oversensing on the atrial channel is the most frequent cause of inappropriate mode switch in dual-chamber paced patients, leading to inadequate non-tracking mode and impaired diagnostics. A new bipolar FF Signal Reduction (FSR) lead with optimized 1.1mm tip-to-ring electrode spacing and surface area was designed to reduce the FF signal. This clinical study was designed to evaluate the chronic performances and stability of the new FSR lead in comparison to a market-released lead with 10mm tip-to-ring electrode spacing.

Methods: 62 patients (29 females, 72 ± 9 years) were enrolled. Indication for pacing was sick sinus syndrome ($n=28$), AV block ($n=23$), binodal disease ($n=8$), not indicated ($n=3$). Patients were randomized at implant to receive either the new SJM Tendril® FSR pacing lead ($n=33$) or a SJM Tendril® ST Model 1688T ($n=29$). 52 leads were placed in the right atrial appendage and 10 at the atrial septal wall. Chronic performances were evaluated at 90 days post implant by standard follow-up and FF sensitivity threshold tests with post ventricular atrial blanking (PVAB) programmed to 60ms. Mode switch episodes were validated with stored IEGMs. An additional 24-hour continuous IEGMs recording was also conducted to analyze undersensing, oversensing, and intrinsic and evoked FF amplitudes.

Results: At 90 days, the FSR lead has a significantly lower bipolar pacing thresholds than the 1688T lead (0.57 ± 0.18 V vs. 0.69 ± 0.22 V, $p=0.02$). Mean impedance was significantly lower for the FSR lead compared to the control lead ($411 \pm 74\Omega$ vs. $493 \pm 85\Omega$, $p=0.0002$). Mean bipolar sensing threshold was also significantly lower for the FSR lead though sufficient and acceptable (2.54 ± 1.13 mV vs. 3.50 ± 1.15 mV, $p=0.003$). FF sensing thresholds were below 0.1 mV for 87% of the FSR patients compared to 62% in the control group. FF sensing thresholds at or above 0.3 mV were reported in 20% of patients with control leads vs. 0% of patients with the FSR lead. The mean FF amplitude was significantly lower in FSR patients for intrinsic beats (0.033 ± 0.008 mV vs. 0.053 ± 0.01 mV, $p < 0.001$) and paced beats (0.063 ± 0.06 mV vs. 0.198 ± 0.26 mV, $p=0.03$). During the follow-up of 90 days, 5% of patients with the FSR lead showed inappropriate mode switch due to FF oversensing in the stored IEGMs compared to 24% in the control group.

Conclusions: The new FSR lead showed significant reduction of FF sensing even at short PVAB and high atrial sensitivity. These results suggest that the FSR lead has significant potential to provide improved pacemaker therapy associated with reliable diagnostic data.

P1332 Reduction of ventricular pacing versus physician indication of AV block status

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Background: Right ventricular apical pacing results in asynchronous ventricular contraction and may have deleterious effects in pacemaker patients (pts). A new algorithm (MVP) that allows AAI(R) pacing with automatic mode change to DDD(R) in case of AV block (AVB) has been demonstrated to reduce ventricular pacing in pts with an AVB indication. The relationship between degree/type of AVB and percentage of ventricular pacing (%VP) has not been assessed.

Methods: The EnRhythm clinical study was a 2-month crossover study comparing %VP in MVP vs. DDD(R). At 2 months, the pacing mode was programmed at physicians' discretion. AVB status was assessed at baseline by clinicians and each patient was assigned using the following hierarchical categories: persistent 3rd degree AVB (p3AVB), episodic 3rd degree AVB (e3AVB), 2nd degree AV (2AVB), 1st degree AVB (1AVB), and no AVB (nAVB). The %VP was tabulated for AVB status categories in MVP and DDD pacing modes.

Results: One hundred and fifty pts were implanted with the EnRhythm device and 129 patients without permanent AF completed both arms of the crossover with complete data. The table shows the median of %VP in MVP mode, %VP in DDD/R mode, and relative reduction of %VP from DDD/R mode to MVP mode. The difference of median relative reduction in %VP between e3AVB and p3AVB pts was 87.8% (95% CI, 1.1%-98.8%). Similarly, the difference of median relative reduction in %VP between pts with p3AVB and pts with some intrinsic conduction (all other pts) was 96.6% (95% CI, 92.4%-98.5%).

AVB Degree	N	%VP in MVP (median with 95%CI)	%VP in DDD/R (median with 95%CI)	Relative Reduction (median with 95%CI)
p3AVB	13	98.9% (93.8%, 99.9%)	99.9% (98.1%, 100.0%)	0.0% (0.0%, 1.3%)
e3AVB	25	1.2% (0.1%, 34.3%)	85.2% (39.6%, 98.8%)	87.8% (1.1%, 99.3%)
2AVB	25	37.6% (6.2%, 81.4%)	97.7% (83.0, 99.4%)	61.5% (4.1%, 88.4%)
1AVB	10	0.9% (0.1%, 2.1%)	67.5% (19.7%, 99.3%)	98.0% (93.9%, 99.9%)
nAVB	56	0.3% (0.1%, 1.0%)	64.4% (36.5%, 84.6%)	99.0% (97.4%, 99.7%)

Conclusion: Physician assessment of AVB status corresponded to decreases in %VP in MVP. Patients with episodic 3rd degree AVB and patients with some evidence of intrinsic conduction were more likely to have a reduction in %VP than pts with persistent 3rd degree AVB. This finding is consistent with heart physiology, since patients with a higher degree of AVB need to be paced more.

P1333 Inequity of access to pacemaker implantation for bradycardia in England

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Purpose: Marked geographic variation in pacemaker implantation has been observed between countries and has been attributed to population demographics, particularly age distribution and to socioeconomic factors. We have examined variation in 7 cardiac networks in England, in relation to these and other factors.

Methods: The UK National Pacemaker and ICD Database was interrogated to determine details of patients receiving first pacemaker implantations in 7 cardiac networks. Pacemaker registration and patients' post codes were also checked with individual pacing centres and are >98% complete. Implantation rates were corrected for age and sex of each network population. Data relating to socioeconomic deprivation and provision of cardiac care were obtained from the UK Departments of the Deputy Prime Minister and Health.

Results: Data relating to 9,567 first pacemaker implants in a population of 12,699,694 during 2002 and 2003 were studied. (annual implantation rate 372 per million). Variation within the 7 networks was up to 41%, and within primary care trusts (PCTs) within the same network was up to 175%. There was no relation between age-adjusted implant rate and socioeconomic deprivation, provision of other cardiac services such as revascularisation by surgery or percutaneously, or number of cardiologists. Although there was no relationship between implantation rate and distance from a pacing centre, there was a relationship between rate and type of centre providing pacing to a PCT. PCTs where pacing was performed in a tertiary pacing centre often (but not always) had a higher implant rate than those in which pacing was provided by a district general hospital. Conversely, however, PCTs in which pacing was provided at a single tertiary pacing centre often had very different implant rates, suggesting important influences at PCT level rather than at pacing centre level.

Conclusions: Inequity of access to pacing in England is marked, but in contrast to Europe does not appear to be related to socioeconomic deprivation, or to provision of other aspects of cardiac care. Rather, so far unidentified local factors appear to be important.

P1334 Midseptal right ventricular pacing and left ventricular dyssynchrony

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Background: Right ventricular (RV) apex is not the optimal site for pacing, since it provides a non-physiological asynchronous contraction, resulting in a decrease in cardiac performance. RV pacing from a midseptal position might cause less left ventricular (LV) dyssynchrony than pacing from the RV apex.

Methods: We studied 21 consecutive patients (pts), mean aged 74±3.1 years, EF 53±5.5%, QRS duration 109±8.9 ms, with A-V block necessitating the implantation of a permanent pacemaker. They were randomly assigned to either RV apex pacing (Group 1) or RV midseptal pacing, the electrode being placed in the middle third between the tricuspid valve and RV apex (Group 2). Two-dimensional echocardiography and fluoroscopy were used to ascertain this position. Twenty-four hours following pacemaker implantation, an echocardiographic study was conducted to assess cardiac function and LV dyssynchrony i) without pacing (baseline), the pacemaker being programmed to VVI 30 bpm and ii) during RV pacing (VDD mode). LV dyssynchrony was assessed by TDI echocardiography, as the standard deviation (SD) of the time to peak myocardial contraction of 12 LV segments, 6 basal and 6 mid LV (SD index, as described by Yu et al). ANOVA for repeated measures was used for statistical evaluation.

Results: Twenty-four hours following pacemaker implantation, 3 pts were excluded because of pacemaker dependency. LV dyssynchrony values during intrinsic ventricular rhythm were similar in the 2 groups (RVA vs IVS: 33.1±8.4 vs 46.2±7.8 ms, p: NS). Midseptal pacing induced a more synchronized pattern of LV contraction changes (SD index 34.8±4.8 vs 46.2±7.8 ms at baseline) as compared to those induced by RV apical pacing (42.9±5.2 vs 33.1±8.4 ms at baseline, ANOVA p<0.05).

Conclusion: Midseptal RV pacing induces a favorable pattern of changes in LV synchrony, in contrast to RV apical pacing. This implies that midseptal RV pacing, as presently described, may offer a more physiological LV contraction pattern and be preferable to RV apical pacing.

ARRHYTHMIAS, VARIA

P1335 Prevalence of electrocardiographic abnormalities in adult patients with chronic, difficult to control epilepsy and learning disabilities

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Background: The prevalence of electrocardiographic (ECG) abnormalities in patients suffering from epilepsy is not known. Currently, only 4% of patients with epilepsy undergo an ECG in the United Kingdom. Sudden unexpected death in epilepsy (SUDEP) is encountered more often in young, difficult to control epileptics with coexisting learning difficulties. The precise mechanism of SUDEP is not known, though arrhythmia's remain a possibility.

Aim: To evaluate the prevalence of ECG abnormalities in an adult population with chronic, difficult to control epilepsy and learning disabilities.

Methods: Between May and December 2005, 12 lead ECG's with rhythm strips were undertaken on 85 patients. ECG's were systematically analysed by a cardiologist for abnormalities in rate, rhythm, axis, PR interval, QRS duration and morphology, ST, T wave changes and the QT/QTc interval. Manually analysed results were compared to those automatically read by the machine.

Results: Mean age: 53.3±13.2 (range: 20-83 years). 53(62.4%) were males. Mean duration of epilepsy: 46.3±13.2 (range: 17-79) years. Mean number of comorbid conditions: 4.6±5.0 (range: 0-40). Mean number of medications: 6.9±2.6 (range: 2-15). All patients were in sinus rhythm. Only 38/85 (44.7%) ECG's were classed as normal. In those with an abnormal ECG, one abnormality was seen in 33/38 (86.8%), 2 abnormalities in 11/38 (29%) and 3 abnormalities in 3/38 (7.9%) patients. Commonest abnormality was non progression of R waves across precordial leads, occurring in 13/85 (15.3%) patients. Other abnormalities detected were: 1° degree heart block in 10/85 (11.8%), RVH in 7/85 (8.2%), LVH and sinus bradycardia in 5/85 (5.9%); RBBB in 4/85 (4.7%), abnormal Q waves in inferior leads, non specific ST-T changes and artefacts in 3/85 (3.5%) patients each; low voltage complexes in precordial leads in 2/85 (2.4%) patients and T inversion V2-V6, left sided accessory pathway, right axis deviation, right atrial enlargement, old AWMI, IVCD, early repolarisation pattern and SVE's in 1/85 (1.2%) each. There was no difference in the heart rate, PR interval, QT interval and the QTc interval calculated manually versus that determined automatically by the machine.

Conclusion: Only a minority of adult patients with chronic, difficult to control epilepsy have normal ECG's. Those with abnormal ECG's (a majority), need further investigations to fully characterise their cardiac conditions. This has significant implications for service providers. Whether these ECG abnormalities are the cause of SUDEP is not known and requires further systematic studies.

P1336 Sustained ventricular arrhythmias and mortality among patients with acute myocardial infarction



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Introduction: Primary ventricular fibrillation (VF) or rapid polymorphic ventricular tachycardia (VT) are the main cause of high mortality in the early stage of acute myocardial infarction (AMI).

Aim: to investigate the in-hospital incidence, most appropriate treatment and mortality of patients (pts) with AMI complicated by initial sustained ventricular arrhythmias (VF/VT).

Methods: Total of 9406 pts with AMI admitted in the CCU were included in the study. The study period was January 1994 to December 2005. We have analyzed separately the data of subgroup of pts with AMI+VF/VT treated in the period 1999-2005 (4153 pts with AMI, 349 with VF/VT) because of predominant use of PCI vs Thrombolysis.

Results: In-hospital incidence of VF/VT in total group was 6.3% (601 pts) with total mortality of 40.5%. In the subgroup the incidence of VF/VT was 6.3% with mortality rate of 37.5%. Independent predictors of in-hospital VF/VT were anterior wall AMI (65% pts), lower SBP (<100mmHg), higher Killip class and shorter time to PCI/thrombolysis (<3 hours). After initial cardioversion, thrombolytics (Streptokinase, TPA) were used in 20% pts and PCI was performed in 25.2% pts. The 3rd group of pts was treated with LMWH + Amiodarone or beta blockers. Acute heart failure occurs in 23% pts. The mortality rate in PCI group was 23.9%, in thrombolytic group 27.5% and in the 3rd group (no PCI/fibrinolysis) 46.3%. Most of deaths in all groups happened during the first 3 hours of admission.

Conclusions: Despite the considerable improvement in the treatment of AMI in recent years, the onset of VF/VT is associated with a poor prognosis. Patients admitted for AIM+VT/VF are less often submitted to revascularization procedures during hospital stay. According to our results primary PCI and thrombolysis have significant effect ($p<0.05$) on lowering the mortality rate of AMI+VT/VF.

P1337 K201 (JTV519), a novel cardioprotective agent, prevents torsades de pointes induced by the K⁺ channel blocker, clofilium



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Background: K201 is a novel cardioprotective agent and multi-channel blocker with K⁺ channel blocking effect such as clofilium which induces the prolongation of QTc interval and torsades de pointes (TdP). In this study, we determined the effect of K201 on QT and QTc intervals, and induction of TdP, and examined K201 inhibition of TdP caused by clofilium with methoxamine in rabbits.

Methods and Results: Infusion of K201 at 40, 100, 200 and 400 $\mu\text{g/kg/min}$ for 30 min ($n=6$ in each group), dose-dependently, resulted in decreased blood pressure and HR, and prolongation of QT and QTc intervals. The QTc interval was significantly prolonged by 54% from baseline at 400 $\mu\text{g/kg/min}$ K201. But no TdP was induced. In the group receiving 50 $\mu\text{g/kg/min}$ clofilium with methoxamine ($n=6$), the QTc interval increased by 95% and TdP occurred in all animals. K201 significantly suppressed these clofilium-induced TdP, but still caused the prolongation of QTc interval.

Conclusions: K201 induces QTc interval prolongation, but not TdP and inhibits TdP caused by clofilium. The results show that K201 which has suppressive effects on the diastolic Ca²⁺ leak from the cardiac SR, may inhibit TdP caused by K⁺ channel blocker.

P1338 Does carvedilol have electrophysiological effects on human ventricular myocardium? The role of left ventricular function



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Purpose: Although carvedilol, a non-selective beta-blocker with multiple pharmacological actions has proved to be superior to other beta-blocking agents in reducing sudden death and total mortality in a number of clinical trials with patients suffering from congestive heart failure (CHF), its effects on human electrophysiological properties have not been assessed. We therefore evaluated these effects on ventricular refractoriness and repolarization in these patients.

Methods: We studied 22 patients (64 $\pm$ 11 yrs old) with ischemic or idiopathic dilated cardiomyopathy (EF <40%), presenting complex ventricular arrhythmias at Holter monitoring. Right ventricular effective refractory period (VERP) at three basic cycle lengths (600,500,400 ms), as well as monophasic action potential duration (MAPd90) at a drive cycle length of 500 ms, were measured before and after treatment with carvedilol (12.5-50 mg b.i.d.) for 4-8 weeks. Holter monitoring for 24 hours was performed before and after active carvedilol therapy.

Results: Right ventricular effective refractory period at 600 ms changed from

232 $\pm$ 9 ms to 248 $\pm$ 10 ms ($p=0.03$), VERP at 500 ms changed from 222 $\pm$ 9 ms to 237 $\pm$ 12 ms ($p=0.05$) and VERP at 400 ms changed from 216 $\pm$ 7 ms to 230 $\pm$ 15 ms ($p=0.05$). MAPd90, also, increased from 204 $\pm$ 16 ms to 224 $\pm$ 17 ms after treatment ($p<0.05$). Regression analysis revealed that change in refractoriness was correlated with ejection fraction ($R=0.616$, $p<0.01$) suggesting that patients with more preserved left ventricular function (EF >30%) responded to treatment with refractoriness and repolarization prolongation.

Carvedilol significantly reduced total ventricular premature contractions from 326 $\pm$ 77 to 161 $\pm$ 55 per hour ($p<0.01$) and episodes of non-sustained ventricular tachycardia from 10 $\pm$ 12 to 5.1 $\pm$ 4 per day, ($p<0.05$).

Conclusion: These results suggest that carvedilol prolongs ventricular refractoriness and repolarization in patients with CHF, while reducing premature ventricular activity. These electrophysiological effects would be beneficial in the treatment of patients with CHF and ventricular arrhythmias and may contribute to the positive outcome of clinical trials with carvedilol.

P1339 Interaction of mechano-electrical feedback, class III antiarrhythmic actions and heart failure



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Acute ventricular dilatation (AVD) may be superimposed on chronic ventricular dilatation in patients with cardiomyopathy. By activation of mechano-sensitive ion currents this may be arrhythmogenic due to a decrease in action potential duration. As it is unknown, whether mechano-electrical interactions are influenced by antiarrhythmic drugs in heart failure, we studied the effects of AVD on the antiarrhythmic properties of a repolarization prolonging drug in a rabbit model of pacing-induced heart failure.

Methods and results: In 10 rabbits, heart failure was induced by 4 weeks of rapid pacing leading to a decrease of ejection fraction from 73 $\pm$ 14% to 15 $\pm$ 3%. AVD via a fluid filled balloon placed in the left ventricle of the isolated rabbit heart, led to an increase in diastolic pressure to 50mmHg. Eight simultaneously recorded endo- and epicardial monophasic action potentials (MAP) demonstrated prolonged repolarization in heart failure as compared to 12 control hearts (mean MAP₉₀ 177 $\pm$ 18 vs. 161 $\pm$ 12ms; $p<0.05$). AVD reduced MAP duration (controls: -10ms; heart failure: -9ms, $p=ns$) and increased dispersion of repolarization (controls: +5ms; heart failure: +12ms; $p=ns$) due to greater shortening of left as compared to right ventricular action potentials. Administration of sotalol (50 μM) in non-dilated failing hearts led to a greater prolongation of MAP duration as compared to controls (+39ms vs. +13ms; $p<0.05$). In the presence of additional AVD, sotalol led to a further increase, especially in heart failure (+19ms vs. +6ms in control hearts; $p<0.01$). The further increase in dispersion (heart failure: +30ms; controls: +17ms; $p<0.01$) was due to less prolongation of left ventricular MAP as compared to right ventricular MAP.

Conclusion: During AVD, the class III effect of sotalol is almost not influenced in control hearts, but enhanced in heart failure hearts most likely due to downregulation of I_{Kr}. Prolongation of repolarization is more predominant than shortening of action potential duration due to AVD-induced activation of mechano-sensitive ion channels. Thus, in situations of acute volume changes in heart failure, the ventricle may still benefit from treatment with a repolarization prolonging agents.

P1340 Unstable VT ablation using NavX guided mapping reduces implantable cardioverter defibrillator (ICD) discharges



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Introduction: Recurrent discharges are a significant cause of morbidity in ICD patients (pts). Multiple Antiarrhythmic medication (AAR) use is frequently poorly tolerated. Ventricular Tachycardia (VT) mapping and ablation may reduce these discharges. We evaluated the effect of NavX (EnSite, St Jude Medical, MN) guided VT ablation on ICD discharges.

Methods: Patients with recurrent VT despite medical therapies were studied. Limited isochronal mapping was performed in stable VT to permit identification of the earliest activation. In the absence of stable VT, limited voltage mapping was used to identify scar (<0.5 mV), and further guide ablation.

Results: 6 patients (pts), 63 yrs (range 30-72 yrs) 5 males with coronary artery disease (CAD), 1 female ARVD were studied. Prior to ablation, pts had a mean of 16 discharges and were receiving an average of 2.4 AAR. A mean of 3 different VTs were inducible, 95% were hemodynamically unstable. At mean follow up of 180 days the mean discharge rate has dropped to 2 ($p<0.05$) per patient and AAR use to 1.2 per patient ($p<0.05$).

Conclusion: NavX guided VT mapping significantly reduced ICD discharge rates and antiarrhythmic use in this population. In patients with recurrent ICD discharges VT ablation using this approach merits consideration.

P1341 Right atrial ablation of ectopic atrial tachycardia using a 20-pole mapping catheter



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Introduction: Ectopic atrial tachycardia (EAT) are frequently unresponsive to a medical antiarrhythmic therapy. Radiofrequency ablation seems to be a safe approach to treat those arrhythmias. In the present study we report our results of radiofrequency ablation of EAT with a multipolar mapping catheter.

Methods: In 15 patients (G1) with right atrial tachycardia a 20-pole mapping catheter was used for localization of the arrhythmia foci. Data were compared with a control group (G2, n=15), in which mapping was performed conventionally. The demographic characteristics and the distribution of the different cardiac diseases were comparable in both groups. In group 1 the identification of the EAT was facilitated by the placement of a 20-pole mapping catheter in the right atrium. In group 2 point by point measurements were carried out to find the earliest local atrial activation compared to a reference electrode in the high right atrium (activation mapping), or foci were identified by analysis of the P-wave morphology during stimulation (pacemapping).

Results: It was possible to successfully ablate all atrial tachycardias. The distribution of the foci was similar in both groups (G1/G2): near to the superior (3/5) and inferior (1/0) caval vein ostium, on the free wall (3/3), at the coronary sinus ostium (3/3) and on the interatrial septum (5/4). The mean investigation (G1: 88±33 vs. G2: 151±61 min; p<0.05) and fluoroscopic time (G1: 19±9 vs. G2: 38±28 min; p<0.05) were significantly shorter in group 1. Moreover, the mean number of radiofrequency applications was reduced significantly by using the multipolar mapping catheter (G1: 10±10 vs. G2: 16±13; p<0.05).

Conclusion: Radiofrequency ablation of EAT with right atrial focus can be performed safely and successfully using a 20-pole mapping catheter. The greatest advantages compared to conventional mapping and ablation strategies lies in the shortened investigation and fluoroscopic time.

P1342 Ablation of atrioventricular nodal reentrant tachycardia by short radiofrequency energy delivery



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Introduction: Catheter ablation of atrioventricular nodal reentrant tachycardia (AVNRT) is usually performed by delivering radiofrequency (RF) energy at the slow pathway region during 60 to 90 seconds. However, the efficacy of shorter applications has not been evaluated.

Aim: to assess the efficacy and safety of short applications of radiofrequency energy to the slow pathway region.

Methods: Ninety eight consecutive patients with AVNRT (40 males, age 50±16) underwent RF ablation. Following an anatomical approach, slow pathway ablation was performed by applying RF energy for a maximum of 20 seconds. If junctional beats were obtained during the application, electrical stimulation was repeated to assess inducibility of AVNRT. If not, ablation catheter was repositioned and an additional 20 seconds application was performed. Only if despite obtaining junctional beats AVNRT remained inducible, RF delivery was prolonged for a maximum of 60 seconds. Success was defined as non inducibility of AVNRT under programmed stimulation at baseline and under isoprenaline infusion during a waiting period of 30 minutes. Outpatients follow-up was scheduled at 3, 6 and 12 months after the procedure.

Results: AVNRT ablation was successful in 90/98 (92%) ptes. 77/90 ptes were successfully ablated by RF delivery for 20 seconds or less (average 17±4 sc) (Group I). In 13/90 ptes RF delivery was prolonged more than 20 seconds (50±15 sc) (Group II) p 0.003. The average of RF pulses for each group was 3.5±2 and 8.5±4 respectively (p 0.05). Acute complications were right bundle branch block and transient AV block in two patients. During the follow up, recurrence was observed in 2 patients from Group I.

Conclusion: AVNRT can be successfully ablated with short pulses of RF energy. This approach may be beneficial in avoiding extensive tissue damage and reducing the risk of AV block.

P1343 Anatomic-Electrophysiological Correlations Concerning the Superior Vena Cava. Implications for Catheter Ablation



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Background: Superior vena cava (SVC) is a source of atrial fibrillation (AF). Correlation between anatomy and electrical activity (EA) of SVC has not been previously reported.

Purpose: The aim of the study was to correlate the characteristics of myocardial extensions towards SVC with the EA registered in this vein.

Method: Thirty five postmortem human hearts were dissected (group 1). Presence, location and extension of MS; location and number of myocardial breakthroughs (MB) from RA to SVC were studied in 4 quadrants: right anterior (RAQ), right posterior (RPQ), left anterior (LAQ) and left posterior (LPQ). Histological analysis was performed. Thirty five patients (pts) underwent EP study (group 2); 15 for paroxysmal AF, the rest for other supraventricular (SV) arrhythmias. SVC angiography was performed to detect the RA-SVC junction. SVC potentials were mapped with a Lasso[®] catheter from the RA-SVC junction, ascending until SVC potentials disappeared. This was performed during sinus rhythm and RA stimulation. The RA-SVC junction was established at the ridge that separates the right atrial appendage (RAA) from SVC in both groups.

Results: Group 1 showed MS in all cases, reaching maximum highness in the LAQ (15 to 56 mm, average 38,6); group 2 exhibited SVC potentials in all pts at the RA-SVC junction, that extended up to 60 mm into the LAQ (20 to 60 mm, average 35,8). MB were located: in the LAQ in 35/35 (100%) in group 1, and in 35/35 (100%) in group 2; in the RAQ in 28/35 (80%) in group 1 and in 25/35 (71%) in group 2; in the LPQ in 17/35 (48, 5%) in group 1, and in 4/35 (11%) in group 2. In group 1, 2 MB were found in 23/35 (65,7%), 3 MB in 9/35 (25,7%) and 4 MB in 4/35 (11,4%), coming from the lateral RA and RAA. There were no significative differences between patients with and without AF in the studied parameters (group 2).

Conclusions: Topography and extension of MS and characteristics of MB in post-mortem human hearts were closely correlated with EA coming from SVC in pts studied for SV arrhythmias. These findings could have implications for catheter ablation of arrhythmias arising in SVC.

P1344 Particular surface ECG pattern of Cavo-tricuspid isthmus localisation of anterograd accessory pathways



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Objective: The aim of this study was to determine in what way the CTI localisation of an AAP is associated with a double transition aspect on the surface ECG's precordial leads;

Means and Methods: In this retrospective, descriptive, study we screened 592 consecutive patients who had an Endocardiac Electrophysiological Exploration (EEE) for WPW syndrome from 1996 to 2005 in the Service and examined the surface ECGs of all patients who's AP was located in the CTI. As comparison we examined 20 randomly selected surface ECGs for each of the more classical locations of AAPs: left lateral; right lateral; right and left postero-septal; right and left anterior.

Results: 11 patients had their AAP located in the CTI representing 1.8% of all patients and 1.7% of all AAPs (several patients having more than one AAP). 10 had the double transition aspect on their surface ECGs. None of the patients with other-than-CTI location of their AAP had a double transition aspect on the surface ECG. Therefore the double transition aspect on surface ECG is associated with CTI localisation of the AAP with a 91% sensitivity and a 100% specificity

Cavo-tricuspid isthmus: a rare Kent pathway

Location		POLARITY OF DELTA/of QRS					
		V1	V2	V3	V4	V5	V6
right lateral	35	(~)/(-)	(~)/(-)	(~)/(-)	(+)/(~)	(+)/(+)	(+)/(+)
postero-septal	174	(+)/(~)	(+)/(~)	(+)/(+)	(+)/(+)	(+)/(+)	(+)/(+)
antero-septal	62	(~)/(-)	(+)/(~)	(+)/(~)	(+)/(~)	(+)/(+)	(+)/(+)
anterior left	21	(+)	(+)	(+)	(+)	(+)	(+)
anterior right	20	(~)	(+)	(+)	(+)	(+)	(+)
left posterior	53	(+)/(+)	(+)/(+)	(+)/(+)	(+)/(+)	(+)/(+)	(+)/(+)
left lateral	264	(+)/(~)	(+)/(+)	(+)/(+)	(+)/(+)	(~)/(+)	(~)/(+)
CTI	11	(+)/(~)	(+)/(+)	(+)/(~)	(+)/(+)	(+)/(+)	(+)/(+)
	640						

Conclusion: The aspect of double transition on the precordial leads of surface WPWS ECG seems to be constantly and specifically associated to the CTI location of the AAP.

P1345 Comparison of 8 mm or irrigated-tip catheters for radiofrequency ablation of the inferior vena cava - tricuspid annulus isthmus



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Introduction: Radiofrequency catheter ablation of the inferior vena cava-tricuspid annulus isthmus (CTI) is an established approach for atrial flutter treatment. The ablation success depends on creating deep contiguous (linear) lesions, usually obtained with an 8 mm-tip catheter. Radiofrequency ablation using a 4 mm irrigated-tip catheter creates also sizable lesions, without temperature-related limitation in the amount of energy delivered, and permits more precise mapping. However irrigated catheters are more expensive and complicated to use, as an infusion-pump is needed. Our purpose was to compare the efficacy and safety of an 8 mm-tip or a 4 mm open irrigated-tip catheter in CTI ablation.

Methods: Twenty consecutive patients with atrial flutter submitted to CTI ablation

were included. Seventeen were male and their mean age was 57 ± 6 y.o. Structural heart disease was present in eleven patients: hypertensive (in 4), ischemic (in 2), valvular (in 2), dilated cardiomyopathy (in 2) and Ebstein disease (in one). In 10 patients each were used 8 mm-tip or open irrigated 4 mm-tip catheters. A computerized mapping system was used in 17 patients (LocaLiza® in 3 and Carto XP® in 14).

Results: Complete isthmus block was obtained in 15 patients (75%). There were no immediate complications. Two patients had atrial flutter recurrence in the follow-up period (in both isthmus block had not been obtained). There were no statistically significant differences between the use of the 8-mm-tip or the irrigated-tip catheters comparing the total duration of the procedure (186 ± 26 vs. 155 ± 44 min), fluoroscopy exposition ($17, 8 \pm 9$ vs. $17, 7 \pm 7$, 7 min), average duration of energy application (827 vs. 859 secs), complete isthmus block (80% vs. 70%) or clinical recurrence (10% each).

Conclusion: In radiofrequency catheter ablation of the CTI, the success and safety of the procedure using an 8 mm or a 4 mm irrigated-tip catheter is similar. The utilization of the more expensive and complex irrigated-tip catheters is apparently not justified in atrial flutter ablation.

P1346 Diabetes and thyroid hormones affect intercellular gap junction coupling in the rat heart ventricles



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Background: Myocardial remodeling and intercellular gap junction channels connexin alterations have been shown involved in the development of malignant arrhythmias, including ventricular fibrillation (VF). Hyperthyroidism and diabetes are known accompanied by myocardial remodeling and increase a risk for VF in human. The aim of the study was to examine whether major intercellular channel protein, connexin-43, and PKC ϵ signaling are altered due to diabetes and thyroid hormones.

Methods: Type 1 of diabetes was induced in Wistar Kyoto rats by a single streptozotocin injection (50mg/kg, i.v.) and ventricular tissues were examined 4 and 9 wks after (acute and chronic stage). Triiodothyronine, T_3 (0.3 or 10 μ g/100/day) was applied via gastric tube during 10 days to non-diabetic and part of diabetic rats. Cx43 and its P(phospho)-isoforms as well as PKC ϵ expression were analyzed using WB and anti-Cx43 and anti-PKC ϵ antibodies. Microelectrodes and superfused ventricular muscle strips were used for conduction velocity (CV) measurements and isolated perfused heart for electrically inducible VF.

Results: A significant increase of Cx43 and its P-isoforms as well as PKC ϵ expression was found in ventricles of diabetic rat hearts. In contrast, marked decrease of PKC ϵ and Cx43 expression as well as Cx43 P-isoforms were found in the ventricles of non-diabetic rats treated with higher dosage of T_3 . The later, in addition, suppressed significantly phosphorylation of Cx43 and expression of both Cx43 and PKC ϵ in diabetic rat ventricles. Compared to age-matched controls CV was significantly decreased in diabetic while increased in T_3 -treated non-diabetic rat hearts and enhanced in diabetic rats treated with higher dosage T_3 . The highest VF susceptibility exhibited non-diabetic rats treated with higher dosage of T_3 , while the lowest diabetic rat hearts.

Conclusions: The results indicate that down-regulation of myocardial intercellular coupling protein Cx43 is associated with increased, while up-regulation with decreased susceptibility of the rat heart to VF. PKC ϵ signaling is most likely involved in the modulation of cell-to-cell coupling and diabetes as well as thyroid hormone-related electrical remodeling.

BRAIN NATRIURETIC PEPTIDE AND LEFT VENTRICULAR FUNCTION

P1347 Left ventricular compliance rather than relaxation determines elevated end-diastolic pressure in isolated diastolic dysfunction

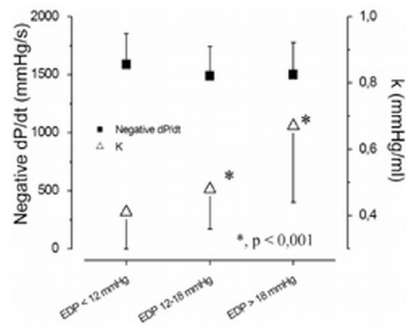


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Background: Isolated diastolic dysfunction and diastolic heart failure will be a concern with the ageing population and the prevalence of hypertension. The question whether preventive or curative drugs have to restore appropriate left ventricular (LV) relaxation or compliance is unsolved. We sought to establish the principal diastolic determinant of elevated end-diastolic pressure in an invasive-based study.

Methods and results: Left-sided heart catheterisation was performed in 118 consecutive patients with an ejection fraction $> 45\%$ and no heart disease. LV pressure was digitally recorded for end-diastolic (EDP, mmHg) and peak negative dP/dt measurements. LV end-systolic and end-diastolic volumes (EDV, ml) were measured from single plane planimetry using the modified Simpson's rule and ejection fraction was calculated. LV compliance was $k = (\ln EDP + 0.8)/EDV$. Patients were divided in 3 groups: G1 if $EDP < 12$ mmHg, G2 if EDP was between 12 and 18 mmHg and G3 if $EDP > 18$ mmHg. Overall, ejection fraction was $69 \pm 10\%$ and LV EDP was 14 ± 6 mmHg (range 2 to 33 mmHg). By ANOVA, k was significantly greater in G2 and G3 than G1 while negative dP/dt was un-

changed among groups (figure). A linear relationship was found between k and EDP ($y = 179x + 5$, $r = 0.55$, $p < 0.001$) whereas negative dP/dt was not correlated to EDP. By stepwise multiple regression analysis k was the strongest determinant of EDP ($F = 190$, $p < 0.001$).



Compliance, Relaxation and EDP

Conclusion: Elevated EDP is related to LV compliance rather than relaxation. Drugs restoring LV compliance should be concerned in the future to prevent and to treat isolated diastolic dysfunction.

P1348 Cardiac fibrosis correlates with cardiac diastolic stiffness in patients with diastolic heart failure



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Introduction: Isolated diastolic dysfunction is characterized by a disturbed compliance of the left ventricle (LV). The mechanisms leading to this diastolic dysfunction may include changes in the myocyte as well as changes in the cardiac extracellular matrix. Therefore, we investigated LV cardiac stiffness and cardiac fibrosis in patients with suspected diastolic heart failure (DHF).

Methods: 40 patients with exercise intolerance despite normal EF ($> 50\%$) were included in this study and compared with 8 control patients. In all patients pressure-volume loops were measured by conductance technique (CDLeicom, Netherlands). As marker for diastolic function LV stiffness was analyzed during preload reduction by transient occlusion of the v.cava and the PV relationship was calculated using an exp. fit of the enddiastolic PV points. All patients underwent cardiac biopsies for analysis of cardiac fibrosis (PICO, Sirius red).

Results: Patients with suspected DHF had increased EDPVR ($0.0275 + 0.0036$ vs. $0.0107 + 0.002$, $p < 0.05$) compared to controls as indicator for diastolic dysfunction. The systolic function was unchanged when DHF patients were compared to controls. Furthermore, increased LV stiffness correlated with cardiac fibrosis in patients with DHF ($R = 0.58$, $p < 0.05$).

Conclusion: We could demonstrate, that DHF is characterized by increased cardiac stiffness measured by conductance technique without changes in systolic function. Furthermore, increased cardiac stiffness correlated with cardiac fibrosis. These data suggests, that DHF is an isolated diastolic dysfunction accompanied by increased fibrosis. Therefore, future therapy for DHF should include pharmacological inhibition of fibrosis as a destiffening therapy.

P1349 Relationship between soluble cytokines levels and tissue Doppler derived indexes of left ventricular performance in patients with first diagnosed heart failure



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Introduction: Inflammation has been recognized to play significant role in the development, as well as in the progression of heart failure. Furthermore, tissue Doppler imaging provides a rapid assessment of both systolic and diastolic left ventricular function. In this study we aimed to evaluate the existence of any relationship between inflammatory markers and tissue Doppler derived indexes of left ventricular function in patients with first diagnosed heart failure.

Methods: We enrolled 66 consecutive patients (mean age 65 ± 13 years old) with acute heart failure who were hospitalized in our institute. Echocardiographic assessment was performed in all patients during the third day of their initial hospitalization. Mitral inflow velocities were recorded by standard pulsed-wave Doppler at the tips of the mitral and tricuspid valves, (E and A, respectively). The pulsed TDI of the mitral annulus was characterized by the myocardial systolic wave (Smv) and two diastolic waves (Emv and Amv), expressed in cm/sec. The ratio of trans-mitral peak E velocity to peak Emv recorded at the level of the lateral wall of the mitral annulus was also calculated (E/Emv). We measured plasma levels of interleukin-6 (IL-6), soluble tumor necrosis factor receptor 1, CD-40 and CD-14 and white blood cells counts (WBC) in all patients during their third day of hospitalization. Linear regression models were used to evaluate the association be-

tween inflammatory markers and echocardiographic indexes, after adjustment for several confounders.

Results: It was found that 1 pg/ml increment in IL-6 levels were associated with 0.25 units increase in the ratio E/Emv ($b = 0.25$, $p = 0.009$), while 1 $\mu\text{g/ml}$ increment in CD14 were associated with 1.25 units increase in the ratio E/Emv ($b = 1.25$, $p = 0.022$). Moreover inverse relationship was observed between the height of Smv and CD14 levels ($b = -1.065$, $p = 0.016$). The aforementioned relationships remained even after controlling for potential confounders.

Conclusion: This study revealed that increased plasma levels of IL-6 and CD14 are significantly correlated with increased E/Emv ratio, which reflects end-diastolic left ventricular pressure, and inversely correlated with Smv, which reflects left ventricular systolic performance, in patients with first diagnosed heart failure. These findings may suggest that high cytokine levels correlate with more impaired left ventricular diastolic and systolic function.

P1350 Immune activation in patients with diastolic heart failure



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Background: Systemic immune activation is well established in patients with systolic heart failure and inflammatory cytokines and their receptors serve as important prognostic markers. Patients with diastolic heart failure (CHF) have an impaired prognosis as well. It is not known whether these patient have signs of systemic immune activation.

Methods and results: We investigated 17 patients with diastolic CHF (72 $\pm$ 9 years, NYHA II (n=7), NYHA III (n=10)), 17 patients with systolic CHF (70 $\pm$ 8 years, NYHA II (n=1), NYHA III (n=16)) and compared the results with 16 healthy control subjects. Echocardiographic results demonstrated in patients with diastolic CHF significant left ventricular hypertrophy with preserved LV function (LVEF 59 $\pm$ 9%) whereas LVEF was 23 $\pm$ 5% in patients with systolic CHF. All patients were on stable medication and had no signs of decompensation at the time of testing. We evaluated serum levels of TNF-alpha, soluble TNFR 1 und 2, Interleukin 6 (IL-6) and Interleukin 10 (IL-10). Furthermore, NT-pro BNP was measured. The highest levels of TNF-alpha were present in systolic CHF (2.87 $\pm$ 0.65 vs 1.67 $\pm$ 0.58 pg/mL, $p < 0.001$) compared to diastolic CHF. No differences were found between diastolic CHF and controls. However, in patients with diastolic CHF sTNFR1 (1618 $\pm$ 384 vs 1013 $\pm$ 302 pg/mL, $p < 0.001$) and sTNFR2 (3554 $\pm$ 916 vs 2122 $\pm$ 586 pg/mL, $p < 0.001$) were significantly higher compared with controls. The same was true for IL-6, IL-10 and NT-pro BNP. As anticipated the highest levels of all cytokines and NT-pro BNP were present in patients with systolic CHF. We found significant correlations between IL-6 and TNF-alpha with the thickness of the LV Septum (all $r = 0.49$, $p < 0.05$). In conclusion, patients with diastolic CHF already show signs of systemic immune activation which may contribute to the impaired prognosis.

P1351 Precipitating factors in the elderly patients admitted with the diagnosis of Heart Failure. Are easy to find?



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Aim: The precipitating factors for Heart Failure (HF) are not easy to find. We found series in literature where these factors are unknown in 40% of the cases. There is little information about that in the elderly populations.

Methods: Prospective study of consecutive patients admitted for hospitalization in the period of the year 2004 in an Internal Medicine Department with the diagnosis of HF. Demographics, comorbidity, drug therapy and possible precipitating factors were abstracted from the case notes.

Results: We studied 228 patients, mean age 76.5 $\pm$ 10.8 years, 50.4% women, 52.2% hypertension, 51.8% atrial fibrillation, 28.2% chronic obstructive pulmonary disease, 28.1% with diabetes mellitus, 24.1% ischaemic cardiomyopathy. In the lab studies we found hemoglobin levels under 12 gr/dL in the 46.9% of the patients and a 55.3% of the population with a moderate or severe renal dysfunction. The mortality at the end of the year 2005 was 43% with a median of follow-up of 14 months. After a conducted interview and a careful review of all the information at the admission we could get that the precipitating factors at the admission were: a single factor in 91 cases (39.9%), multiple factors in 103 patients (45.2%) and an unknown decompensation factor in just 34 subjects (14.9%). Analyzed in a separate way, the main precipitating factor in our research was infection with 124 cases (54.4%) followed by anemia in 66 patients (28.9%), arrhythmia 56 (24.6%), hypertensive crisis or bad control of arterial pressure in 25 subjects (10.9%) and acute coronary syndrome in 21 cases (9.2%). The principal source for the infection was the respiratory tract with 95 cases (76% of all the infections). Other elements of decompensation in a less number of patients were: Overhydration, dietetic transgression, non-compliance with medication, hyperthyroidism, pulmonary embolism, pericardial tamponade.

Conclusions: In the real world of the elderly populations the precipitating factors for developing a HF seem to be easier to find than in the scientific literature with young patients where these factors are unknown in near the 40% of the cases.

We were not able to find a precipitating factor in only the 14.9% of the cases. A careful search for these factors in the elderly patients will help us to diminish the preventable new episodes of HF.

P1352 Classification of diastolic dysfunction in elderly patients with heart failure



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The aim of this study was to assess and classify diastolic dysfunction (DD) in different types of heart failure (HF) in hospitalized, elderly patients.

Methods: 157 cases (age > 60 yrs) of suspected HF, but no mitral valve disease were consecutively studied by complete echocardiography in a community hospital. Echocardiography (echo) included standard transthoracic echo, pulsed tissue Doppler echo (TDI) at the lateral mitral annulus and pulmonary venous flow velocities. There were 65 males, 92 females, age: 76.2 $\pm$ 9.1 yrs. HF was defined as clinical signs and symptoms with systolic dysfunction (EF < 40%) - systolic HF or moderate to severe diastolic DD - diastolic HF or HF with preserved systolic function (HFPSF). DD was classified in sinus rhythm (SR) as mild (E/A < 0.75 and deceleration time DT > 240 ms), moderate (E/A > 0.75, DT 150-240 ms, and mitral E/annular Ea ratio > 7.0 and/or pulmonary vein systolic/diastolic velocity S/D < 1.0) or severe (DT < 150 ms). Atrial fibrillation (AF) was considered to be indeterminate diastolic function. Patients were divided into 4 groups: group 1 no HF, group 2 systolic HF (SHF), group 3 diastolic HF (DHF) and group 4 HFPSF.

Results: SR was present in 111 cases: mild DD in 44/51 in group 1, 4/20 in group 2, none in group 3, 6/8 in group 4 ($p < 0.01$ group 1 vs 2 and group 2 vs 4, no difference between group 1 and 4); moderate DD in group 2 (5/20) and in group 3 (13/23) $p = 0.02$; severe DD in group 2 (9/20) and in group 3 (10/23), NS. AF was present in 24, 39, 26 and 53% in the groups resp ($p = 0.02$ in group 1 vs 4). E/Ea was significantly higher in group 3 (8.2 $\pm$ 1.3) than in group 1 (4.2 $\pm$ 2) and in group 4 (5.3 $\pm$ 0.6) $p < 0.005$ but not different from group 2. There was no age difference between the groups. Within the groups age and left atrial dimension were higher in AF than in SR (age: group 1: 80.3 $\pm$ 7.8 vs 74.9 $\pm$ 9 yrs $p < 0.05$, group 3: 83.0 $\pm$ 4.3 vs 72.7 $\pm$ 9.2 yrs $p < 0.005$, group 4: 81.2 $\pm$ 8 vs 71.1 $\pm$ 8.4 yrs $p < 0.05$; left atrium: group 4: 60.2 $\pm$ 7.4 vs 48.8 $\pm$ 6.8 mm $p < 0.01$), but there was no difference in E/Ea.

Conclusions: 1) the rate of mild DD was similar in groups without HF and HF-PSF; 2) moderate to severe DD was similarly frequent in DHF and SHF; 3) the prevalence of AF was higher in HFPSF than in either SHF or DHF.

P1353 Diabetic heart failure patients have significantly worse systolic and diastolic functions, by conventional echocardiography and tissue Doppler imaging, than non-diabetic heart failure patients



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Purpose: In patients with chronic heart failure (CHF) prognosis is worse if they also have diabetes. The aim of this study was to examine to which extent right ventricular (RV) and left ventricular (LV) systolic and diastolic functions were impaired in diabetic CHF patients, compared to CHF patients without diabetes, and to compare both groups to patients with various degrees of glucometabolic status but without CHF.

Methods: The Malmö Preventive Project (1974-1992) was a population-based study of 33,000 adults, designed to identify risk factors for cardiovascular disease (CVD). An ongoing re-screening project started in 2002, with approximately 13,600 individuals participating by the end of year 2005. All subjects answer a questionnaire, undergo a physical examination and have blood samples drawn. A sub-sample of subjects undergoes cardiac ultrasound. In the current analysis, 577 individuals (58% men, mean age 72 $\pm$ 3.2 years) who had undergone echocardiography were divided into 5 groups. Patients with known CHF with and without diabetes, respectively, formed 2 groups. Individuals without known CHF formed 3 additional groups, based on glucometabolic status: fasting-plasma glucose (FPG) < 6.0 mmol/l, impaired fasting glucose (IFG) and new-onset diabetes, and previously known diabetes. LV and RV diastolic and systolic functions, measured by tissue Doppler imaging (TDI) and 2-dimensional assessment of LV ejection fraction (EF), were compared among the groups in multiple regression analysis, first adjusting only for age and gender, and subsequently for relevant cardiovascular risk factors, medication, and echocardiographic variables.

Results: LVEF was significantly reduced among both CHF patients with and without diabetes, compared to subjects with normal FPG ($p < 0.0001$), adjusted for age and gender. With the exception of LV E lateral, diabetic CHF patients had significantly impaired values of all TDI variables ($p = 0.02$ - 0.0001), especially systolic TDI variables (RV and LV Vmax). Vmax in RV and LV lateral walls were also impaired in non-diabetic CHF patients, although not to the same extent as in diabetic CHF patients. Diastolic TDI measures did not differ significantly in CHF patients without diabetes compared to non-diabetic subjects. Significance was lost for most variables in the fully adjusted model, although the trend towards impaired values for diabetic CHF patients was still observed.

Conclusions: Among CHF patients, RV and LV systolic and diastolic functions

were significantly impaired in those with diabetes, compared to those without. This might partly explain the worse prognosis among the former.

P1354 Left ventricular diastolic dysfunction in human immunodeficiency virus infection: an echocardiographic study



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Aims: Acquired immunodeficiency syndrome (AIDS) is a systemic illness affecting multiple organs, including the heart. Left ventricular (LV) diastolic dysfunction has been reported as the first echocardiographically detectable abnormality in several cardiovascular disorders. We tested the hypothesis that Human Immunodeficiency Virus (HIV) carriers have LV diastolic impairment when studied early in the clinical course of the infection.

Patients and Method: Transthoracic echocardiography was performed in 69 consecutive patients (82.6% male, mean age 40.7 ± 10.3 years) with HIV infection without cardiac involvement or diabetes mellitus and 34 healthy organ donors (59% male, 36.7 ± 10.5 years). The HIV population consisted of 39 totally asymptomatic subjects and 28 patients with incipient AIDS. The immunologic situation was determined by CD4 lymphocyte counts.

Results: As compared to controls, the HIV group had similar LV dimensions and fractional shortening, E- wave deceleration time and Tei Index, but decreased early mitral flow peak velocity (E) ($p < 0.001$), E/A Ratio ($p < 0.01$) and increased LV mass index (LVMI) ($p < 0.01$) (Table 1). Doppler- derived parameters of diastolic function were significantly altered in the HIV group vs. controls (52.2% in HIV group, 14.7% in control group).

Diast. parameters in the studied groups

	HIV patients (n=69)	Healthy organ donors (n=34)
E wave (cm/s)	64.8 ± 14.3	$79.4 \pm 17.2^{**}$
A wave (cm/s)	58.1 ± 11.5	60.3 ± 15.4
E/A ratio	1.16 ± 0.32	$1.38 \pm 0.47^{*}$
E'(cm/s)	17.5 ± 5.7	18.1 ± 6.8
A'(cm/s)	18.1 ± 6.8	14.9 ± 16.2
E/E'	3.8 ± 1.01	4.9 ± 2.2
DT (ms)	181.2 ± 76.7	186.7 ± 40.2
Tei Index	0.34 ± 0.12	0.32 ± 0.15
LV mass index (g/m ²)	119.3 ± 30.8	$99.2 \pm 29.1^{*}$

Values are mean $\pm$ standard deviation. * $p < 0.01$, ** $p < 0.001$

Conclusion: The results of our study demonstrate that in asymptomatic HIV-positive subjects a significant impairment of diastolic function is present, which could be detected by echocardiography and echo- Doppler examination. These results suggest an early involvement of the heart in HIV disease.

P1355 Behavior of left ventricular systolic and diastolic function after renal transplantation



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Purpose: The aim of this study was to assess the changes of left ventricular systolic and diastolic function in patients (pts) with end-stage renal failure (ESRF) one year after renal transplantation.

Methods: Twenty seven pts (18 males - 9 females, aged 46 ± 11 years) with ESRF underwent complete echocardiographic study before and one year after renal transplantation. Parameters measured included: Left ventricular (LV) contractility variables as fractional shortening (FS), mitral annulus systolic excursion (MAPSE), circumferential fibre shortening velocity (Vcf) and end systolic stress/volume index (ESS/ESVI). Parameters of LV diastolic function as early and late atrioventricular flow velocities (E and A wave respectively), E/A ratio, deceleration time (DT), isovolumic relaxation time (IVRT) and Tei-index was also calculated.

Results: see Table 1.

Table 1

Parameters	First study	Last study	P-value
E/A	1.19 ± 0.35	1.26 ± 0.29	NS
D T (ms.)	189 ± 45	162 ± 34	$p < 0.05$
IVRT (ms.)	96 ± 15	85 ± 12	$p < 0.01$
LV Tei-index	0.47 ± 0.11	0.41 ± 0.08	$p < 0.05$
MAPSE (mm)	10.8 ± 0.90	11.5 ± 0.79	NS
FS (%)	34 ± 6.3	36 ± 6.1	NS
ESS/ESVI(kdyn/cm ³)	$2.25 \pm 0.55 \times 10^4$	$2.59 \pm 0.42 \times 10^4$	$p < 0.05$
Vcf (sec)	1.18 ± 0.45	1.27 ± 0.36	NS

Conclusion: Our results show that after renal transplantation there is significant improvement in LV diastolic and systolic function. Longer follow-up is needed to verify the above findings.

P1356 Prevalence and determinants of diastolic dysfunction in dialysis patients



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Purpose: Cardiovascular morbidity and mortality due to heart failure is high in dialysis patients. While the prevalence of systolic dysfunction in dialysis patients has been thoroughly documented, the prevalence of diastolic dysfunction has not. In this cross-sectional study, we investigated the prevalence and determinants of diastolic dysfunction in haemodialysis (HD) and peritoneal dialysis (PD) patients.

Methods: We included 131 patients (95 HD, 36 PD, 65% male) aged 58 ± 16 years from the Dialysis Center Groningen who underwent standard echocardiography. Diastolic dysfunction was defined as either a tissue velocity imaging (TVI) ≤ 8 cm/sec and/or an abnormal E/A ratio, isovolumetric relaxation time (IVRT), and deceleration time (DCT).

Results: Diastolic dysfunction was present in 92 (70%) patients. No difference in prevalence was found between HD and PD patients. Patients with diastolic dysfunction were older ($p < 0.0001$), had experienced more cerebrovascular accidents and/or transient ischemic attacks ($p = 0.013$), had a lower Kt/V urea (marker for dialysis quality; $p = 0.048$), a lower calcium-phosphate product ($p < 0.0001$), and a shorter duration of dialysis ($p = 0.008$). No relation was found with blood pressure, other laboratory parameters (haemoglobin, HbA1c, CRP, PTH, ferritin, cholesterol), and medication.

Patients characteristics

Parameter	Diastolic Dysfunction		P-value
	yes	no	
Age (years)	61 ± 13	48 ± 18	< 0.0001
Sex (male)	26 (67)	59 (64)	NS
CVA/TIA (yes)	13 (17)	0 (0)	0.013
Kt/V urea	3.4 ± 1.2	3.9 ± 1.1	0.048
Calcium-Phosphate Product	3.9 ± 1.0	4.6 ± 1.0	< 0.0001
Duration of Dialysis (months)	36 ± 38	62 ± 72	0.008

CVA: Cerebrovascular accident; TIA: transient ischemic attack; Kt/V urea: marker for dialysis quality based upon urea clearance; high Kt/V equals better dialysis quality

Conclusion: Diastolic dysfunction is frequently present in dialysis patients and related to dialysis quality. Unexpectedly, we found that patients with diastolic dysfunction had a lower calcium-phosphate product and a shorter duration of dialysis.

P1357 Evolution of cardiac damage in a targeted group of asymptomatic patients with advanced systemic sclerosis: an echocardiographic study



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Objective: To characterize cardiac lesions in systemic sclerosis (SSc) patients who remain asymptomatic at the advanced phase of the disease, and investigate their progression over the following years.

Patients and Methods: Patients who survived the early phase of SSc (i.e. the first 3 years) without clinical evidence of cardiac involvement (104 and 94 with diffuse and limited SSc, respectively, mean age of 55 years, disease duration 3-15 years) were studied by echocardiography. Repeated measurements, performed during a follow-up period of at least 3 years, were compared to baseline in 118 of these patients. Fifty healthy subjects, age- and sex-matched, served as controls.

Results: Left ventricular (LV) mass index and LV fractional shortening were found significantly increased and decreased, respectively, in both subtypes of SSc compared to healthy controls. Right ventricular systolic dysfunction and pericardial effusion were frequent findings among SSc patients of either subtype, while pulmonary hypertension was present in 20% of patients, but in none of controls. During a 4.5 ± 1.5 year-follow up, 4% of patients died of cardiopulmonary causes. Analysis of echocardiographic measurements at the end of follow-up showed that pulmonary artery systolic pressure increased significantly in both SSc subtypes by almost 20%, whereas the LV systolic dysfunction and the LV mass index progressed significantly only in patients with diffuse SSc.

Conclusion: Even in the absence of clinically overt disease, myocardial damage is common in the advanced phase of systemic sclerosis, and its evolution is more rapid in diffuse than in limited SSc. In addition to clinical evaluation, frequent echocardiograms in this population are mandatory, especially for the prompt diagnosis of pulmonary hypertension which is more frequent than currently thought.

P1358 Impaired global ventricular function and aortic distensibility in ankylosing spondylitis



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Background: Cardiac involvement in patients with Ankylosing spondylitis (AS) includes aortic root and valvular abnormalities, conduction defects, and arrhythmias.

Objectives: To evaluate echocardiographically ventricular function and aortic

stiffness in AS patients without symptoms of heart disease, and correlate the cardiac parameters with clinical and laboratory indices.

Methods: Complete echocardiography was performed in 51 AS patients (49 men, age 41.08 ± 9.31 yrs) with a mean disease duration of 15.58 ± 9.78 yrs, Modified Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 1.24 ± 1.13 and Functional Index (BASFI) of 2.89 ± 2.48 . A group of 45 healthy controls (34 men) with a mean age of 39.92 ± 9.11 yrs was also studied. The left (LV) and right (RV) ventricular Tei-index and aortic distensibility (Aod) were also calculated.

Results: In the AS patients, the LV and RV Tei-index were greater than controls ($p < 0.001$ for both, Table) and correlated with age, disease duration, and history of arterial hypertension (AH). In multivariate regression analysis, only patient age was associated with increased LV Tei-index ($R^2=0.35$, $p < 0.001$) or RV Tei-index ($R^2=0.398$, $p < 0.001$). Aortic distensibility, which was lower in AS patients than in controls (Table), also correlated with age, disease duration, AH, BASDAI or BASFI. In the multivariate analysis, BASFI ($R^2=0.401$, $p=0.003$) and AH ($R^2=0.241$, $p=0.001$) were found to be the only independent predictors of the impaired aortic distensibility in AS patients.

Parameters	AS	Controls	p
LV Tei Index	0.392 ± 0.02	0.37 ± 0.01	< 0.001
RV Tei Index	0.370 ± 0.021	0.034 ± 0.01	< 0.001
Aod ($\text{cm}^2/\text{dyn}/1000^2$)	2.21 ± 0.14	2.58 ± 0.09	< 0.001

Conclusion: Patients with AS and no clinically apparent heart disease have more often than healthy controls impaired left and right ventricular function which are associated with disease duration and arterial hypertension but not with clinical indices of the disease activity. In contrast, the patient functional status (BASFI) is an important independent predictor of aortic wall stiffness which is, also, impaired in these patients. Our data may suggest that cardiac and aortic abnormalities may be more prevalent in patients with long duration of disease and functional status impairment.

P1359 left atrial volume is an independent predictor of exercise capacity in patients with isolated diastolic dysfunction



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Background: Left atrial (LA) volume reflects left ventricular (LV) diastolic properties and is a marker of the severity and duration of diastolic dysfunction. LV diastolic dysfunction is an important determinant of exercise capacity in patients with normal LV systolic function. We hypothesize that LA volume predicts exercise capacity in patients with isolated LV diastolic dysfunction.

Methods: We performed echocardiography and maximal exercise testing in 256 patients with normal LV systolic function (LVEF $\geq 50\%$). Diastolic dysfunction was determined using on standard Doppler criteria. LA volume was measured using the ellipsoid method and maximum LA volume (Vol_{max}) was indexed to the body surface area. Univariate and multivariate predictors of exercise capacity in patients with isolated diastolic dysfunction were then determined.

Results: Mean age was 45 ± 15 years, with 73% male, 119 patients had diastolic dysfunction. Patients with diastolic dysfunction had higher indexed LA Vol_{max} ($20 \pm 6 \text{ ml/m}^2$ vs $18 \pm 4 \text{ ml/m}^2$, $p = 0.004$) and lower exercise capacity ($10 \pm 3 \text{ METs}$ vs $12 \pm 3 \text{ METs}$, $p < 0.001$). Univariate predictors of exercise capacity were age, gender, LV mass index, mitral E/A, E wave deceleration time, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/Ea), and indexed LA Vol_{max} . On multivariate analysis, only age ($p < 0.001$) and indexed LA Vol_{max} ($p = 0.003$) were independent predictors of exercise capacity. Exercise capacity was similar in the patients with normal diastolic function and those with diastolic dysfunction and normal indexed LA Vol_{max} . In contrast, patients with diastolic dysfunction and increased indexed LA Vol_{max} had reduced exercise capacity ($p = 0.002$).

Table 1. Exercise capacity in METs stratified according to diastolic function groups

	I Normal diastolic function n=137	II Abnormal diastolic function with preserved LA volume n=64	III Abnormal diastolic function with enlarged LA volume n=55	
Exercise capacity (METs)	11.5 ± 2.9	11.0 ± 2.8	9.1 ± 3.2	$p=0.19^1$ $p=0.01^2$ $p < 0.001^3$

¹ between groups I and II; ² between groups II and III; ³ between groups I and III.

Conclusion: Indexed LA volume is an independent and reliable predictor of exercise capacity in patients with isolated diastolic dysfunction. In these patients, exercise capacity is reduced only if LA volume is increased.

P1360 Prevalence and severity of pulmonary vascular disease in diastolic dysfunction with preserved left ventricular function



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Pulmonary hypertension and RV dysfunction are adverse prognostic features in

heart failure, but their prevalence and determinants in diastolic dysfunction are unclear. We sought to define their prevalence according to the degree of diastolic filling abnormalities, filling pressure and myocardial characteristics. We classified 1008 consecutive pts with preserved left ventricular systolic function according to diastolic filling abnormality; normal filling (NF), delayed relaxation (DR), pseudonormal filling (PSN) and restrictive filling (RF). PASP, pulmonary vascular resistance (PVR) from TR velocity and RVOT TVI, and RV function from tissue doppler of the RV free wall (RV S') were assessed. Between-group comparisons were made by ANOVA and comparison between categories was made by chi-square. The prevalence of normal filling, DR, PSN and RF were respectively 39%, 35%, 22% and 4%. Figure 1 shows mean PASP is greatest in those with increased filling pressure (PSN and RF page-corrected normal range) was 36% in PSN and 41% in RF vs 20% in NF and 17% in AR (NF vs. PSN $p=0.001$; NF vs. RF $p=0.01$). Fig 2 shows PVR to be greater in RF than all other groups (2.4 vs. 1.7 Wood units, $p=0.01$).

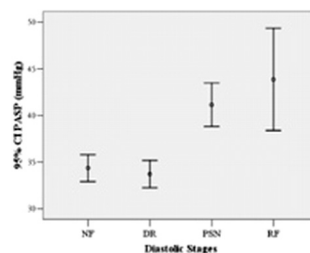


Fig. 1. PASP diastology.

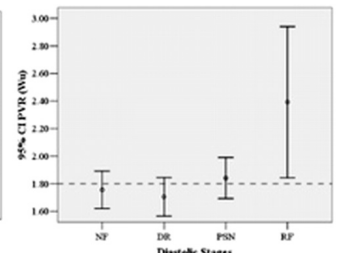


Fig. 2. PVR Diastology

Prevalence of increased PVR (> 1.8 Wood units) was higher in RF (79%) than NF (38%), DR (29%) and PSN (41%, $p=0.003$). An incremental increase in the proportion with RV dysfunction (RV S' $< 10 \text{ cm/sec}$) was seen with advancing diastolic dysfunction (4% among NF vs. 17% among RF, $p=0.009$). In patients with preserved systolic function, pulmonary pressure is normal in those with mild diastolic dysfunction. Increased PA pressure develops during the PSN stage and PVR increases at the RF stage. RV dysfunction is uncommon and associated with RF and increased PASP and PVR.

P1361 Pulmonary artery pressure is positively correlated with the degree of diastolic dysfunction in subjects with normal left ventricular systolic function



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Objectives: The aim of this study was to evaluate the correlation between diastolic dysfunction and pulmonary artery pressure (PAP) in patients with normal left ventricular (LV) wall motion. Background: Pulmonary arterial hypertension is a well-established sequel of LV systolic dysfunction; however its association with diastolic dysfunction in subjects with normal LV systolic function has not been thoroughly studied.

Methods: We analyzed retrospectively 477 consecutive echocardiographic studies that were performed in our medical center echocardiography laboratory in subjects with normal LV systolic function and correlated the state of diastolic function (normal, impaired relaxation, pseudo normal and restrictive pattern) to the magnitude of PAP assessed by echocardiography. None of the subjects that were studied had any other established causes of pulmonary hypertension.

Results: Mean PAP for subjects with normal diastolic function ($n=110$) was $31.1 \pm 6 \text{ mmHg}$; for grade 1 diastolic dysfunction (impaired relaxation) ($n=256$) $35.6 \pm 10.2 \text{ mmHg}$; for grade 2 (pseudo normal) ($n=102$) $38.9 \pm 10.6 \text{ mmHg}$ and for grade 3 (restrictive pattern) ($n=9$) the pressure was $55.1 \pm 11.4 \text{ mmHg}$ ($p < 0.001$ by one way ANOVA, the differences were between each 2 groups of diastolic dysfunction).

Conclusions: LV diastolic dysfunction is associated with an increase in PAP in subjects with normal systolic function. PAP is significantly increased for each step-up in diastolic dysfunction grade.

P1362 Diagnostic implications of Right Ventricular Systolic Dysfunction in patients with Dilated Cardiomyopathy



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Background: Unlike left ventricular (LV) function, right ventricular (RV) function has not been widely studied in ischemic patients. The role of RV function is emerging in patients with heart failure of different etiologies.

Objectives: To investigate the diagnostic role of RV systolic dysfunction (RVSD) in idiopathic dilated cardiomyopathy (IDC) & ischemic cardiomyopathy (ICM).

Methods: A series of 102 patients with dilated cardiomyopathy, either non-ischemic ($n=49$, IDC group) or ischemic ($n=53$, ICM group) & 20 healthy volunteers as a control group were included in this study. RVS function was assessed by pulsed - wave Doppler tissue imaging (PWDTI) of tricuspid annular systolic

(TAS) motion. Ejection Fraction (EF) of both RV & LV were estimated by Simpson's rule. Coronary angiography was performed to rule in or out coronary artery disease. RVD was defined as a RV EF < 35% or TAS velocity (TASV) < 12 cm/s & ventricular concordance (VC) was defined as a < 10% difference between RV and LV EF.

Results: Patients with IDC and ICM had comparable LV EF ($36.7\% \pm 7.2\%$ vs. $39\% \pm 6.6\%$, $p < 0.1$) and pulmonary artery systolic pressures (38.1 ± 5.7 mm Hg. Vs. 35.8 ± 7.5 mm Hg., $p < 0.08$). TASV & RV EF were significantly lower in IDC compared to ICM (10.6 ± 1.2 cm/s vs. 12.7 ± 1.4 cm/s, $p < 0.001$) & ($34.1\% \pm 4.1\%$ vs. $47.6\% \pm 7.5\%$, $p < 0.001$) respectively. The prevalence of RVD & VC was significantly higher in the IDC compared with ICM (67.4% vs. 17% , $p < 0.001$) & (85.7% vs. 15.1% , $p < 0.001$) respectively. Reduced RV EF, low TASV & VC were powerful independent predictors of IDC compared with ICM (OR for each = 0.78, 0.21, 0.63 respectively & 95% CI [0.72-0.85], [0.12 - 0.38] & [0.54-0.73] respectively, $p < 0.001$ for each). Reduced TASV had a positive predictive value (PV) of 88% & a negative PV of 90% to diagnose IDC, for reduced RV EF these values were 79% & 73%, & for VC, 85% & 87% respectively. The correlation between TASV & RV EF was stronger in IDC compared with ICM ($r = 0.87$, $p < 0.001$ in IDC while $r = 0.69$, $p < 0.001$ in ICM) respectively.

Conclusions: PWDTI has a high predictive power for RVSD & in the presence of LVD, the combination of low TASV, VC & reduced RV EF is a powerful marker for IDC compared with ICM, independent of pulmonary hypertension & LV EF. These findings support the concept that IDC is frequently characterized by a biventricular affection & that the presence of RVD represents a distinguishing feature of this disease.

P1363 First in man non-invasive monitoring of pulmonary artery pressure from an implantable device using acoustic telemetry: a one year follow-up data



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Purpose: The left ventricular end diastolic pressure (LVEDP), a critical hemodynamic parameter serves as the basis for most decompensation events in Congestive Heart Failure (CHF). Frequent monitoring of pulmonary artery (PA) pressure (PAP) supplies the feedback loop for direction of therapy, which presently is available invasively by Swans-Ganz catheterization. Remon CHF Implant (Impressure[®]) measures the PAP waveform based on non-invasive acoustic activation and communication, as frequently as necessary. Following successful animal studies, this first-in-man pilot study is set up to demonstrate the delivery system, safety and functionality of Impressure[®] in ambulatory patients.

Methods: 10 NYHA class III/IV patients were included in the study. Baseline hemodynamic assessment was obtained prior to implantation by Right Heart Catheterization (RHC). A control pressure measurement was also performed using a Millar Catheter. The Impressure[®] (3mm x 3mm x 16mm), made of titanium case, encapsulating an energy exchanger, control chip, pressure sensor and energy reservoir with ultrasonic capabilities was percutaneously implanted, using a delivery system (internal jugular approach) in the Right PA. It was positioned using a self expandable nitinol anchor attached to it. When interrogated by the desktop system, through a handheld transducer, in contact with the chest, Impressure is activated. The energy exchanger (piezoelectric transducer) converts applied external ultrasonic pressure to electrical energy. Once energized, the control chip interrogates the pressure sensor and ultrasonically transmits the digital reading to an external receiver. PAP was measured using the Impressure[®] till 6 months. RHC was repeated at 6 months for authenticating the Impressure[®]'s functionality and accuracy. One year follow up will also be studied.

Results: The Impressure[®] was deployed in the right PA in 10 patients. High quality accurate (compared to Millar catheter) pressure waveforms were obtained using the implant and the external desktop system. PA pressures were accurately available till 6 months. Impressure[®]'s functionality and accuracy were comparable to the control pressure measurements from Millar Catheter at baseline and 6 months. Patients are being followed for 1 year.

Conclusions: Impressure[®]'s unique telemetric technology enables easy repeated non-invasive measurement of the PAP waveform and PA Diastolic pressure in ambulatory patients. Such continuous noninvasive monitoring of PAP by an implantable device may improve the prognosis and management of CHF patients.

P1364 First-In-Man: comparison of impressure device measuring pulmonary artery pressure non-invasively with conventional contrast echocardiography In Congestive Heart Failure



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Purpose: Patients with heart failure will develop rise in pulmonary venous and arterial pressures. Reduction in pulmonary artery pressure (PAP) with improved cardiac output is a good clinical indicator of response to therapy. PAP measurement helps to assess efficacy of treatment. Assessment of PAP by contrast echo-

cardiography is one such available non-invasive method. Remon CHF implant (Impressure[®]) is a first of its kind device for the noninvasive monitoring of PAP. The study compares the functionality and precision of this device in measuring systolic PAP as compared to conventional contrast echocardiography.

Methods: It was a First In Man, prospective single arm study in 10 NYHA class III/IV CHF patients with LVEF $26.5 \pm 4.3\%$ enrolled for the Impressure[®] implantation. The Impressure[®] (3mm x 3mm x 16mm), made of titanium case, encapsulating an energy exchanger, control chip, pressure sensor and energy reservoir with ultrasonic capabilities was percutaneously implanted, using a delivery system (internal jugular approach) in the Right PA. A self expandable nitinol anchor is attached to it for its positioning. On interrogation by the a handheld transducer, in contact with the chest, Impressure[®] is activated and based on non-invasive acoustic activation and communication PAP waveforms are generated on the desktop system. Following the implantation, PAP was measured using this novel device non invasively and by Contrast echocardiography (Vivid 4, GE) by two blinded independent echocardiographers. Intravenous saline was used for the echocardiography to obtain adequate tricuspid regurgitation Doppler signal for right ventricular and PA systolic pressure assessment.

Results: The mean($\pm$ SD) systolic PAP measured by Contrast echocardiography was $38.23(\pm 10.23)$ mm Hg whereas by Impressure[®] was $38.3(\pm 17.7)$ mmHg. The Impressure[®] also measured non invasively Diastolic PAP which was $19.03(\pm 11.6)$ mm Hg. Systolic PAP measurement from contrast echocardiography correlated only fairly with Impressure[®] ($r=0.68$, $p=0.03$). Additionally, diastolic or mean PAP or repeated measures as available with Impressure[®] are not possible with contrast echocardiography Doppler.

Conclusions: Impressure[®]'s unique telemetric technology enables easy repeated non-invasive measurement of the PA pressure waveform and PA Diastolic pressure in ambulatory patients. Such frequent noninvasive monitoring of PAP by an implantable device may improve the management of patients with CHF and PAH and should reduce need for repeated hospitalization and better optimization of drug therapy.

P1365 Thoracic ultrasonography in evaluation of patients with heart failure



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Background: Pulmonary congestion is useful marker of congestive heart failure (CHF). The diagnosis of pulmonary congestion is confirmed by clinical and Roentgenological examination, there are not any known ultrasonographic (US) symptoms of this condition.

Methods: We studied 169 patients with heart diseases (cardiomyopathy, CHD, AH, Valvular diseases) who had different grade CHF (NYHA class, II-59, III-78, IV-32) and X-ray signs (venous redistribution, interstitial or alveolar pulmonary edema) of pulmonary congestion (I group) and 80 normal persons and patients with heart diseases who had no signs of heart failure (II group). Left ventricular cavity dimension, and EF% was determined by 2D-EchoCG, pulmonary artery pressure - by Dopplerographic evaluation of tricuspid or pulmonary regurgitation flow. Sonographic evaluation of a lung was done in horizontal and vertical positions of patient, from 12 points of thoracic wall which corresponded to the projection of lower, middle and upper lobes of a right lung and upper and lower lobes of left lung.

Results: In patients with CHF we significantly often found the one of the sorts of reverberation - "Comet tail Phenomenon" (CTPh) (100% versus 46%, $p < 0.005$). The count of points from where the CTPh was registered in HF group was 9.21 ± 3.14 , in persons without HF - 1.36 ± 1.30 ($p < 0.001$). There was good correlation between the count of CTPh registration points from the thoracic wall and the heart failure NYHA class ($r=0.56$), left ventricular systolic ($r=0.40$) and diastolic ($r=0.32$) diameters and negative correlation with EF% ($r=-0.42$). In the I gr. CTPh was registered from 3 or more points of thoracic wall, in II gr. - from 5 points or less. If we take 5 points and more as a reference value the sensitivity of sign in diagnosis of pulmonary congestion was 84.6% an specificity - 98.8%. In CHF group CTPh was prominent, protracted and multiple while in the II group it was single and short lasting.

Conclusion: Thoracic US is sensitive and accurate method for evaluation pulmonary congestion in patients with CHF. The US sign of pulmonary congestion in HF is a "Comet tail phenomenon", which is protracted, prominent, multiple and registered from larger area of thoracic wall (5 points or more).

P1366 The case for echocardiographic assessment of volume overload beyond B-type natriuretic peptide levels



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Background: B type-natriuretic peptide (BNP) has been shown to be of diagnostic and prognostic significance in patients with clinical evidence of volume overload (VOL) and left ventricular systolic dysfunction. Echocardiography (Echo)

utilizing Doppler tissue imaging of the Mitral annulus (DTI) is a validated method to derive pulmonary capillary wedge pressure (PCWP) and has been shown to correlate with BNP levels making a case for a simple blood test to measure the wedge pressure. However, marked elevations of BNP have been noted without VOL. Thus, we hypothesized that elevated BNP levels may reflect non-specific neuro-humoral activation due to multiple co-morbidities rather than due to VOL confirmed clinically or with Echo-derived PCWP.

Methods: Over a one-year period, all patients admitted with BNP levels greater than 1000 pg/ml were identified and the demographics, co-morbidities including the presence of sepsis and any clinical evidence of VOL were detailed. Echo parameters including the Mitral inflow, DTI, Left Ventricular Ejection Fraction (LVEF) and derived PCWP $[(1.29 (E/E') + 1.9)]$, were obtained within 48 hours of BNP.

Results: A total of 99 patients (61±14 years, 45 male/54 female) had a mean BNP (pg/ml) of 2727±1376 (SD). BNP values were higher if LVEF<40 (3001±1409, n=36, PCWP=19) versus LVEF>40 (2573±1354, n=60, PCWP=15). Univariate linear regression models for factors age, creatinine and hemoglobin and 2-D echocardiographic parameters including left atrial size and LV internal diastolic dimension along with Doppler parameters of left ventricular filling including E/A, E/E' and PCWP, each independently explained very little variation of BNP values (maximum $R^2 = 0.03$). There were 52 patients (53%) with sepsis, 47 had no evidence of VOL with mean BNP of 2797 ± 1311pg/ml (p=ns). Among these, 38 had DTI with a mean PCWP of 17mmHg and a LVEF>40. BNP values, although all elevated, were higher in VOL (3050±1521, n=28, PCWP of 18) versus No VOL (2572±1294, n=71, PCWP of 16) (p=ns).

Conclusion: In patients admitted with cancer and multiple co-morbidities, markedly elevated BNP values do not correlate with non-invasive measurement of PCWP by Echo. Echo parameters and derived hemodynamics support clinical observations, and therefore therapeutic decisions may need to be guided more by them as opposed to BNP levels alone. Entities like sepsis and other inflammatory cytokines may be important in causing these non-specific elevations of BNP

P1367 MMP-2 and N-BNP in the prediction of left ventricular impairment post acute myocardial infarction



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Background: LV dysfunction post acute myocardial infarction is a poor prognostic marker and evidence of such may imply the need for altered patient management. Matrix metalloproteinase -2 (MMP-2) is a member of the zinc dependant metalloproteinase family. Levels have been shown to alter following acute myocardial infarction and have been implicated in the pathogenesis of LV dysfunction and remodelling. The aim of this study was to investigate the utility of MMP-2 and N-BNP levels at predicting significant LV impairment post AMI.

Methods: We studied 91 patients with AMI (85%STEMI, 72.5% male, mean age 63.4 years). MMP-2 and N-BNP was measured at 0-12, 12-24 and 24hr periods after symptom onset until discharge. Echocardiographic assessment of LV function via bi-planar ejection fraction (LVEF) taken from apical 2 & 4 chamber views was performed prior to discharge. MMP-2 and N-BNP were measured using our validated in house assay.

Results: MMP-2 was similar at all times with lower levels in inferior AMI (p=0.007-0.019). Within the first 12 hrs MMP-2 was lower in smokers (p=0.018) and males (p=0.013). N-BNP showed a peak at 12-24hrs post event followed by a fall to plateau at 24-48hrs onwards, levels were higher in anterior v inferior infarcts at all time periods other than 96+ hours (p=0.018 to <0.001) and correlated with age being most significant at 72-96hrs (r=0.545, p<0.001). Smoking was associated with lower levels of N-BNP between 24 and 96 hrs (greatest at 48-72hrs, p=0.001). Using a multivariate binary logistic model both log MMP-2 (OR 0.06, p=0.009) and log NT-BNP (OR 3.1, p=0.044) at day 3 (48-72hrs) post infarct independently predicted LVEF <40%. The receiver-operating curve for N-BNP yielded an area under the curve (AUC) of 0.754 (p<0.001) whereas the logistic model combining the 2 markers yielded an AUC of 0.813 (p<0.001).

Conclusion: MMP-2 in combination with N-BNP is superior to N-BNP alone in the prediction of post AMI LV impairment

P1368 Do BNP levels correlate with left ventricular filling pressures in the morbidly obese? An invasive hemodynamic and echo-Doppler study



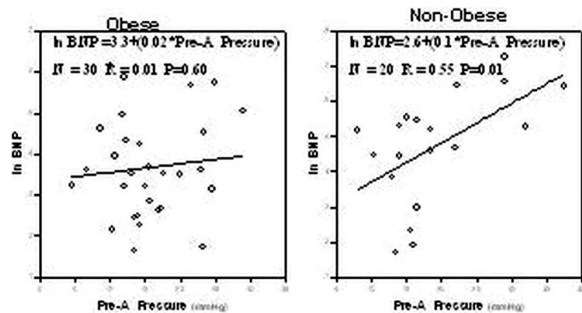
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Introduction: Although obesity results in lower circulating B-type natriuretic peptide (BNP) levels, it is unknown whether BNP correlates with invasively measured left ventricular (LV) pressures in the morbidly obese.

Methods: Consecutive patients referred for left heart catheterization at our institution underwent simultaneous BNP measurement, retrograde LV catheterization, and echo-Doppler examination. Patients with non-sinus rhythm, significant valvular disease (>mild), and renal failure (creatinine>150 mmol/L) were excluded. Morbid obesity was defined as a body mass index (BMI) >35 kg/m².

Results: 50 patients were studied (30 obese, 20 non-obese). Morbidly obese patients had a mean BMI of 42.5±6.9 versus 28.1±3.3 kg/m² in the non-obese (p<0.001). There were no significant differences in age (mean 54.5±8.7 years), gender (62% women), diabetes (60%), hypertension (80%), significant CAD on catheterization (49%), LV ejection fraction (mean 55±15%) right ventricular function (89% normal), or pulmonary artery systolic pressure (mean 32.5±9.1 mmHg) between the obese and non-obese. The correlation of LV pre-A pressure with natural log (ln) BNP in the obese was non-significant (R=0.01, p=0.60) compared to a significant correlation (R=0.55, p=0.01) in the non-obese (Figure). Similarly, the correlation of LVEDP in the obese was non-significant (R=0.20, p=0.28) compared to a significant correlation (0.57, p=0.01) in the non-obese.



BNP and LV Pre-A Pressure

Conclusions: In contrast to non-obese patients, invasively measured LV filling pressures do not correlate with BNP levels in morbidly obese patients.

P1369

Levosimendan induced NT-ProBNP rate variation relates with the immediate and short term patient functional improvement. A three-month follow-up study

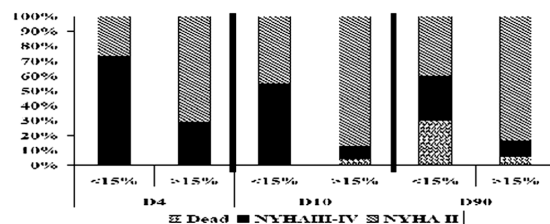


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Background: Levosimendan therapy in decompensate severe chronic heart failure (SCHF) improves neurohormonal markers.

Aim: To assess the relationship between NT-ProBNP plasma levels rate variation after levosimendan infusion and patient's functional class during a short term follow-up (3 months). Population and methods: 29 patients (pts), 24 men, 60.5 ± 13.0 years with SCHF (74.3% NYHA class IV; 25.7% class III), all with cardiac index < 2.5L/min/m², corresponding to 35 levosimendan administrations (bolus+24h infusion). NT-ProBNP was measured at baseline, day (D) 1, D4 and D10 after infusion, and its rate variation (rv) determined for D1 and D4 in relation to baseline. NT-ProBNP-rv was stratified in tertiles, in order to determine its relation with clinical status (composite of NYHA class and death).

Results: (1) At D1, D4 and D10, 20%, 57.1% and 74% of the pts, respectively, were in NYHA II class. (2) The lower the NT-ProBNP-rv decrease at D1, the greater the NYHA class at D1 (p=0.049). Pts not achieving the lower NT-ProBNP-rv tertile (<15%) remained in NYHA class III-IV. (3) The lower the NT-ProBNP-rv decrease at D4 (see figure) the worst the clinical status at D4 (p=0.027), D10 (p=0.010), D30 (p=0.317) and D90 (p=0.056). Pts in lower tertile (<15% rate) had a greater risk of being in NYHA class III-IV at D4 (Odds Ratio=2.494, p=0.027), D10 (OR= 5.750, p= 0.016) and D90 (OR= 3.640, p=0.088).



Conclusion: NT-ProBNP-rv after levosimendan infusion relates with immediate and short-term functional improvement.

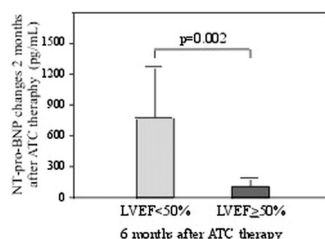
P1370 Amino-terminal pro-B-type natriuretic peptide: a predictive marker of left ventricular systolic dysfunction after anthracyclines at standard doses



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Background: Cardiotoxicity is a frequent side effect of anthracyclines (ATC) that are commonly used in patients (pts) affected by cancer. Recently, N-terminal pro-BNP (NT-pro-BNP) has been proposed as a marker of cardiac dysfunction. We sought to evaluate the role of NT-pro-BNP in predicting the development of left ventricular dysfunction (LVD) in pts treated with ATC at standard doses. Patients and methods. NT-pro-BNP was measured in 43 pts affected by aggressive malignancies (20 pts with leukaemia and 23 pts with lymphoma) who were scheduled to receive standard dose ATC. Blood samples were drawn before the start of ATC administration and 2 months later. Clinical examination, 12-lead electrocardiograms, and two-dimensional echocardiograms were performed at baseline, 2, and 6 months after chemotherapy administration.

Results: A significant correlation between increase in NT-pro-BNP plasma levels and reduction in left ventricular ejection fraction (LVEF), respectively 2 and 6 months after ATC infusion, was observed ($r=-0.55$, $P=0.001$). Seven (16%) pts had a significant decrease in LVEF values after 6 months of ATC therapy (from $58\pm7\%$ at baseline to $45\pm7\%$, $P=0.017$). It is worthy of note that LVD development after 6 months of chemotherapy administration was significantly associated with increased NT-pro-BNP plasma levels measured after 2 months of ATC therapy (Figure).



Conclusions: Increased NT-pro-BNP levels evaluated early after administration of ATC at standard doses are strongly related with LVD development. This finding suggests that NT-pro-BNP may be considered a new neuro-hormonal marker useful for identifying patients at high risk of developing ATC-induced cardiotoxicity, thus needing of careful echocardiographic monitoring and early protective cardiologic therapy.

P1371 Value of level of brain natriuretic peptide for risk stratification and monitoring of beta-blocker therapy in chronic heart failure



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Background: Brain natriuretic peptide (BNP) is a useful marker for diagnosis and prediction of prognosis in patients with severe chronic heart failure (CHF). However, the prognostic value of BNP changes during heart failure therapy has not been well clarified.

The aim of study was to assess the value of BNP level in the risk stratification and association between changes in BNP level and modification of prognosis in pts with IV NYHA class CHF and dilated cardiomyopathy (DCM).

Methods: 88 pts (age 58.3 ± 1.7) with an echocardiographic diagnosis of cardiomyopathy (LV end-diastolic dimension >60 mm, ejection fraction $<35\%$) of ischemic origin were prospectively studied for an average 14 ± 0.7 months. These clinically stable pts were randomly assigned to groups receiving (46 pts) and non-receiving carvedilol (C) (up to 50 mg) in addition to ACE inhibitors, digoxin and diuretics. Plasma levels of BNP (pg/ml) were measured at baseline and 12 month of treatment.

Results: The distribution of pts in groups according to baseline BNP level (BNP <300 , $300 < \text{BNP} < 600$ and $\text{BNP} \geq 600$ allowed to identify patients with low (10.4%), moderate (20.5%) and high risk (37.7%) of one-year mortality from cardiac causes ($p < 0.01$). Plasma baseline level of BNP were not significantly differs in C receiving and non-receiving groups, however, long-term treatment with C has resulted to higher incidence of decreasing of $\text{BNP} \geq 50\%$ (78%) compared to pts non-treated by C (32%, $p < 0.01$). Among patients with a $\geq 50\%$ reduction of baseline BNP values, the number of patients with events was significantly lower as compared to patients with a $<30\%$ BNP reduction (relative risk [RR] 0.35 [95% CI 0.30 - 0.41], $p < 0.01$). One-year mortality rates were 6.7, 13.3 and 25% in the C group and 14.3, 28.6 and 50% in pts not treated with C in the lower, middle and upper tertiles ($p < 0.01$). This improvement of prognosis is related to changes in BNP level during long-term C treatment.

Conclusions: 1) The prognostic importance of BNP was highly significant, irrespective of thresholds or treatment groups. 2) The changes of BNP level $\geq 50\%$ identified patients with major cardiac events risk reduction. 3) Improvement of prognosis in patients with CHF during long-term C therapy is related to significant decrease of plasma BNP level.

P1372 Impact of a BNP strategy to improve medical treatment in CHF patients on Haemodynamical and homeostasis parameters A STARS post hoc study



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Aim: To evaluate the impact of a therapeutic strategy using plasma BNP level on renal and homeostasis parameters.

Methods: STARS design: 220 NYHA class II-IV considered optimally treated CHF patients were included. Patients were randomized to medical treatment according to current guidelines ("clinical group") or to medical treatment aiming at decreasing BNP plasma levels below 100 pg/ml (BNP group). Outpatient visits were scheduled every month for three months (titration phase) and every 4 months thereafter. Natriemia, kaliemia, Nitrogen, creatininemia weight, NYHA class systolic and diastolic pressure were measured in the two groups during titration phase.

Results: At baseline, the two groups were similar for NYHA fonctionnal class, clinical features, creatininemia, natriemia, etiology of CHF, systolic blood pressure and heart rate. During follow-up significantly fewer patients reached the combined endpoint in the BNP group than in the clinical group (15.6% vs 26.8%; $p=0.001$). Treatment modification occurred on 134 occasions in the clinical group while treatment modification occurred on 66 occasions in the clinical group ($p < 0.05$). The most frequently pharmacological agent modified was diuretics (41% of the modifications in the BNP group, 39% of the modifications in the clinical group; $p=NS$). The mean increase in furosemide was 9 ± 20 mg and was similar in the 2 groups. However all the treatment were modified more frequently in the BNP group. (diuretics 55 vs 26; spironolactone 17 vs 7; ACEI: 21 vs 9; beta-blockers 36 vs 20) During titration phase, the mean daily dose of ACE-I increased in the 2 groups (from 94 to 106% of recommended dosage in the BNP group, $p < 0.05$ and from 94 to 98% in the clinical group, $p=ns$), as well as the mean dosage of betablocker (from 58 to 70% of recommended dose in the BNP group, $p < 0.05$ and from 57 to 67% in the clinical group, $p < 0.05$). However, at the end of the first 3 months, the mean dosage of ACE-I and betablocker, expressed as % of recommended dosage, were significantly higher in the BNP group than in the control group. During titration phase, creatininemia increase in a comparable way in the two groups ($p < 0.05$). Kaliemia and Natriemia were not modified. Heart rate, weight and systolic arterial pressure decreased in the both groups (all NS between the two groups).

Conclusion: In patients with systolic heart failure, a BNP-guided strategy reduces the risk of death or hospitalization for heart failure with a limited impact on systolic arterial pressure, heart rate and creatininemia despite an aggressive therapeutic management.

P1373 Measurement of B-type Natriuretic Peptide in an emergency department using the Abbott AxSYM immunoassay



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Congestive heart failure (CHF) diagnosis is routinely based on the clinical history, physical examination, ECG and chest x-ray. B-type Natriuretic Peptide (BNP) is a cardiac hormone secreted as a response to ventricular volume expansion, pressure overload and resultant increase in wall tension. The objective of this study is to assess the clinical utility of BNP as an additional diagnostic tool for patients with acute dyspnea.

A total of 270 patients (127 women and 143 men) presenting to the emergency department were screened. The overall age median was 80 years for women and 75 years for men. The diagnosis of CHF was based on physical examination, ECG, chest x-ray and echocardiogram. Three patient categories were established depending on results these diagnostic tools: (1) dyspnea due to CHF, (2) dyspnea of pulmonary origin and (3) dyspnea due to cardiac causes but without CHF. Blood (plasma) concentrations of BNP were determined on an AxSYM analyzer (Abbott Laboratories). Diagnostic accuracy of BNP was assessed by ROC curve analysis.

The final diagnosis was dyspnea due to congestive heart failure in 165 patients with a BNP median of 573 pg/mL (95% Interval of Confidence: 477 - 666 pg/mL), dyspnea with a pulmonary origin in 61 patients with a BNP median of 59 pg/mL

(95% IC: 49 - 84 pg/mL) and dyspnea due to non-CHF cardiac causes 44 patients with a BNP median of 187 pg/mL (95% IC: 128 - 333 pg/mL). Differences between the three medians (Figure 1) were statistically significant (Kruskal-Wallis test, $p < 0.001$).

Used in conjunction with other clinical information, BNP measurement made with Abbott AxSYM BNP assay is useful in establishing or excluding heart failure in patients with acute dyspnea coming to a emergency department. In order to discard an existing CHF, 100 pg/mL BNP cut-off would be acceptable (negative predictive value of 88%). However, if we want to be focused on specificity, 400 pg/mL BNP cut-off would be more efficient (positive predictive value 92%). The majority of patients with non CHF cardiac disease had BNP values between both cut-off.

P1374 No incremental value of NT pro BNP at peak exercise over resting levels in patients with impaired left ventricular function



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Purpose: There is an increasing use of NT Pro BNP blood levels after peak exercise testing. Their possible superiority over resting levels in congestive heart failure or the factors associated with their increase have not been adequately studied.

Methods: We studied 65 patients, 51 males and 14 females with impaired left ventricular function. Mean Left Ventricular Ejection Fraction (LVEF) was $35 \pm 9\%$. Blood samples for NT Pro BNP assessment were taken at baseline and immediately after peak exercise during treadmill exercise testing. LV cavity diameters, left atrial (LA) size and LVEF were measured by echocardiography.

Results: NT Pro BNP plasma levels increased during treadmill exercise. Changes from baseline to peak exercise were significant ($p < 0.001$) and inversely associated with peak VO_2 ($p < 0.001$), LVEF ($p < 0.001$), and directly associated with left atrial diameter ($p < 0.005$), VE/VO_2 slope ($p < 0.005$), VE/VCO_2 slope ($p < 0.005$) and NYHA ($p < 0.005$). NT Pro BNP levels correlated with peak VO_2 both at baseline ($r = -0.78$, $p < 0.001$) and peak exercise ($r = -0.77$, $p < 0.001$), with VE/VO_2 slope ($r = 0.58$, $p < 0.001$) and VE/VCO_2 slope ($r = 0.63$, $p < 0.001$) at baseline and peak exercise ($r = 0.48$, $p < 0.001$), ($r = 0.57$, $p < 0.001$). LVEF correlated with NT Pro BNP at baseline ($r = -0.60$, $p < 0.001$) and peak exercise ($r = -0.60$, $p < 0.001$). NT Pro BNP correlated well with LA size at baseline ($r = 0.65$, $p < 0.001$) and peak exercise ($r = 0.64$, $p < 0.001$). NT Pro BNP plasma levels correlated significantly with NYHA both at baseline ($r = 0.68$, $p < 0.001$) and peak exercise ($r = 0.69$, $p < 0.001$). Basal NT Pro BNP values > 400 pg/mL, showed 73% sensitivity and a specificity of 71% for detecting VO_2 values below < 20 mL/kg/min (AUC=77%, $p < 0.005$). NT Pro BNP plasma levels > 1500 pg/mL showed 93% sensitivity and specificity 88% for detecting $\text{VO}_2 < 14$ mL/kg/min (AUC=96%, $p < 0.001$). Peak values were similar (AUC = 75%, AUC = 97%).

Conclusions: Our findings suggest that NT Pro BNP plasma levels immediately after peak exercise do not provide incremental information over resting levels, and influenced by similar variables.

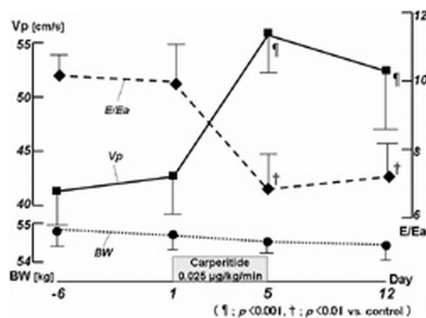
P1375 Effects of a low dose of carperitide, an atrial natriuretic peptide, on both left ventricular diastolic function and neurohormonal activity in patients with idiopathic cardiomyopathy



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Purpose: Patients (Pts) with systolic dysfunction have impaired diastolic function and neurohormonal profile. We sought to investigate if low-dose carperitide, recombinant human atrial natriuretic peptide, has a positive effect on left ventricular (LV) relaxation and modify abnormal neurohormonal response in Pts with idiopathic dilated cardiomyopathy (DCM).

Method: 0.025 $\mu\text{g/kg/min}$ of carperitide was administered to 25 Pts (NYHA 2-3, 58 ± 18 years) for 96 hours. We measured plasma renin activities (PRA), and plasma aldosterone (PAC) and brain natriuretic peptide (BNP) levels and the parameters of LV diastolic function using a tissue Doppler imaging of echocardiography, i.e. early diastolic transmitral flow velocity (E), annulus velocities (Ea) and



Parameters of Diastolic Function

propagation velocity (Vp), before and immediately after the continuous infusion and also one week after the administration.

Results: Although heart rate, blood pressure or PRA (from 10.3 ± 10.8 to 7.3 ± 7.4 pg/mL, p : n.s.) were not changed, PAC (from 23.3 ± 13.9 to 10.5 ± 6.2 pg/mL, $p < 0.001$) and BNP (from 633 ± 558 to 222 ± 276 pg/mL, $p < 0.001$) levels significantly decreased. The average values of septal and lateral Ea (from 7.5 ± 3.2 to 9.8 ± 2.5 cm/s, $p < 0.05$) and Vp (from 41.9 ± 6.5 to 55.6 ± 6.6 cm/s, $p < 0.001$) increased, whereas, E/Ea decreased (from 10.1 ± 3.4 to 6.9 ± 2.4 , $p < 0.01$). Even one week after the termination of the infusion, all these neurohormonal and LV diastolic parameters remained almost unchanged (PAC: to 12.6 ± 7.4 pg/mL, BNP: to 246 ± 269 pg/mL, Ea: to 9.5 ± 2.5 cm/s, Vp: to 48.1 ± 8.3 cm/s, E/Ea: to 7.3 ± 2.3).

Conclusion: These results implicate that the short-term, low-dose intravenous infusion of carperitide promptly and persistently improved both LV diastolic dysfunction and neurohormonal activity in DCM Pts and would merit long-lasting effects.

P1376 Lack of significant decrease in plasma N-terminal pro-BNP despite clinical stabilisation identifies patients with decompensated chronic heart failure at high risk of poor outcome



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Background: Patients hospitalised due to decompensation of chronic heart failure (CHF) have high morbidity and mortality after discharge. We assessed whether serial measurements of N-terminal pro-BNP-type natriuretic peptide (NT-proBNP) may be useful to identify those at high risk of complication.

Methods: We prospectively evaluated 106 patients admitted with decompensated CHF (age: 64 ± 13 yrs, 88 men, LVEF: $28 \pm 8\%$) who survived hospital stay. NT-proBNP plasma level (Roche, Elecsys) was measured on admission and on discharge. There were 2 primary end-points: all-cause mortality and all-cause hospitalisation combined with all-cause mortality during a 6-month follow-up.

Results: Mean plasma NT-proBNP levels were 8810 ± 9314 vs 5223 ± 7272 pg/mL (baseline vs pre-discharge, respectively, $p < 0.0001$) which corresponded with mean of $18 \pm 105\%$ decrease in NT-proBNP during hospital stay. The rates of primary end-points were 18% for all-cause mortality and 47% for combined mortality and hospitalisation during a 6-month follow-up. Both elevated pre-discharge NT-proBNP level and lack of a significant decrease in NT-proBNP (defined as $\geq 20\%$ of baseline level) were predictors of higher risk of death ($p < 0.01$ in univariate analysis). However in the multivariate analysis, when adjusted for clinical prognosticators (low systolic blood pressure, need for inotropes and hyponatremia) only lack of significant decrease in NT-proBNP remained independent predictor of death (hazard ratio [HR]: 2.9; 95%CI: 1.5-4.7, $p = 0.04$). For combined mortality and hospitalisation, again, only lack of significant NT-proBNP decrease remained risk predictor in the univariate ($p < 0.001$) and multivariate analyses (HR: 2.5; 95%CI: 1.4-4.4, $p = 0.002$). The discriminative power (area under receiver operating characteristic curve) of % in NT-proBNP decrease was 0.67 (0.57-0.76) for mortality and 0.72 (0.62-0.80) for combined mortality and hospitalisation. Kaplan-Meier analysis showed very poor outcome in patients with lack of significant NT-proBNP decrease with only 31% (95%CI: 18-47%) event-free survival during 6-month follow up vs 64% (95%CI: 53-75%) in the remaining patients, $p = 0.0002$.

Conclusions: Prognosis of patients after CHF decompensation remains very poor. Serial measurement of plasma NT-proBNP level is useful for identification those at particularly high risk of death and rehospitalisation. Management based on NT-proBNP monitoring may be an interesting option in this group of patients.

P1377 Plasma B-type natriuretic peptide levels in right heart dysfunction and pulmonary hypertension



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Plasma B-type natriuretic peptide (BNP) levels are closely related to symptoms of left ventricle (LV) systolic heart failure (HF). Although BNP may have a role in the diagnosis and management of HF, its marked heterogeneity levels among subjects, only partially explained by differences in LV function are reported. We hypothesized that not only LV but also right ventricle (RV) is the important source of plasma BNP.

To elucidated the potential RV contribution to plasma BNP levels we assessed the patients presenting with symptoms of HF but normal LV function and different grades of RV dilatation, due to pulmonary hypertension (PH) secondary to severe mitral valve stenosis (MVS).

The study group was composed of 27 patients (pts) presenting HF symptoms due to the severe MVS (valve area $0.9 \text{ cm}^2 \pm \text{SE } 0.04$). In initial Echo the left atrial (LA) enlargement ($51 \text{ mm} \pm 0.13$), PH (systolic PAP $52 \text{ mmHg} \pm 3.8$), RV dilatation (RV $28 \text{ mm} \pm 0.13$). All the pts presented normal LV diameters and function (EDD $47 \text{ mm} \pm 0.1$; ESD $29 \text{ mm} \pm 0.08$; EF $67\% \pm 0.57$). In comparison to the respective healthy controls MVS pts had higher BNP levels (pg/mL - 167 ± 26 vs. 6 ± 2.4 , respectively, $p < 0.0001$).

All the pts underwent valve replacement and the follow up (FU) visit with Echo and BNP assessment 12 months after operation.

In comparison to the baseline, FU assessment revealed significant reduction in

LA (delta -10 mm $\pm$ 1.8), RV (delta -4 mm $\pm$ 0.13) size and BNP levels (51 mm $\pm$ 3.1) without apparent changes with regard to LV. FU Echo confirmed correct prothesis function.

Among baseline parameters we found the significant correlation between BNP levels and RV ($r = 0.80$, $p < 0.0001$), PH ($r = 0.50$, $p = 0.01$), EDD ($r = -0.40$, $p = 0.50$). However the regression analysis found RV to be the strongest predictor ($p < 0.0001$) for BNP levels.

Moreover BNP levels decrease correlates with the changes in RV size ($r = -0.80$, $p < 0.0001$), LVEDD ($r = -0.58$, $p = 0.04$) and regression analysis found RV size reduction to be the strongest factor for BNP ($p < 0.0001$) decrease.

Conclusions: 1. Between several parameters characterised patients presented PH and RV failure but preserved LV function, RV dilatation determines BNP plasma levels. 2. Also RV size reduction was found to be the strongest predictor of BNP levels decrease. 3. In the assessment of pts with heart failure also the right ventricular dilatation as a potential source of plasma BNP should be taken into account.

P1378 Correlation between NT-proBNP levels and peak VO₂ in chronic heart failure - the influence of body mass index



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Background: Recent studies have suggested that obesity is an independent predictor of lower N-terminal pro brain natriuretic peptide (NT-proBNP) in chronic heart failure (CHF). However, the effect of obesity on the correlation between NT-proBNP levels and peak oxygen uptake (PVO₂) is uncertain.

Methods: We studied 86 (17 female) stable CHF patients who underwent a symptom-limited treadmill cardiopulmonary exercise test. The study population was divided in three groups according to their body mass index (BMI): lean (< 25 kg/m²), overweight (25 to 29.9 kg/m²), and obese (≥ 30 kg/m²). The correlation between resting NT-proBNP levels and PVO₂ was calculated for each group. The effect of different body composition was adjusted by indexation of PVO₂ (iPVO₂) to estimated lean body mass (James's method).

Results: Mean BMI was 27.0 ± 4.4 kg/m²; 33.7% were lean, 43.0% overweight and 23.3% obese. There were no significant differences between the 3 groups with respect to age, sex, estimated creatinine clearance, CHF etiology or cardiovascular risk factors. A significant inverse correlation was found between NT-proBNP levels and iPVO₂ in the overall population (Spearman's $r = -0.67$; $p < 0.001$). There was a trend for weaker NTproBNP-iPVO₂ correlation in obese patients compared to the non-obese ($r -0.39$ vs -0.72 ; Z difference 1.82; $p = 0.058$). In obese patients, the NTproBNP-iPVO₂ correlation did not reach statistical significance - Table 1.

Table 1

	Lean (n=29)	Overweight (n=37)	Obese (n=20)
BMI (kg/m ²)	22.5 ± 2.2	27.6 ± 1.5	32.9 ± 2.4
Ejection Fraction (%)	28.3 ± 3.9	34.1 ± 9.1	30.2 ± 5.1
PVO ₂ (ml/min)	1013 ± 390	1390 ± 430	1378 ± 372
iPVO ₂ (ml/min/kg of lean body mass)	21.3 ± 7.4	24.8 ± 6.4	22.7 ± 6.5
NT-proBNP (pg/mL) Median, interquartile range	2440(1719-7437)	657(326-1533)	1209(405-2127)
Correlation between NT-proBNP and iPVO ₂ (Spearman's r)	- 0.70	- 0.55	- 0.39
p	< 0.001	< 0.001	0.088

Conclusion: Higher BMI seems to influence the correlation between NT-proBNP levels and PVO₂, suggesting that the prognostic value of this natriuretic peptide may be impaired in obese CHF patients.

P1379 Diagnostic value of N-Terminal pro-brain natriuretic peptide for prediction of coronary artery disease



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Background The level of the inactive N-terminal fragment of pro-brain (B-type) natriuretic peptide (BNP) is a prognostic marker among patients with acute and chronic coronary artery disease and might be valuable for noninvasive diagnosis of coronary artery disease as well. We assessed the relationship between N-terminal pro-BNP (NT-proBNP) and coronary artery disease in a large cohort of patients with suspected coronary artery disease and normal systolic left ventricular function.

Methods NT-proBNP was measured in 781 consecutive patients with normal left ventricular function and normal renal function referred for coronary angiography because of symptoms or signs of coronary artery disease. The angiographic diagnosis of coronary artery disease was made by interventional cardiologists who were blinded to the results of NT-proBNP measurements.

Results The angiographic diagnosis was significant coronary artery disease with 50% or more stenosis of the lumen diameter of a major coronary artery in 516 patients (66%), non-obstructive coronary artery disease in 133 patients (17%), and

no finding of coronary artery disease in 132 patients (17%). NT-proBNP was an independent predictor of coronary stenosis. Elevated serum levels of NT-proBNP were associated with the presence and severity of coronary artery disease. NT-proBNP levels at a cut-off value of 30 pg/dl for men and 60 pg/dl for women had a sensitivity of 90% and at a cut-off value of 185 pg/dl for men and 300 pg/dl for women had a specificity of 90% for detecting significant coronary artery disease. In multiple logistic regression analysis, measurements of NT-proBNP added significant independent predictive power to other clinical variables in models predicting which patients had coronary artery disease.

Conclusion NT-proBNP is a marker of the presence and extent of coronary artery stenosis, independent of left ventricular function. In conjunction with other clinical information, measurement of NT-proBNP is useful for noninvasive estimation of angiographically significant coronary artery disease. Sex-specific NTproBNP cut-off values should be applied for men and for women.

P1380 Prognosis value of Brain Natriuretic Peptide kinetics during cardiopulmonary exercise test in chronic heart failure patients



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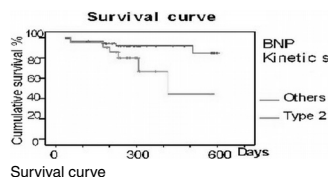
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Background: The aim of this prospective study was to evaluate Brain Natriuretic Peptide (BNP) kinetics during cardiopulmonary exercise test and to determine the prognosis value of different BNP kinetics in chronic heart failure (CHF).

Methods: Seventy-two consecutive stable CHF patients were included. All patients underwent an echocardiography, a standard cardiopulmonary exercise test and BNP measurements before exercise, at peak exercise and 15 minutes after recovery. BNP kinetics (K) were defined according to peak and recovery BNP variations (K2: increase-increase; K1 others kinetics).

Results: Most of the patients were in NYHA class 2 (82%) with optimal therapy (Beta-blockers: 100%; IEC or ARB: 100%; Diuretics: 66%; Spironolactone: 56%). All of them were rehabilitated (mean peak VO₂=21.7 ml/kg/mn). Mean age was 58 ± 12 years. Exercise significantly increased BNP values, and K2 pattern was observed in 31% of the patients. With a median follow-up of 328 days, there were 20 cardiac events including 11 major cardiac events (MCE): cardiac death (2 sudden death) or threatening ventricular arrhythmia (9 ventricular arrhythmias with internal cardiac defibrillator intervention). MCE were significantly more frequent in patients with type 2 BNP kinetic versus others patients (32% vs. 8%, $p = 0.027$; RR=3.98; CI=1.3-12.2). There was no significant difference in other characteristics between these 2 groups.



Conclusions: In stable CHF patients, a continuous elevation of BNP both at peak exercise and after recovery may indicated an increase risk of cardiac death or threatening ventricular arrhythmia. These results may allow identifying high risk NYHA class 2 CHF patients.

P1381 Anaemia and renal function independently associated with B-type Natriuretic Peptide and N-terminal pro B-type Natriuretic Peptide in patients hospitalised for heart failure



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Background: B-type Natriuretic Peptide (BNP) and N-terminal proBNP (NT-proBNP) are well-established diagnostic and prognostic markers in patients with heart failure (HF). In HF diagnosis, anaemia (by increased plasma overload) and renal function (by decreased clearance) may result in biased interpretations of these natriuretic peptides. We therefore aimed to study the independent associations of anaemia and renal function with BNP and NT-proBNP in hospitalised HF patients.

Methods: From 364 patients who were admitted for decompensated HF in the Netherlands, BNP and NT-proBNP plasma levels were determined before discharge. Univariable and multivariable linear regression analyses were performed for both BNP and NT-proBNP. Clinical data on anaemia and renal function were collected from the medical chart during admission.

Results: Of the 364 hospitalised HF patients (70 ± 11 years of age, 62% males, left ventricular ejection fraction 0.34 ± 0.14), 30% ($n = 104$) was anaemic ($Hb < 7.5$ mmol/L for women and $Hb < 8.1$ mmol/L for men). Of the anaemic patients 70% had renal dysfunction ($eGFR < 60$ ml/min/1.73m²) and of the non-anaemic patients 57% had renal dysfunction. In multivariable analyses plasma haemoglobin

was associated with both BNP and NT-proBNP levels (standardised beta's of -0.22 and -0.23 respectively) and eGFR was relatively stronger associated with NT-proBNP levels (standardised beta=-0.32) compared to BNP levels (standardised beta=-0.16), independent of severity of heart failure (left ventricular ejection fraction and the Boston score). Additionally, body mass index was independently associated with both BNP and NT-proBNP (standardised beta's of -0.31 and -0.29 respectively).

Conclusion: Haemoglobin levels and renal function were independently associated with BNP and NT-proBNP plasma levels in this large group of hospitalised HF patients. Renal function was a stronger independent determinant of NT-proBNP compared to BNP. These results indicate that in HF diagnosis BNP but especially NT-proBNP levels might be overestimated particularly in patients with renal dysfunction and anaemia.

P1382 Natriuretic peptides, kidney disease and outcome in patients with chronic heart failure



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Background In patients (pts) with chronic heart failure (CHF), the N-terminal pro brain natriuretic peptide (NT-proBNP) and kidney disease (KD) are of prognostic importance, but the relationship between NT-proBNP, renal function and outcome has not been studied.

Methods We prospectively enrolled 144 pts with stable CHF and a wide spectrum of renal function (glomerular filtration rates (GFR's) ranging from 8.1 ml/min/1.73 m² to 102.2 ml/min/1.73 m², mean GFR 60.3±18.5 ml/min/1.73 m²). KD defined as a GFR < 60 ml/min/1.73 m² was present in 65 pts (45%). NT-proBNP measurements were carried out on a Elecsys-2010 bench top analyzer. All study subjects underwent a comprehensive 2-D/Doppler echocardiogram. Cardiac death or urgent cardiac transplantation were considered as combined study end point.

Results During a follow-up of 330±233 days, 20 pts suffered a cardiac event (cardiac death, n=18; urgent cardiac transplantation, n=2). Pts with or without event did not differ significantly with respect to NYHA class (2.8±0.6 vs. 2.6±0.5, p=0.08) or ejection fraction (27±10% vs. 31±10%, p=0.07), but in pts with an event NT-proBNP was higher (10314±20265 vs. 2361±4624, p=0.004), the GFR was lower (58.2±26.6 ml/min/1.73 m² vs. 74.7 ml/min/1.73 m², p=0.011), and KD was more frequent (75% vs. 40%, p=0.007) as compared to pts without event. By multivariate Cox analysis including clinical and echocardiographic variables, NT-proBNP and KD were independent prognostic predictors (hazard ratio 3.41 and 2.91, p<0.05, respectively). By linear regression analysis, NT-proBNP levels were related to NYHA functional class (R=0.40, p<0.001), and inversely related to GFR (R=-0.33, p<0.001) and ejection fraction (R=-0.40, p<0.001). A risk-stratification model based on two factors (NT-proBNP > 1127 pg/ml, presence of KD) separated low, intermediate and high risk groups (event-free survival rates of 97%, 78% and 48%, p=0.0003, respectively).

Conclusions: In CHF patients, NT-proBNP and KD provide independent and incremental prognostic information. In this patient population, NT-proBNP levels are not only reflective of a reduced clearance (i.e. a lower GFR) but also of the severity of the underlying structural heart disease.

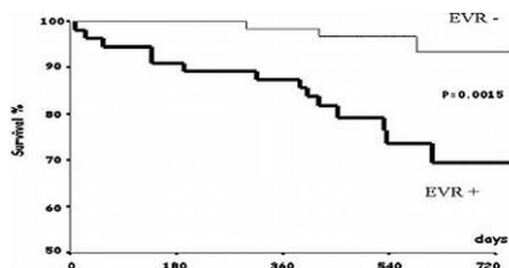
P1383 In chronic heart failure patients an enhanced ventilatory response to exercise predicts mortality better than BNP



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Background: Whether brain natriuretic peptide (BNP) correlates with an enhanced ventilatory response (EVR) during cardiopulmonary exercise test and has independent prognostic value in systolic heart failure (HF) is currently unknown.

Methods and Results: Resting BNP was measured in 123 consecutive stable outpatients with mild to moderate HF and LV ejection fraction (LVEF) < 45%, who performed a maximal exercise test. EVR was assessed as slope of the relation between minute ventilation and carbon dioxide production (VE/VCO₂ slope) > 35. LVEF averaged 32 ± 7%, BNP averaged 351 ± 396 pg/mL. 56/123 patients (45%) had EVR. BNP correlated with EVR (r = 0.453; p < 0.01). By logistic regression,



plasma BNP was the only independent predictor of EVR (RR 1.004 per unit increment, 95% CI 1.002 to 1.006, p < 0.0001). During 540 ± 176 days, 20 patients (16.2%) died. A BNP ≥ 160 pg/mL was the best cut-off for predicting mortality by ROC analysis (AUC 0.64, 95% CI 0.52 to 0.76). By Cox multivariate analysis, EVR (RR 4.27, 95% CI 1.39 to 13.92, p=0.01) and left bundle branch block (RR 2.76, 95% CI 1.04 to 7.33, p=0.04) independently predicted outcome.

Conclusions: In systolic HF, plasma BNP is related to an enhanced ventilatory response to exercise. However EVR is superior for BNP in predicting mortality. BNP assay might offer a simple alternative in patients with inability or contraindications to exercise, but, whenever a cardiopulmonary test can be performed, EVR will more accurately predict prognosis.

P1384 C-type natriuretic peptide increases in patients with idiopathic dilated cardiomyopathy with or without overt heart failure



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Purpose: C-type natriuretic peptide (CNP) is widely expressed throughout the vasculature and is found in particularly high concentrations in the endothelium. Elevated CNP levels in heart failure, similarly to other natriuretic peptides, are interpreted as part of a compensatory vasodilating response counteracting depressed endothelial NO-dependent function. So far, no data are available on plasma levels of this peptide in patients with dilated cardiomyopathy (DCM) with or without overt heart failure. The aim of this study was to evaluate the relationship of CNP peripheral levels with other neurohormones, heart failure symptoms and LV function in patients with DCM.

Methods: Plasma CNP levels of 51 no diabetic DCM patients (32 males, 37 in NYHA class I-II, 14 in NYHA class III, LVEF% 34.1±1.3, age 62±1 years, mean±sem) and 64 healthy controls were determined by a radioimmunoassay (RIA) after a preliminary solid-phase extraction on Sep-Pak C18. Plasma atrial and brain NP, (ANP, BNP), renin activity (PRA) and aldosterone were measured by specific immunometric assays; noradrenaline and adrenaline were measured by HPLC procedure.

Results: The plasma levels of CNP in healthy subjects were 2.5±0.12 pg/ml, mean±sem, and resulted significantly increased in DCM patients with (7.0±0.9 pg/ml) or without (6.1±0.53) overt heart failure (p<0.0001, patients in NYHA class I-II or in NYHA class III vs controls). A significant correlation was observed between CNP and LVEF (r=0.46, p=0.0008) in the whole DCM population. Accordingly, CNP levels progressively increased from patients with moderate (35% ≤ LVEF < 50%) to patients with severe LV dysfunction (LVEF < 35%) (4.8±0.5 pg/ml vs. 7.8±0.7, p=0.0015). CNP was significantly and positively correlated with ANP (r=0.73, p<0.0001, 71.9±10.9 pg/ml), BNP (r=0.74, p<0.0001, 151.5±27.1 pg/ml) and noradrenaline (r=0.35, p=0.01, 515±48 pg/ml). No correlation was found with PRA (2.9±0.6 ng/ml/h), aldosterone (182.3±17.7 pg/ml), and adrenaline (37.4±5.4 pg/ml).

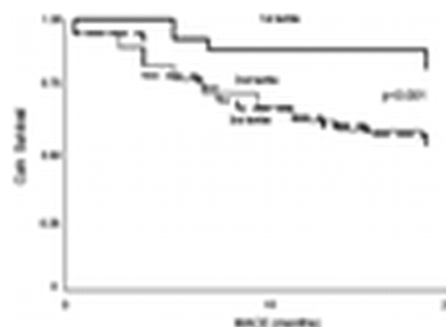
Conclusions: Plasma CNP levels were significantly elevated in DCM patients with or without HF. CNP elevation was correlated with the severity of LV dysfunction and the increase of other markers of cardiac impairment (ANP, BNP) while was not related with plasma levels of other hormones. These observations suggested that CNP, together with other natriuretic peptides, could be early activated in tune with ventricular dysfunction in DCM.

P1385 N-terminal-pro-Brain natriuretic peptide levels predict major adverse cardiac events in heart failure patients on cardiac resynchronization therapy



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N-terminal-pro-Brain natriuretic peptide levels predict major adverse cardiac events in heart failure patients on cardiac resynchronization therapy Objective - To evaluate if NT-pro-BNP is a predictor of major adverse cardiac events (MACE: cardiac death from any cause or unplanned re-hospitalization) in patients with



heart failure (HF) on cardiac resynchronization therapy (CRT), as there are no data available.

Methods - We prospectively studied 140 HF patients (on optimized medical therapy; III-IV NYHA class; ejection fraction: 29.9 ± 9.6 , with intraventricular dyssynchrony), 71 with ischemic and 69 with idiopathic dilated cardiomyopathy, who underwent CRT. Plasma levels of NT-pro-BNP were evaluated immediately before CRT (Roche Diagnostics, USA). MACE (follow-up: 9.1 ± 5.3 months) were observed in 38 patients (27%): 20 (14.3%) due to cardiac causes, 18 (13%) due to unplanned re-hospitalization. To evaluate the potential associations between NT-pro-BNP and MACE we divided the study population into tertiles of distribution of this variable (1st tertile: 3558.1 pg/mL). Highest tertiles of baseline NT-pro-BNP resulted to be a significant predicting variable for MACE (2nd tertile HR: 5.8; 95%CI 1.9-17.6; $p=0.002$; 3rd tertile HR: 5.3; 95%CI 1.7-16.9; $p=0.003$).

Conclusions - High plasma levels of NT-pro-BNP predict MACE in HF patients on CRT. This may have implications for a better future risk assessment of patients with potential benefit from CRT.

P1386 Different effects of treadmill and bicycle exercise on functional capacity and B-type natriuretic peptide levels in patients with congestive heart failure



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Background: In patients with congestive heart failure (CHF), peak oxygen consumption (peak VO₂) and B-type natriuretic peptide (BNP) levels provide important prognostic information. In addition, BNP levels at rest and peak exercise have been suggested as biomarkers that predict peak VO₂. However, the exercise response depends on the test modality. We therefore sought to compare bicycle and treadmill testing with respect to exercise capacity, BNP kinetics, the relationship between peak VO₂ and BNP, and predictors of peak VO₂ in patients with CHF.

Methods: Twenty-three patients with mild-to-moderate systolic CHF [median (interquartile range) age 72 (64-77) years, left ventricular ejection fraction 30 (27-40) %] underwent a treadmill and a bicycle ramp exercise test in random sequence within 5 (3-7) days. BNP was measured before the test and at peak exercise. To correct BNP levels for impaired renal function, the product of BNP and estimated creatinine clearance was included in a multiple regression analysis to identify predictors of peak VO₂.

Results: Peak VO₂ was higher when using the treadmill as compared to the bicycle stress test [treadmill: 21.6 (17.7-25.2) vs. bicycle: 19.7 (15.5-20.6) ml/kg/min; $p=0.004$]. BNP levels at rest levels did not differ at the two test days [treadmill: 253 (116-508) vs. bicycle: 317 (115-542) pg/ml; $p=0.28$]. Resting BNP values were inversely correlated to peak VO₂ during treadmill testing ($r=-0.51$; $p<0.05$), whereas this relationship was not significant for the bicycle tests. The percent exercise-induced increment in BNP was higher during the treadmill tests [treadmill: 26 (13-37) vs. bicycle: 13 (7-31) %; $p=0.006$]. Peak exercise BNP levels were related to peak VO₂ only during treadmill exercise ($r=0.47$; $p<0.05$). The product of BNP at rest and estimated creatinine clearance was an independent predictor of peak VO₂ in both test modalities, whereas BNP levels at rest and at peak exercise were not.

Conclusions: In patients with CHF, peak VO₂, BNP kinetics, and the relationship between peak VO₂ and BNP critically depend on the mode of exercise. To assess a patient's peak VO₂ level, the treadmill is preferable to bicycle exercise. Correction of BNP levels for impaired renal function enhances its ability to predict peak VO₂. These observations should be taken in account while using peak VO₂ and BNP levels for risk stratification in patients with CHF.

P1387 Intraventricular dyssynchrony influences exercise tolerance and BNP levels in patients with stable congestive heart failure



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Background: Intraventricular dyssynchrony is a major predictor of response to cardiac resynchronization therapy, but it is unclear if intraventricular dyssynchrony contributes to the severity of heart failure. We evaluated the relationship among intraventricular dyssynchrony, BNP levels, systolic and diastolic function and aerobic exercise capacity in CHF patients.

Methods: 43 CHF patients (age 67 ± 9 years, 53% with an ischemic etiology), underwent cardiopulmonary exercise test with expired gas measurement and standard echocardiography: LV diastolic function was evaluated with transmitral filling patterns and tissue Doppler (TDI). BNP levels were determined on blood samples withdrawn at baseline. Left ventricular dyssynchrony was defined as the maximum delay between time the onset of the QRS and the onset peak systolic velocity on TDI between the interventricular septum and the lateral wall within the LV.

Results: Ejection fraction was $34 \pm 8\%$ and NYHA class 2.2 ± 0.5 . Intraventricular dyssynchrony was directly related to NYHA functional class ($r=0.42$, $p=0.011$),

BNP level (Figure), value of ratio E wave mitral flow and early diastolic velocity mitral annulus ($r=0.653$, $p<0.001$), and left atrial diameter ($r=0.39$, $p=0.013$), and inversely related to LV ejection fraction ($r=-0.363$, $p=0.027$), peak oxygen consumption (Figure). In multiple regression analysis intraventricular dyssynchrony ($p=0.027$) and BNP level ($p=0.008$) were independent predictors of exercise tolerance.

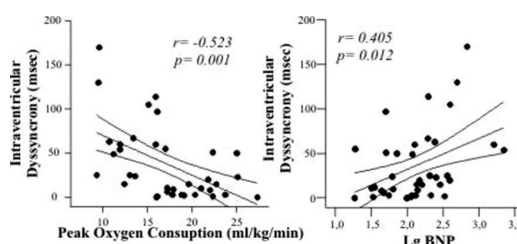


Fig. 1

Conclusions: In patients with stable CHF, intraventricular dyssynchrony was related to higher BNP levels, worse systolic and diastolic function and poorer exercise tolerance.

P1388 Patients with left ventricular dysfunction in clinical practice: NT-proBNP predicts mortality in men as well as in women



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Objective: To compare the prognostic value of NT-proBNP with clinical parameters concerning longterm mortality in men versus women with left ventricular dysfunction (LVD) in clinical practice with optimized therapy.

Methods: 1245 patients (P) were enrolled consecutively and prospectively in a regional LVD-registry in Germany. Inclusion criteria for this analysis were ejection fraction (EF) < 40%, non valvular genesis of LVD and determined NT-proBNP at discharge. The fourth quartile of NT-proBNP serum levels was chosen as cut-off point for increased risk (NT-proBNP of 3300ng/l).

Results: 990 P (80%) were male, 255 P were female, mean age was 61 years. Mean EF was 28%. Etiology of LVD was ischemic heart disease in 45%, idiopathic dilated cardiomyopathy in 48%, and other reasons in 7%. Medication at discharge: ACE-inhibitors or ARB 90%, betablockers 70%, aldosterone antagonists 31% and diuretics 75%. One-year mortality was 14% in men and 12% in women, three-year mortality was 29% in men and 24% in women. Independent predictors of long-term mortality as determined by multivariate analysis (Cox regression) are shown for men and women in table 1.

Table 1

	Men		Women	
	Hazard Ratio	p-value	Hazard Ratio	p-value
NT-proBNP > 3300 ng/l	2.4	< 0.001	2.8	0.006
EF < 30%	2.1	< 0.001	1.3	0.43
NYHA III/IV	1.8	< 0.001	1.8	0.07
Ischemic heart disease	1.8	< 0.001	2.0	0.07
Age > 70 years	1.4	0.08	1.4	0.44
β-blocker therapy	0.4	< 0.001	0.7	0.22

Conclusions: NT-pro-BNP was found to be the strongest independent predictor of longterm mortality in men as well as in women when compared with established clinical parameters.

P1389 Variability of NT-ProBNP levels in patients with stable heart failure



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Background: Brain natriuretic peptide (BNP) and N-terminal Pro-BNP (NT-proBNP) levels are established markers for heart failure (HF) diagnosis and prognosis, and potentially useful for therapy monitoring. However, little is known about how NT-proBNP levels fluctuate over time in patients with stable HF. We aimed to evaluate how large can be the variation between two consecutive measurements of NT-ProBNP in clinically stable HF patients.

Methods: NT-proBNP was measured at 3-week intervals in ambulatory patients with stable HF: no change in therapy or clinical status as represented by NYHA class for at least 2 months before baseline. During the study period, patients were followed by a physician blinded to the laboratory findings and therapy remained unchanged. Seven patients were excluded due to decompensation of HF (4 with

hospital admission and 3 with increase NYHA class managed as outpatients), 1 due to heart transplantation and 1 due to temporal arteritis. One hundred and eighteen pairs of NT-proBNP measurements were performed in 67 patients: 51 males; mean age 69 (range 39-87); 24 NYHA class I, 40 NYHA class II and 3 NYHA class III; 6 with preserved left ventricular (LV) systolic function, 24 with mild-moderate LV systolic dysfunction and 37 with severe LV systolic dysfunction; median baseline NT-proBNP 1477 pg/ml (25th-75th percentiles: 402-2342). We calculated the absolute (pg/ml) and relative (% of baseline) difference between the 2 NT-proBNP measurements in each pair, as well as their mean. The distribution of differences was assessed and the 5th and 95th percentiles are presented. We used absolute differences for pairs whose mean was 450 pg/ml and relative differences for those whose mean was > 450 pg/ml.

Results: Among pairs of measurements with mean > 450 pg/ml ($n=90$), the 5th and 95th percentiles of the distribution of relative differences were -35% and +51% of the baseline value, respectively. Among pairs of measurements with mean <450 pg/ml ($n=28$), the 5th and 95th percentiles of the distribution of absolute differences were -181 pg/ml and +185 pg/ml, respectively.

Conclusions: In clinically stable chronic HF patients, NT-proBNP varied largely within 3-week periods. Our results should be taken into account when using NT-proBNP to monitor and guide therapy of HF patients.

P1390 Early follow-up of patients with acute heart failure by serial assessment of plasma NT-proBNP can further discriminate outcome after hospital discharge



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In-hospital measurement of NT-proBNP has been proposed for risk assessment in acute heart failure (AHF). Little is known about the value of proBNP post-discharge.

Aim: To evaluate whether measurement of NT-proBNP in the early follow-up after hospital discharge can further discriminate patients' risk profiles.

Methods: NT-proBNP was measured in 149 patients attending early follow-up at 5 weeks after hospitalisation for AHF, in a multicenter study, and compared to values obtained in-hospital at 48 hours after admission. Uni- and multivariate Cox regression analyses were performed to analyse the 6-month risk of combined end-point of death or heart failure hospitalisation.

Results: Mean age of patients was 72.1 years, 56% men, 68% had a history of hypertension, 36% diabetes, 50% coronary heart disease. The combined incidence of death or HF hospitalisation was 33.6%. Patients with NT-proBNP below median of 3457 pg/ml at day 2 did not have significantly lower risk for subsequent event compared to patients with proBNP above median, 29.3% vs 37.9%, HR 0.73 (CI 0.41-1.29, NS). A decrease in proBNP in 5 wks by $\geq 30\%$, achieved in 76/149 patients (51%), was associated with significantly lower event rate, 21.1% vs 46.6% in those with no decrease, HR 0.36 (0.19-0.66, $P=0.001$). Particularly in those with initial proBNP above median, the decrease in proBNP was associated with a significantly lower risk, 21.9% vs 67.6% in those with no decrease, HR 0.27 (0.12-0.62, $P=0.002$). Moreover, proBNP level above the median of 2422 pg/ml at 5 weeks significantly affected the event rate, 47.3% vs 20.0% below median, HR 2.94 (1.59-5.41, $P=0.01$). In Cox multivariate regression analysis including age, anemia by WHO criteria, diabetes, creatinine >120 $\mu\text{mol/l}$, systolic blood pressure >160 mmHg on admission, history of heart failure, and decrease in proBNP, the only significant predictors of outcome were anemia: HR 2.60 (1.42-4.76, $P=0.002$) and decrease in proBNP: HR 0.44 (0.23-0.83, $P=0.01$). After replacing proBNP decrease in the model with 5-week proBNP above median, anemia remained a significant risk factor, as well as, 5-week proBNP with HR 2.14 (CI 1.12-4.09, $P=0.02$).

Conclusion: In this population attending early follow-up after discharge from hospital, decrease of proBNP in the early follow-up by at least 30% is associated with a significantly diminished risk of death or HF hospitalisation in 6 months. Moreover, proBNP above median at follow-up confers a significantly increased risk. Serial measurement of NT-proBNP in the early follow-up may help to identify a HF population with the highest risk.

P1391 The prognosis of left ventricular systolic dysfunction in community subjects: a comparison with N-Terminal pro-brain natriuretic peptide



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Introduction: Left ventricular systolic dysfunction (LVSD) and raised natriuretic peptide levels both impart poor prognosis, with little data on mild LVSD. Furthermore, LVSD may fail to predict prognosis once natriuretic peptide levels are included. This study therefore aimed to assess the prognosis of mild LVSD and whether it imparts poor prognosis independent of the natriuretic peptide N-terminal pro-brain natriuretic peptide (NTproBNP) in community subjects.

Methods 1392 community subjects ≥ 45 years old were randomly selected from 7 local general practices. Mild LVSD was defined as left ventricular ejection fraction (LVEF) 45-50% and definite LVSD as LVEF <45%. Raised NTproBNP levels exceeded previously defined age- and gender-stratified upper reference values. Attendees were reassessed by telephone interview and/or postal follow up 1-2 years after initial assessment for evidence of heart failure hospitalisation, new major adverse cardiac events (MACEs) or death.

Results 710 of 734 attendees (97%) were reassessed, median follow-up 651 days. There were 12 deaths, 15 deaths or heart failure hospitalisations, and 25 deaths or MACEs. Those with LVEF <50% and LVEF <45% had worse prognosis than those with LVEF $\geq 50\%$ for death, death or heart failure hospitalisation and death or MACEs ($p<0.0001$, all analyses). When assessing mild LVSD, LVEF 45-50% gave an increased risk of death or heart failure hospitalisation than LVEF $\geq 50\%$ ($p=0.028$), but decreased risk of death or MACEs than LVEF <45% ($p=0.035$). In those with LVEF <50%, overall mortality was 3% at 6-month, 5% at 12-month, 11% at 18-month and 21% at 22-month follow up; death or heart failure hospitalisation were 8% at 6-month, 11% at 12-month, 19% at 18-month and 27% at 22-month follow up, and death or MACEs were 11% at 6-month, 19% at 12-month, 27% at 18-month and 35% at 22-month follow up.

Prognosis was worse in those with raised NTproBNP levels vs normal levels. Multivariate predictors of death were increasing age ($p=0.01$) and LVEF <45% ($p=0.05$). Multivariate predictors of death or heart failure hospitalisation were NT-proBNP levels >3 times normal ($p=0.01$), LVEF <50% ($p=0.02$) and increasing age ($p=0.03$). Multivariate predictors of death or MACEs were NTproBNP levels >3 times normal ($p<0.001$), prior MI ($p=0.03$), hypertension ($p=0.03$) and LVEF <45% ($p=0.05$).

Conclusion Thus even mild degrees of LVSD in community subjects imparts high morbidity and mortality, independently predicting poor prognosis, with NTproBNP levels adding further prognostic information, independent of LVSD in this study.

P1392 Relation between preoperative plasma N-terminal pro-B-type natriuretic peptide level and long-term survival after major vascular surgery



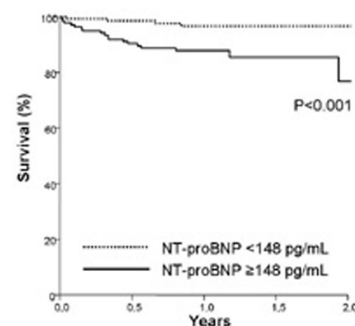
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Background: Elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels have prognostic value in patients with heart failure and acute coronary syndromes. The predictive value of NT-proBNP for survival after major non-cardiac vascular surgery has not yet been determined.

Methods: In a prospective cohort study, 276 consecutive patients scheduled for aortic aneurysm repair, lower extremity bypass surgery and carotid artery surgery were evaluated for risk factors according to the Cardiac Risk Index. Prior to surgery, dobutamine stress echocardiography (DSE) was performed to detect stress-induced myocardial ischemia and baseline NT-proBNP levels were measured. The prognostic value of NT-proBNP for the endpoint all-cause mortality and cardiac events (cardiac death or non-fatal myocardial infarction) was evaluated.

Results: In this patient cohort (mean age: 62.3 years, 74% male, 48% ischemic heart disease), median baseline NT-proBNP level was 148.4 ng/L (interquartile range: 56.9-425.0 ng/L). During a mean follow-up of 2.0 ± 1.1 years, 27 patients (9.5%) died and 22 (7.7%) experienced a cardiac event. After adjustment for baseline clinical variables, each 1.0 increment of log(NT-proBNP) was associated with an increased risk of 1.91 for all-cause mortality (95% CI: 1.38-2.65, $p<0.001$) and 2.97 for cardiac events (95% CI: 1.94-4.53, $p<0.001$). The prediction of all-cause mortality and cardiac events remained significant after adjustment for stress induced myocardial ischemia during DSE (HR: 1.60, 95% CI: 1.12-2.30, $p=0.01$, and HR: 2.44, 95% CI: 1.54-3.86, $p<0.001$, respectively).



Survival curves during 2 year follow-up

Conclusion: Preoperative NT-proBNP levels predict all-cause mortality and adverse cardiac events during long-term follow-up after major non-cardiac vascular surgery.

P1393 Ischemia is an independent stimulus for BNP-expression

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Purpose: Diastolic stretch and neuroendocrine activation are known to induce gene expression and release of the B-type natriuretic peptide (BNP). However, it is widely unknown whether an increased BNP-values found in ischemic heart disease are triggered directly by ischemic and metabolic alterations or whether they are caused indirectly by ischemia through diastolic contractures or regional wall motion abnormalities. Therefore, we investigated the BNP expression in isolated human atrial and ventricular muscle strips under conditions of metabolic stress with and without contracture.

Methods: Muscle strips were isolated from human left ventricles (n=25) from patients undergoing heart transplantation due to end-stage dilated cardiomyopathy. Contractures were induced by glucose and oxygen withdrawal. In n=10 contractures were prevented by means of the calcium desensitizing agent butanedione-monoxime (BDM). The gene expression of BNP was determined in all muscle strips using rt-PCR and compared to control muscle strips contracting under physiological conditions (n=5).

Results: Withdrawal of oxygen and glucose resulted in a reduction of the systolic contractile force from 8.05 ± 2.1 mN/mm² to 1.45 ± 1.34 mN/mm². The diastolic contracture after 20 and 30 min was 8.62 and 6.13 mN/mm², respectively. Adding BDM (30 mmol) before glucose and oxygen withdrawal completely prevented systolic contractions and diastolic contractures. The gene expression of BNP increased in the group without BDM (contracture) 71-fold after 30 min and 218-fold after 60min in comparison to control ($p < 0.05$). In the group with a BDM-induced prevention of contractures, the BNP expression increased 65-fold after 30 min and 185-fold after 60 min in comparison control ($p < 0.05$). There was no significant difference between the both groups.

Conclusions: The gene expression of BNP under metabolic stress is independent from BDM. These results indicate that ischemia is an autonomous mechanism for the expression of BNP and independent from mechanical alterations.

P1394 By which mechanism does N-terminal pro brain natriuretic peptide predict cardiovascular outcome in the general population?

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Background: We have previously shown that N-terminal pro brain natriuretic peptide (NT-proBNP) predicted cardiovascular (CV) events in a general population aged 41, 51, 61 or 71 years. The aim of this study was to investigate the mechanism behind this.

Methods: In 1993 we measured traditional CV risk factors, ambulatory 24-hour systolic blood pressure (24-hour-SBP), left ventricular mass index (LVMI) and ejection fraction (LVEF), pulse wave velocity (PWV), atherosclerotic plaques in the carotid arteries (0, 1, 2 or ≥ 3 plaques), urine albumin/creatinine ratio (UACR), serum high sensitivity C-reactive protein (hsCRP) and serum NT-proBNP in 1642 subjects without prior stroke or myocardial infarction. The composite CV endpoint (CEP, n=106) of CV death (n=56) and non-fatal stroke or myocardial infarction was assessed after 9.5 years.

Results: In following Cox regression analyses all hazard ratios (HR) are adjusted for all significant traditional CV risk factors (age, gender, smoking, waist/hip ratio, glucose, office SBP, heart rate, CV and metabolic treatment). Log(NT-proBNP) predicted CEP (HR=2.58[1.70-3.91] per 10 fold increase) as well as CV death (HR=3.95[2.30-6.78] per 10 fold increase, both $P < 0.001$). The HRs decreased when adjusting for 24h-SBP, LVEF, carotid plaques and UACR (Table 1, all $P < 0.001$), but not LVMI, PWV and hsCRP. Even after adjusting for all four significant factors, log(NT-proBNP) predicted CEP (HR=1.75[1.15-2.67] per 10 fold increase) and CV death (HR=2.40[1.37-4.21] per 10 fold increase, both $P < 0.01$) reducing HRs by 30-40%.

Cox HRs for CV events by log(NT-proBNP)

HR adjusted for:	24-hour-SBP	LVEF	Carotid plaques	UACR
CEP	2.29[1.51-3.48]	2.37[1.56-3.60]	2.46[1.62-3.74]	2.21[1.45-3.37]
CV death	3.40[1.97-5.89]	3.20[1.83-5.57]	3.73[2.17-6.42]	3.05[1.77-5.28]

Conclusion: The prediction of CV events by NT-proBNP was partly as a marker of high BP load, decreased LVEF, micro- and macrovascular subclinical disease, but not as a marker of LV hypertrophy, increased vascular stiffness or inflammation.

P1395 Brain natriuretic peptide identifies patients at low risk for severe myocardial hemosiderosis in beta thalassemia major

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Background: Iron overload results in congestive heart failure in patients with β -thalassemia major. The aim of this study has been to evaluate if brain natriuretic peptide plasma levels could identify patients with severe iron deposition to myocardium. Patients and Methods: In 76 thalassemic patients, with left ventricular ejection fraction $\geq 50\%$, myocardial iron load was estimated by measurement of myocardial T2-relaxation time on a magnetic resonance imaging examination. Estimation of peripheral brain natriuretic peptide plasma levels was also performed. The target group of our study were patients with severe hemosiderosis (T2-relaxation time < 24 msec).

Results: Median brain natriuretic peptide was 45 pg/ml (32, 78), in patients with severe iron load (n=17) and 23 pg/ml (14, 47), in the rest of patients (n=59) ($p=0.008$). Brain natriuretic peptide levels correlated inversely with T2-relaxation time values (Spearman $R=-0.26$, $p=0.03$). Area under the receiver operator characteristic curve for identification of patients in the target group was 0.71 (95% CI=0.59-0.81). A brain natriuretic peptide value of 29 pg/ml had a sensitivity of 88% and a specificity of 58%. Negative predictive value was 94% while positive predictive value was 37%. Therefore 46% of patients (those with brain natriuretic peptide < 29 pg/ml) could be excluded from further testing with reasonable certainty.

Conclusion: Brain natriuretic peptide could be used as a means of identifying patients at low risk for severe myocardial iron deposition and exclude them from unnecessary further magnetic resonance imaging testing.

P1396 NT-pro BNP-levels in patients with dilated left ventricles due to congestive heart failure or an athletes heart

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Differentiating congestive heart failure (chf) from athlete heart is of extreme importance in elderly patients presenting with poor symptoms and dilated myocards. The purpose of this study was to assess whether NT-proBNP levels drawn in patients with echocardiographic dilated ventricles can be consulted to discriminate between pathologic dilatation from physiologic adaptation as it is well known from athlete hearts.

Methods: Our study population consisted of 22 healthy male (group A, age 56 ± 10 years) with a healthy cardiovascular system, 20 male patients with known stable chf (group B, age 59.6 ± 10 years) and 21 competition rowers (group C, age 53.7 ± 5.3 years); both latter groups had documented dilated left ventricles by transthoracic echocardiogram (TTE). First, clinical status and the echocardiogram were assessed and NT-pro BNP levels were determined before and after a standardized exercise stress test.

Results: In group A the left ventricles had normal dimensions (50.8 ± 3.9 mm LVEDD) in comparison to group B (61.8 ± 3.1 mm LVEDD) ($p < 0.001$) and group C (58.8 ± 1.7 mm LVEDD) ($p < 0.001$). The determined left ventricular mass was normal for group A (149.92 ± 27.23 g) and increased in group B (211.56 ± 26.33 g) and C (213.69 ± 41.90 g). The difference was significant between group A and both other groups ($p < 0.001$), as there was no significant difference between group B and C with the increased LVEDDs. For group A as well as for group C the NT-proBNP levels at rest were within normal values (group A 40.4 ± 43.3 pg and group C 32.9 ± 34.9 pg (n.s.)). The NT-proBNP levels for group B were significantly elevated (1702.3 ± 1724.3 pg) ($p < 0.001$) in comparison to the groups A and C. At peak exercise the NT-proBNP levels increased in all three groups (group A 6 ± 6.4 pg, group C 11.8 ± 14 pg), while only in group C we observed significant increased NT-proBNP levels ($D 246 \pm 296.6$ pg) ($p < 0.001$).

Conclusion: We conclude that the determination of the biomarker NT-proBNP appears to be a sensitive test to differentiate between pathologic dilatative cardiomyopathies and dilatation from physiologic adaptation. The additional measurement of the NT proBNP levels after the exercise stress test gave no more important information.

Our findings may be important in the evaluation of patients who exercise regularly and show poor symptoms and dilated left ventricles in an age where the burden for coronary artery disease and heart failure is highly present.

P1397 Utility of B-type natriuretic peptide in predicting postoperative complications and outcomes in patients undergoing noncardiac surgery

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Objective: The purpose of the present study was to investigate whether pre- and

postoperative B-type natriuretic peptide (BNP) levels could be used as predictors of postoperative outcomes in patients undergoing noncardiac surgery.

Methods: The study group consisted of 102 patients (54 female, 48 male, 71±11 years) with a history of cardiovascular disease. All patients were evaluated according to ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and underwent transthoracic echocardiographic examination. Pre- and postoperative BNP levels were analyzed, and each subject was followed for six months. Primary outcome was composite of total mortality, cardiovascular mortality, myocardial infarction, cardiac arrhythmias and heart failure.

Results: During six months follow-up 37 patients experienced adverse events (10 in-hospital death, 11 out-of hospital death, 3 arrhythmias and 13 acute/worsened heart failure). Both preoperative and postoperative BNP were significantly higher in patients with adverse events (Preoperative BNP: 761±1017 pg/ml vs. 256±567 pg/ml, $p<0.001$; postoperative BNP: 808±1129 pg/ml vs. 235±477 pg/ml, $p<0.001$) (Table). Receiver operating characteristic curves demonstrated preoperative BNP levels as predictors of total mortality, in-hospital cardiovascular mortality, and heart failure with areas under the curve of 0.75, 0.81, and 0.78 respectively. A BNP cut-off value ≥ 133 pg/ml demonstrated a sensitivity of 76% and a specificity of 69% for predicting primary outcome. Postoperative BNP measurement was not superior to preoperative BNP measurement in predicting outcome.

Table. Preoperative BNP levels (pg/ml)

Event Free	Total mortality	In-hospital cardiovascular mortality	Heart Failure
256 ± 570	754 ± 809	1022 ± 833	885 ± 1385
p^*	<0.001	0.003	0.006

Conclusions: Preoperative BNP levels >133 pg/ml predict the postoperative complications and 6-months mortality after noncardiac surgery. Postoperative BNP measurement has a similar value in predicting outcome and is not superior to preoperative measurements.

P1398 BNP predicts exercise time, mitral valve area and left atrial pathology in mitral stenosis



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Introduction: Plasma levels of Brain Natriuretic Peptide (BNP) are known to increase in patients with left ventricular dysfunction but there is limited data on BNP in mitral stenosis (MS), which is characterised by increased left atrial pressure and volume, and normal LV function.

Methods: We studied 34 patients with pure MS and 14 age and gender matched controls. A trans-thoracic echocardiogram and blood samples for BNP were obtained. Exercise tolerance tests were performed in controls and 30 patients.

Results: MS patients predominantly had NYHA class I and II (97%) symptoms. The mean mitral valve area was 0.77 to 1.97cm². Compared to controls, MS patients had larger left atrial (LA) area (19.7±3.6 vs. 35.4±10.5cm², $p<0.0001$) and higher right ventricular systolic pressure (RVSP) (22.6±4.4 vs. 35.5±11.7mmHg; $p=0.0002$). There was no difference in LV ejection fraction (68.3±4.0 vs. 64.1±7.7%, $p=0.08$). Plasma levels of BNP (6.0±3.0 vs. 20.6±13.5pmol/L, $p<0.001$) were higher in MS and exercise times were shorter (654±179 vs. 376±174secs, $p<0.001$) than controls. For MS patients higher BNP was associated with shorter treadmill times ($r=0.48$; $p=0.008$). There was a good correlation between LA area and BNP ($r=0.70$; $p<0.0001$). BNP was higher in patients with atrial fibrillation compared to those in sinus rhythm (31.2±16.8 vs. 16.2±9.0 pmol/L; $p=0.002$). Raised BNP ($r=0.42$; $p=0.02$) correlated with decrease in mitral valve area (MVA). In contrast there was no clear association between BNP and RVSP, RV size, RV systolic function assessed by tricuspid annular TVI S' or LV ejection fraction.

Conclusion: In MS plasma levels of BNP increase with LA size and the presence of atrial fibrillation. These observations and the lack of association with measures of LV or RV function suggest an atrial origin for raised BNP in MS.

P1399 The integrative value of natriuretic peptide and troponin T testing for prognosis estimation in acute heart failure



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Objectives: We examined the role of natriuretic peptides (amino-terminal pro-brain natriuretic peptide, NT-proBNP and BNP) combined with troponin T (cTnT) for predicting 60-day and one year mortality in patients with acute heart failure (HF).

Methods: 209 subjects with acute HF at an urban academic center were studied. Concentrations of NT-proBNP, BNP, and cTnT were examined with respect to outcomes at 60 days and one year.

Results: At 60 days or one year, decedents had higher concentrations of both natriuretic peptides (both $p<0.001$, at both time points) and cTnT ($p<0.01$ at both time points). With respect to mortality, a differential pattern of marker concentrations was noted with relation to death rates: at 60 days, the great majority of de-

cedents demonstrated had elevations of both natriuretic peptides and cTnT, where a 25% mortality rate was observed ($p<0.001$); comparatively, the rates of death were low and indistinguishable among those with either isolated or no elevation of either class of marker. At one year, a high rate of death was noted in those with elevation of natriuretic peptides without cTnT elevation ($p=0.01$ compared to those negative for natriuretic peptides), however, the highest death rates (approaching 45%) in those with the combination of an elevated natriuretic peptide (NT-proBNP or BNP) and cTnT ($p<0.001$). The combination of an elevated natriuretic peptide and cTnT was the strongest predictor of death at one year (NT-proBNP plus cTnT, hazard ratio [HR]=7.66, 95% confidence intervals [CI]=3.06-17.8; BNP plus cTnT, HR=6.82; 95% CI=2.99-16.5; both $p<0.001$). Hazard curves demonstrated the risk associated with the combined elevations of natriuretic peptide/cTnT in acute HF developed early and was sustained through 1 year ($p<0.001$).

Conclusions: A multimarker strategy including a natriuretic peptide and cTnT is superior for estimating 60 day and one year prognosis in acute HF than use of either marker alone. Randomized studies are now needed to evaluate whether the deleterious short and longer-term outcomes associated with combination of elevated natriuretic peptide and cTnT can be modified.

P1400 Physical training decreases both plasma CNP and BNP concentration in heart failure patients



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C-type natriuretic peptide (CNP), mainly secreted by the vascular endothelium with vasodilator properties, is structurally related to atrial and brain natriuretic peptides (BNP): its elevation in heart failure (HF) is related to clinical and functional disease severity. Aerobic physical training has established benefits in the management of HF patients, including an improvement of endothelial dysfunction. To evaluate the effect of physical training on plasma CNP level in HF patients, 42 patients (NYHA class I-III) were divided into two groups: 28 patients (group T, age 59±2 years, left ventricular ejection fraction, EF 36.6±2.1%, mean±SEM) underwent a 9-month home-based exercise training program, at 60% of the maximal oxygen uptake (VO₂), while 14 patients did not exercise (group C, age 64±2 years, EF 36.6±2.1%, both NS vs group T). The exercise load was adjusted after three months to achieve a progressive training effect. Plasma assay of CNP (normal reference value <3.5 ng/L) and BNP, echocardiogram, quality of life questionnaire (Minnesota Living With Heart Failure) and cardio-pulmonary stress test were performed in all patients at enrolment and at ninth month. No differences were found between the two groups at baseline. At baseline, a significant relation was found between CNP and BNP ($R=0.45$, $p<0.01$), EF ($R=0.47$, $p<0.001$) and peakVO₂ ($R=0.47$, $p<0.001$). After 9 months, patients in group T showed a significant improvement in quality of life (score from 42±3 to 31±2, $p<0.01$), exercise tolerance (from 106±7 to 120±9 Watts, $p<0.001$), peak oxygen consumption (VO₂, from 15.7±0.1 to 17.5±1.0 ml/min/kg, $p<0.001$), and EF (from 36.6±2 to 39.5±1.7, $p<0.01$). Conversely, CNP decreased from 7.6±0.9 to 5.1±0.6 ng/L ($p<0.01$), as well as BNP (from 174±40 to 123±29 ng/L, $p<0.01$). No changes occurred in group C. In group T, the decrease in CNP was significant related to the increase in peak VO₂ ($R=0.42$, $p<0.05$) and to the decrease in BNP ($R=0.46$, $p<0.01$). Clinical and functional improvement after physical training in HF patients is associated with a decrease both in CNP and BNP concentration toward normal values. Changes in CNP plasma concentration might also be associated with an improvement of endothelial dysfunction after physical training.

P1401 Elevated baseline N-terminal pro-B-type natriuretic peptide levels predict the occurrence of perioperative myocardial ischemia and troponin T release in patients undergoing major vascular surgery



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Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted by the heart in response to wall stress and has prognostic value in patients with heart failure, acute coronary syndromes and stable coronary artery disease. Patients with coronary artery disease and left ventricular dysfunction undergoing major non-cardiac vascular surgery are at increased risk of perioperative cardiac events. NT-proBNP levels may be elevated in high-risk surgical patients and may be a useful as a preoperative screening marker. This study was conducted to determine the association between baseline NT-proBNP levels and the occurrence of perioperative myocardial ischemia and troponin T release.

Methods: In a prospective observational cohort study, a total of 107 consecutive patients scheduled for major non-cardiac vascular surgery were evaluated by clinical cardiac risk factors, dobutamine stress echocardiography, and baseline NT-proBNP levels. Myocardial ischemia was detected by continuous 12-lead electrocardiographic monitoring starting 24 hours before surgery and continuing for two days after. The ischemic burden was defined as the maximum ST segment deviation multiplied by the duration of ischemia. Troponin T was measured on day

1, 3, and 7 postoperatively and before discharge. We performed multivariable logistic regression analysis, evaluating the prognostic value of baseline NT-proBNP levels for myocardial compromise. Patients with congestive heart failure and renal dysfunction were not enrolled.

Results: In this patient cohort (mean age 66.7 ± 10.4 years, 85% male, 43.0% ischemic heart disease), the median NT-proBNP level was 198.7 ng/L (interquartile range: 79.4-460.1 ng/L). Myocardial ischemia during continuous 12-lead ECG registration was assessed in 24 patients (22%) and troponin T release (>0.1 ng/ml) in 20 patients (19%). After adjustment for cardiac risk factors and dobutamine stress echocardiography results, each 1.0 increment of log(NT-proBNP) was associated with a risk of 1.59 (95% CI: 1.12-2.24, $p=0.009$) for myocardial ischemia and 1.69 (95% CI: 1.16-2.46, $p=0.006$) for troponin T release. Interestingly, we found that a higher baseline level of NT-proBNP was associated with a larger ischemic burden during continuous 12-lead ECG monitoring (Spearman correlation coefficient 0.22, $p=0.026$).

Conclusion: Elevated baseline NT-proBNP levels predict the occurrence of myocardial ischemia and troponin T release in patients undergoing major non-cardiac vascular surgery and may be a promising marker for preoperative screening.

P1402 Diagnostic value of N-terminal pro B-type natriuretic peptide (NT-proBNP) in patients with chronic aortic regurgitation



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Purpose: BNP and its N-terminal fragment NT-proBNP have proven to be of diagnostic and prognostic value in patients with valvular aortic stenosis. Data regarding those biomarkers in patients with chronic aortic regurgitation (AR) are sparse. Thus it was the aim of the present study to evaluate the diagnostic and the long term prognostic value of NT-proBNP in patients presenting with AR.

Methods and results: This study included 60 patients with isolated AR and preserved left or mildly reduced ventricular function ($EF > 45\%$). Patients were followed over a median period of 824 (770-921) days. Clinical status, echocardiographic data and NT-proBNP (Elecys proBNP, Roche Diagnostics, Mannheim, Germany) were assessed at baseline and at follow up. Complete follow up data including echocardiography and blood sampling were available in 53 patients (88%). For the remaining patients clinical data has been assessed by telephone interview and/or according to medical report files. Death, rehospitalisation due to congestive heart failure and progression to unscheduled AVR were considered as adverse events.

NT-proBNP at baseline was related to disease severity (161(70-456) pg/ml in AR I, 226 (100-666) pg/ml in AR II and 1268 (522-5446) pg/ml; $p = 0.003$.) and to functional status. An improvement in functional status from baseline to follow up was present in 19 patients who were treated surgically. In those patients NT-proBNP values tended to decrease (748 (138-2292) pg/ml vs. 270 (177-1010) pg/ml at follow up, $p = 0.076$) whereas in patients who did not improve clinically after surgery NT-proBNP values remained unchanged (613 (92-1268) pg/ml vs. 617 (529-1045) pg/ml at follow up, $p = 0.612$). In conservatively treated patients no changes of NT-proBNP were detectable independent of changes in functional status.

Patients experiencing an adverse event ($n=6$) had higher NT-proBNP values at baseline as event free survivors (1271 (613-2992) pg/ml vs. 215 (92-534) pg/ml; $p=0.034$). The AUC of the ROC curve for NT-proBNP as a predictor for an adverse event was 0.76 ($p<0.036$) with an optimised cut off value of 602 pg/ml. Consequently, in Kaplan-Meier analysis NT-proBNP values dichotomised at this cut-off were able to discriminate patients with an adverse outcome (Log rank 9.98, $p=0.0016$).

Conclusion: NT-proBNP is linked to disease severity in patients with chronic aortic regurgitation reflecting hemodynamic stress due to volume overload. It provides prognostic information for the clinical outcome and thus might be a useful biomarker for risk stratification.

P1403 Head-to-head comparison of B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide under "real world" conditions



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Objective: B-type natriuretic peptide (BNP) and N-terminal (NT) -proBNP have been proposed as laboratory markers for the diagnosis of heart failure. The aim of this study was to compare both markers under "real world" conditions in 500 consecutive samples sent from our Department of Internal Medicine for NT-proBNP measurement, and to investigate influences on both markers.

Methods: Only one sample from each patient was included in the analysis, and the final study population comprised of 458 patients (mean age 60 years + 16 years; 159 female, 299 male). Patients suffered from cardiac diseases with ($n = 81$) and without reduced ejection fraction ($n = 317$), renal dysfunction as defined as glomerular filtration rate <60 ml/min/1.73 m² ($n = 104$), hypertension ($n =$

226) or anemia ($n = 53$). BNP was measured by the Abbott assay on the AxSYM analyser and NT-proBNP by the Roche assay on the E170 analyser.

Results: We found a significant increase of BNP and NT-proBNP values in patients with reduced systolic left ventricular function. Values were not significantly increased in patients with other cardiac diseases with normal systolic function compared to patients without cardiac diseases. Linear regression analysis revealed a significant influence of reduced ejection fraction, renal dysfunction, anemia, hypertension and age on both BNP and NT-proBNP values. BNP and NT-proBNP showed a close correlation of $r = 0.885$ ($p < 0.01$) with each other. Using age and gender adjusted normal values the inter-rater reliability of the two parameters was assessed using Cohen's Kappa test. The Kappa of 0.7 indicated a satisfactory agreement between both markers. 376 measurements (82% of total population) revealed concordant BNP and NT-proBNP results. Both tests were positive in 185 patients and both test results were negative in 191 patients. Discordant results comprised 77 patients (16% of the total population). The combination of normal BNP and elevated NT-proBNP was significantly more frequent than vice versa.

Conclusion: Our results demonstrate that BNP and NT-proBNP are frequently elevated in the absence of systolic left ventricular dysfunction. Using age and gender adjusted normal values renal failure is one of the most common reasons for false positive results. The agreement between both markers is satisfactory despite discrepancies, which demonstrates that both markers are not completely equivalent.

P1404 The impact of n terminal pro natriuretic peptide (NT pro BNP) on clinical probability of heart failure in the community. Prospective observational comparative study



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Objective: To assess the value of NT pro BNP levels as a screening tool for left ventricular systolic impairment in patients referred from the community to One Stop Heart Failure Clinics based on the number needed to screen (NNS). The study was designed to determine if NT pro BNP testing could increase the clinical probability prior to echocardiography.

Study design and method: Patients referred by their GP with new onset symptoms and signs of LV impairment were assessed in a pilot One Stop Heart Failure Clinic within 2 weeks of referral. All patients underwent a full cardiologic assessment including echocardiography, ECG and measurement of NT pro BNP. Ejection fraction (EF) of 50% was used as a cut off value for impaired left ventricular function on echocardiography. Receiver Operator Characteristic (ROC) curve was used to determine the most sensitive and specific NT pro BNP level for impaired left ventricular function ($EF < 50\%$). Positive Predictive Value (PPV) & Negative Predictive Value (NPV) were calculated. The number needed-to-screen (NNS) was also calculated based on the prevalence of LVF in our cohort of patients, sensitivity and specificity of NT pro BNP.

Results: 220 patients were included in the study. The mean age was 66 years (18-92). 99 (45%) of patients were females. From 220 patients investigated there were 46 (21%) patients who had EF less than 50%.

Based on results of NT pro BNP and echocardiographic assessment of LV function in the study group of patients ROC curve was constructed. Area under the curve was of 0.92.

The value of NT pro BNP with maximum sensitivity and specificity (96% & 77%) for EF of 50% or more was found to be 125pg/ml or less for all adult age groups males and females. The prevalence of LVF in our cohort of patients referred from the community was 21%. This means that NNS applied to 100 patient model without NT pro BNP testing is $1/\text{prevalence} = 4.7$ and with NT pro BNP testing $1/0.52 = 1.92$. NNS was reduced further to 1.7 when NT pro BNP and ECG were applied together.

Conclusion: As NT pro BNP has very good sensitivity and NPV for impaired LV systolic function, its use in the community in liaison with the One Stop Heart Failure Clinics reduces the number of patients needed to be screened in the clinic for heart failure significantly and more importantly assists primary care physicians with better determination of clinical probability prior to referral. This has great impact on waiting time and overall cost.

P1405 N-terminal pro-brain natriuretic peptide levels increases during weight loss in individuals without heart disease



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Purpose: The cardiac hormone brain natriuretic peptide (BNP), including the N-terminal fragment of the prohormone (NT-proBNP) have in cross-sectional studies been demonstrated to be inversely associated with body mass index (BMI). Clearance of these peptides by adipocyt specific receptors has been suggested. We therefore investigated the impact of weight loss on plasma levels of NT-proBNP in obese individuals without heart disease

Methods: A total of 20 obese women and 2 men (BMI > 28 kg/m²), total body weight 96.1 (±15.1) kg, age 61.7 (± 6.6) year (mean ± SD) were included. All subjects were without cardiovascular disease, and NT-proBNP was < 125 pg/mL at baseline, which is the recommended cut-off value for rule out a diagnosis of heart failure. The participants were on a low energy diet of 3.4–5 MJ/day for 1 year. Body weight, body composition as measured by DEXA scan, as well as plasma levels of NT-proBNP and adiponectin were measured at baseline and after 52 weeks.

Results: Mean total weight loss was 15.4% (± 1.7%) and DEXA scan revealed, that this primarily was due to loss in body fat of 27.2% (±3.2%), the decrease in lean tissue mass was 3.0% (±1.2%) (mean ± SE). Plasma NT-proBNP levels increased from 50.2 (39.7–83.3) pg/mL at baseline to 90.3 (49.0–118.9) pg/mL after 52 weeks, median (interquartile range) (P=0.003). Plasma adiponectin levels increased from 14.2 (9.0–17.25) to 16.5 (10.4–19.9) mg/L (P=0.004). Furthermore, a significant association between percent weight loss and increase in plasma adiponectin levels (R=0.59, P=0.004), and a trend towards an association with increase in NT-proBNP levels (R=0.31, P=0.15) were found.

Conclusions: Plasma levels of NT-proBNP increases significantly during weight loss, suggesting a possible role of adipose tissue in the clearance of this peptide from circulating plasma. The observed increase in adiponectin supports, that plasma levels are regulated by a negative feedback mechanism.

P1406 The importance of NT-proBNP versus echocardiography for evaluation of dyspneic patients in the emergency department



America

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Background: Plasma levels of amino-terminal pro-B type natriuretic peptide (NT-proBNP) correlate with echocardiographic indices of cardiac dysfunction. Whether NT-proBNP results in dyspneic patients have prognostic value above findings on echocardiography is unknown. Also, it is not known whether low NT-proBNP concentrations exclude clinically meaningful findings on echocardiography in such patients.

Methods: Plasma NT-proBNP was measured in 599 dyspneic emergency department (ED) patients enrolled in a prospective study of NT-proBNP testing. Routine echocardiography was performed in 134 patients an average of 51±42 hours after presentation. Clinical and echocardiographic parameters which correlated with one-year mortality in univariate analysis with a p value < 0.1 were entered into a stepwise logistic regression model, using death at 1 year as the dependent variable.

Results: The average age of the 134 patients was 69±14 years; 65 were male. A final diagnosis of the cause of dyspnea was acute HF, non-cardiac cause with prior HF, and no HF in 89, 7 and 38 patients, respectively. The median NT-proBNP level was 2430 pg/ml (IQR 637–7214 pg/ml). Fifty-nine patients had LVEF < 50%; median NT-proBNP was 4686 pg/ml (IQR 1989–12796 pg/ml) in this group compared with 1150 pg/ml (IQR 679–3070 pg/ml) in those with LVEF > 50% (p=0.001). An NT-proBNP <300 pg/ml was associated with minimal structural or functional abnormalities on echocardiography, with >90% NPV. Overall one-year mortality was 20.1% and was independently predicted by NT-proBNP level (HR 8.65, 95% CI 2.7–27.8, p = 0.0003), LVEF (HR 0.95, 95% CI 0.91–0.99, p = 0.009), right ventricular dilation (HR 2.98, 95% CI 1.05–12.8, p = 0.04) and systolic blood pressure (HR 0.97, 95% CI 0.96–0.99, p = 0.01). Early (Ea) and late (Aa) diastolic tissue Doppler velocities of the lateral mitral annulus, E/Ea ratio, tricuspid regurgitation severity, age by decade, creatinine clearance decile, NYHA class, heart rate decile and troponin-T level were not independent predictors of death at 1 year. An NT-proBNP level above the median value, LVEF < 50%, and presence of RV dilation each incrementally increased the risk for mortality: 10% if no factors present; 21% if 1 factor; 30% if 2 factors; 40% if 3 factors (p=0.001 for trend).

Conclusions: In a general population of patients presenting to an ED with dyspnea, elevated NT-proBNP levels provide important prognostic information beyond echocardiographic indices of cardiac structure and function, while an NT-proBNP <300 pg/ml reliably excluded significant life-threatening structural heart disease.

P1407 Long term clinical variation of NT-proBNP in stable chronic heart failure patients



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Background: Long-term clinical variation of NT-proBNP in stable chronic heart failure patients is unknown.

Aims: To identify long-term clinical variation of NT-proBNP in stable chronic heart failure patients.

Methods: Medication, biochemical variables, NYHA-class and weight were noted at one and two year follow up in our heart failure clinic. Only patients without changes in medication or NYHA class, who were not hospitalised or died between the follow up calls and 12 month after were included. 78 out of 310 patients from our database fulfilled the criterias. Percent-changes were calculated

as (Level_{2-year}–Level_{1-year})/Level_{1-year} × 100%. Clinical variation was calculated as the year-to-year-variation-coefficient: SD/mean and variances as: (S(x_i–x_m)/2/(n–1)).

Patients characteristics (n=78): Demographic data (median and range): Age (at 1-year follow up) (yrs): 73 [51–82]; Height (cm): 182 [149–192]; Sex (males/females): 50/28; NYHA class (I/II/III): 8/62/8; left ventricular ejection fraction (LVEF) (fraction): 30 [13–45]; Cardiomyopathy (ischemic/idiopathic/hypertensive/alcoholic/valvular/other): 54/10/6/1/2/5; Sinus rhythm/atrial fibrillation: 58/20; Diabetes (number): 15. Thyroid disease: 6. Medications (numbers) (%): ACE-inhibitors/All-antagonists: 68 (89%); Beta-blockade: 59 (76%); Spironolactone: 33 (43%); Digoxin: 19 (25%); Loop-diuretics: 59 (77%); Thiazide diuretics: 11 (14%) and Potassium supplementation: 52 (68%).

Results: Year-to-year clinical variation was calculated to 30% (median) (range: 0–111%) (%-changes range: –87%–397%). If NT-proBNP were log-transformed (right skewed distribution) the year-to-year clinical variation was calculated to 5% (median) (range: 0–22%) (%-changes range: –18%–38%). Variances of NT-proBNP were level dependent (R=0.66; P<0.001), but after log-transformation this correlation was weak (R=0.28; P=0.017).

Conclusions: Long-term clinical variation of plasma concentrations of NT-proBNP is 30% (range: 0–111%) in stable chronic heart failure patients. Our data demonstrate that long term clinical variation of NT-proBNP can be high without prognostic significance within 12 month. However, plasma concentrations of NT-proBNP are skewed distributed to the right and the low variation of logNT-proBNP indicates that NT-proBNP levels are constant during stable conditions in chronic heart failure patients.

P1408 Plasma Nt-proBNP levels predict 30-days-mortality in patients with cardiogenic shock

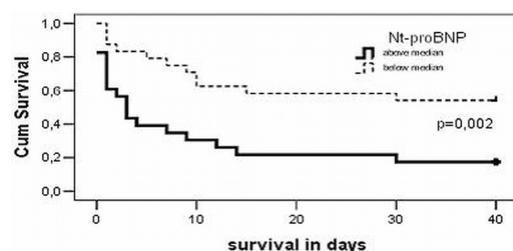


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Introduction: Recently it has also been shown that Nt-proBNP levels are elevated in patients with severe sepsis and that this peptide might reflect temporary ventricular dysfunction in septic shock. However, Nt-proBNP levels have not been investigated yet in patients with cardiogenic shock (CS).

Methods: Plasma levels of Nt-proBNP (Roche Diagnostics, Austria) were determined in blood samples of 48 patients with CS collected at admission to the coronary care unit.

Results: Median of Nt-proBNP levels was 12,579pg/ml (IQ range 5,633pg/ml – 23,449pg/ml) 15.3 ± 9.8 hours after the onset of shock. Nt-proBNP showed no significant correlation with duration of shock, renal or total SOFA score or the presence of SIRS at blood sampling. In multivariate linear regression analysis creatinine and CRP significantly contributed for variation of Nt-proBNP levels (22%; p=0.004) whereas CI, LWSVi, PAOP, CVP, SVRi or mean arterial pressure did not. Kaplan-Meier survival analysis revealed that patients with Nt-proBNP levels below median have significantly better survival than patients with Nt-proBNP above this cut-off (p=0.002; Figure). In multivariate Cox analyses - adjusted for age, gender, total dose of catecholamines, total SOFA score, presence of SIRS, hemodynamic parameters, serum creatinine and CRP - Nt-proBNP was a strong predictor of 30-days mortality (adjusted OR: 2.9 (1.2–6.9); p=0.012).



Conclusion: In the present study we could show that duration of shock, extent of organ failure and hemodynamic parameters are no significant determinants of elevated Nt-proBNP levels in CS. Nevertheless, survival of patients with CS is dramatically impaired when Nt-proBNP is massively elevated early after the onset of shock.

P1409 Change in renal function has little bearing on change in NT-BNP levels in patients with Heart Failure



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Renal impairment is associated with elevated natriuretic peptide in patients with heart failure(HF). We sought to assess whether changes in renal function over time affects NT-brain natiutetic peptide(NT-BNP) levels.

Methods: We retrospectively analysed data from HF patients attending our outpatient department. Concomitant NT-BNP levels, creatinine levels and weight

measurements at two periods in time were collected for each patient and change in NT-BNP and creatinine clearance (CrCl) over this time was calculated. (CrCl calculated using the Gault Cockcroft equation).

Results: Results for 92 patients were collated. The mean time between NT-BNP/CrCl levels was 42 months. 54% (n=50) patients showed deteriorating CrCl over this period with the remainder having improvement or no change. There was no significant difference between these groups (CrCl fall v CrCl rise/no change) in terms of proportion of patients with increasing NT-BNP over time (36/50[72%] v 28/42[66%] respectively, p=NS) or in terms of mean change in NT-BNP (+547pg/ml v +461pg/ml, p=NS). Of the 92 patients, 67% (n=62) had a rise in NT-BNP over time with the remainder showing a fall. Again, there was no significant difference between the groups (NT-BNP rise v NT-BNP fall) in the proportion of patients with deteriorating CrCl (29/64[45%] v 13/28[46%] respectively, p=NS) or in mean change in CrCl over time (-2.14ml/min v -2.9 ml/min, p=NS) (fig 1) Overall, there was not a significant correlation between absolute change in NT-BNP levels and change in CrCl over time (r= 0.13)

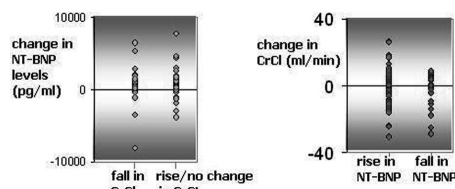


Fig 1. Change over time

Conclusion: Improvement or deterioration in renal function appears to have little influence on change in NT-BNP levels in patients with HF. This suggests that renal function does not need to be considered as a confounding factor when analysing serial NT-BNP levels.

P1410 Prognostic value of NT-proBNP assessment at admission and at the day following admission in patients with acute coronary syndromes



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Purpose Recently BNP and NT-proBNP have been found to be highly predictive for an adverse outcome in patients with acute coronary syndromes (ACS). However, most of these data have been derived from retrospective analysis of large multicenter trials. In most studies patients were not treated by an early invasive approach respectively primary PCI according to current guidelines. Furthermore, the optimal timing of BNP or NT-proBNP assessment for risk stratification remains indistinct.

Therefore, we analysed the prognostic value of NT-proBNP assessed on admission and the day following admission in patients with the entire spectrum of ACS treated by an early invasive approach.

Methods We included 1125 consecutive patients (342 females, age 64 ± 12 years) from April 2003 till March 2005 who were referred for primary PCI (STEMI, n=486) or early invasive diagnostic (NSTEMI-ACS, n=639) within 48 hours after the index event. Follow up data after 6 months were available for 1057 patients (94%).

Results NT-proBNP values at admission were lower as the values at day 1 (519 (136-1722) pg/ml vs. 1175 (450-2939) pg/ml; $p < 0.001$). NT-proBNP values provided prognostic information for death within 6 months. However, the prognostic value of NT-proBNP assessed at day 1 was superior to admission assessment (AUC=0.79, $p < 0.001$ respectively AUC=0.71, $p < 0.001$). Applying an optimised cut-off value of 1850 pg/ml for NT-proBNP at admission and of 2750 pg/ml at day 1, NT-proBNP was able to discriminate between survivors and non-survivors (Log rank 35.11, $p < 0.001$ and 32.3, $p < 0.001$ respectively). In contrast NT-proBNP at admission and at day 1 was not predictive for recurrent ischemic events, either reinfarction or unscheduled revascularisation (AUC=0.528, ns respectively AUC=0.527, ns). 480 patients were admitted within 6 hours after onset of symptoms. NT-proBNP values were lower in those patients compared to those patients admitted later than 6 hours after the index event (186 (79-859) pg/ml vs. 835 (277-2144) pg/ml; $p < 0.001$). However, the predictive value of NT-proBNP at admission was almost identical in both groups (AUC=0.748 respectively 0.718).

Conclusion In patients with acute coronary syndromes treated early invasively according to current guidelines, NT-proBNP at admission provides prognostic information for death within 6 months but not for recurrent ischemic events. The prognostic value of NT-proBNP assessed at the day following admission is superior for risk stratification as compared to admission assessment.

P1411 ProBNP level measured before electrical cardioversion does not predict recurrence of atrial fibrillation



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Purpose: Small studies have indicated that low levels of proBNP measured immediately before electrical cardioversion (EC) for persistent atrial fibrillation (AF) are associated with successful restoration and maintenance of sinus rhythm. The decision to perform EC is typically made 3-6 weeks before the procedure because adequate warfarin treatment is needed. In this study, we hypothesised that low levels of serum proBNP measured 3-6 weeks before EC might predict higher degree of sinus rhythm maintenance.

Methods: In the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study, 171 patients with AF scheduled for EC were randomised to receive candesartan 8 mg o.d. or placebo for 3-6 weeks before and 16 mg o.d. or placebo for 6 months after EC to reduce the recurrence rate of AF. Candesartan had no effect on recurrence rate of AF. As part of this study, levels of proBNP were measured at randomisation 3-6 weeks before EC. Patients with heart failure were not entered into the study. Values are given as median (25, 75 percentiles), and non-parametric statistical tests have been used.

Results: ProBNP levels were not significantly different in patients who were successfully cardioverted (n=129) as compared to patients who were not (n=22): 88.6 pg/mL (57.7, 141.1) vs. 73.9 pg/mL (43.2-145.6), $p=0.324$. ProBNP levels measured before EC in patients remaining in sinus rhythm 6 months after EC (n=40) were not different from proBNP levels in patients with unsuccessful cardioversion or a relapse of AF (n=111): 88.2 pg/mL (59.2, 147.5) vs. 88.5 pg/mL (52.4, 140.5), $p=0.853$. In successfully cardioverted patients, baseline ProBNP-levels were similar in patients still in sinus rhythm 6 months after EC and patients who had a relapse of AF: 88.2 pg/mL (59.2, 147.5) vs. 90.0 pg/mL (55.3, 138.4), $p=0.959$.

Conclusion: In this study, proBNP levels in patients with persistent atrial fibrillation measured 3-6 weeks before electrical cardioversion did neither predict successful restoration nor maintenance of sinus rhythm after the procedure.

P1412 Natriuretic peptide variability in a community heart failure population: is there a difference between BNP and NT-proBNP?



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Background: There is a well established role for the natriuretic peptides B-type natriuretic peptide (BNP) and N-terminal pro B type natriuretic peptide (NT-proBNP) in the screening and diagnosis of Heart Failure (HF). Furthermore, there is increasing interest in their long-term role in HF disease monitoring. Although NT-proBNP is reported to have a lower analytical variability than BNP, there are limited available data on the biological variability of these peptides in a community HF population.

Aims: This study evaluates the biological variability of BNP and NT-proBNP within 1-hour and over 1-week in a community HF patient sample.

Methods: Consecutive patients with a confirmed diagnosis of HF of mixed aetiology and deemed clinically stable by the HF physician (no change in clinical status or HF medication within the previous 4 weeks) were invited to partake in the study. Within-hour variation was calculated from 2 samples taken one hour apart. Within-week variation was calculated from samples taken at the same time and on the same day 1-week apart. Variability was expressed as mean $\pm$ SD for the group. Clinical parameters, medications, urea and creatinine were measured at each visit. Analytic variability was calculated at baseline from repeated analysis of the first 20 samples taken.

Results: In this sample (n=45, mean age 70 ± 12 years, 64% male, 86% left ventricular systolic dysfunction). The average baseline BNP and NT-proBNP respectively was 219pg/ml $\pm$ 210pg/ml and 1176 $\pm$ 1315pg/ml. There was a significant within-hour difference in variability between BNP and NT-proBNP respectively (21.1 $\pm$ 20.8%; range: 0-108%; 9.9 $\pm$ 9.9%; range: 0.2-35%, $p < 0.01$). No significant difference in within-week variability was observed for either peptide. Analytical variability was 13.7% and 3.1% for BNP and NT-proBNP respectively.

Conclusions: In a stable community HF population, the within-hour variability was significantly greater in BNP than NT-proBNP, although no significant differences in within-week variability were observed in either peptide. Any assay specific advantages of NT-proBNP may be outweighed over time by considerable biological variability of natriuretic peptides in HF. This may have implications for choice of assay and natriuretic peptide monitoring of HF patients over time.

P1413 Anemia is associated with enhanced secretion of brain natriuretic polypeptide and increased ventricular mass in diastolic heart failure



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Background: Several studies have demonstrated that an estimated half of all patients with heart failure is diastolic heart failure. Anemia is associated with an increased risk of rehospitalization and cardiac death in heart failure (HF) patients. However, majority of those patients are under the condition of systolic HF. Thus, prognostic importance of anemia has not been well understood in diastolic HF.

Methods: to assess the prognostic value, we prospectively studied 250 consecutive patients with clinical HF on admission. Diastolic HF was defined as a left ventricular ejection fraction (LVEF) > 40%. There were 89 patients with diastolic HF and 118 patients with systolic HF (mean age: 74±11 years vs. 64±13 years, $p<0.0001$). Forty-three patients who had structural heart disease such as valvular and congenital heart disease were excluded in this study.

Results: Hemoglobin level was significantly lower in patients with diastolic HF than systolic HF ($13\pm3\text{g/dl}$ vs. $12\pm3\text{g/dl}$, $p=0.03$). During a mean follow-up of 20 months, 30 patients with systolic HF and 22 with diastolic HF had a cardiac event requiring hospitalization and cardiac death. Hospitalization-free survival was similar between patients with systolic and diastolic HF. Anemia was defined as follows: hemoglobin < 11g/dl in women and < 12g/dl in men. Diastolic HF patients with anemia ($n=38$) showed higher brain natriuretic polypeptide (BNP) level ($642\pm575\text{ pg/ml}$ vs. $393\pm309\text{ pg/ml}$, $p=0.032$) and ventricular mass index ($204\pm67\text{g/m}^2$ vs. $170\pm58\text{g/m}^2$, $p<0.05$), and worse hospitalization-free survival (log rank=13.4, $p=0.0002$) as compared with those without anemia ($n=49$). In diastolic HF patients, multivariate analysis identified age (1.10/year increase, $p=0.003$) and anemia (1.22/1g/dl decrease, $p=0.009$) as independent predictors for a cardiac event.

Conclusions: Anemia is strongly associated with clinical outcome in patients with diastolic HF. Increased ventricular mass and enhanced secretion of BNP may be associated with anemia in diastolic HF.

P1414 N-BNP levels in pregnant women with and without heart disease



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Background: Maternal heart disease during pregnancy is a major problem in cardiological management. Brain natriuretic peptide (BNP) is useful in the diagnosis and prognosis of heart failure. Symptoms such as dyspnoea may be non-specific, especially in the pregnant population, making assessment more difficult. We tested the hypothesis that N-terminal BNP is higher in pregnant women with heart disease compared to pregnant women with healthy hearts.

Methods: Plasma was obtained from sixty-two healthy pregnant women (mean age 32 ± 5 years, mean gestation 26 ± 8 weeks) and forty-one pregnant women with heart disease (mean age 30 ± 7 years, mean gestation 25 ± 8 weeks). The women with heart disease were categorised according to New York Heart Association (NYHA) functional class. N-BNP was measured by in-house non-competitive assay. The lower limit of detection was 0.03 fmol/ml. Within- and between-assay coefficients of variation were 2.3% and 4.8% respectively. All samples were analysed blind to patient data. Each sample was split into two, analysed in duplicate and the average taken as the final measurement.

Results: There was no significant difference between the levels of N-BNP in the group of women with heart disease in NYHA class I and the control group (64.3 [111.3] fmol/ml, median [IQR] vs 41.4 [56.7] fmol/ml, $P=0.107$). However, the group of pregnant women with heart disease in NYHA II had a significantly higher N-BNP than the control group (418.6 [300.3] fmol/ml vs 41.4 [56.7] fmol/ml, $P<0.0001$).

Conclusion: Pregnant women with heart disease do not necessarily have high levels of N-BNP compared to healthy pregnant women, especially if they are in NYHA class I. However, N-BNP was significantly raised in the group in NYHA II, suggesting that it may be a simple test to identify a subgroup of pregnant women with heart disease who may require further investigations. This will require larger scale outcome studies.

P1415 Prognostic significance of NTproBNP in patients with a clinical diagnosis of heart failure and preserved left ventricular systolic function



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Background: A high proportion of patients with clinically suspected heart failure

are aged >70 years and have neither a low ejection fraction nor valve disease. These patients are currently the focus of several clinical trials but problems exist, both with diagnosis and with prognostic risk stratification, that hinder progress.

Methods: The PEP-CHF trial enrolled patients aged at least 70 years with a clinical diagnosis of chronic heart failure requiring treatment with diuretics who had two or more of the following echocardiographic abnormalities; left ventricular hypertrophy, left atrial dilatation, atrial fibrillation, Doppler filling abnormalities or regional wall motion abnormalities but with preserved global left ventricular systolic function. Patients were randomised to perindopril, target dose 4mg/day, or placebo and followed for at least one year. NTproBNP (Roche Elecsys) was measured, after completion of the study, from plasma taken in a subset of patients at baseline and at one year after randomisation.

Results: NTproBNP was measured in 375 patients at baseline, mean age 77 (SD 5.3) years, 55% of whom were women. Median plasma NTproBNP was 409pg/ml (interquartile range 176 to 1036pg/ml; full range 9 to 13,328pg/ml). Higher plasma concentrations of NTproBNP were related to a greater risk of the primary end-point (death or heart failure related hospitalisation) and all-cause mortality. Plasma samples were obtained at baseline and one year in 280 patients. NTproBNP fell by a median of 123pg/ml (IQR -195 to +134) on perindopril and rose by 57 (IQR -142 to 211)pg/ml on placebo. However, these trends did not differ statistically.

Conclusion: Most older patients with a clinical diagnosis of heart failure and preserved LV function have elevated plasma concentrations of NTproBNP. Patients with higher levels have a worse prognosis.

P1416 BNP levels-guided therapy for heart failure: a comparative study against usual clinical monitoring



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Introduction and aims: Prognosis of heart failure is still unfavourable despite advances in medical therapy in recent years. Optimisation of medical therapy, based in clinical monitoring, may not be the best strategy. The aim of our study is to assess the effect of optimisation the medical therapy for heart failure patients based in BNP levels.

Methods: We have assessed 60 consecutive patients discharged from our institution with the main diagnosis of heart failure. Thirty of them were randomly assigned to clinical monitoring (Framingham score) and the rest received BNP levels-guided therapy. Mean follow-up for all patients was 16 ± 4 months.

Results: Both groups of patients were similar with respect to age, sex, aetiology of heart failure, ejection fraction and cardiovascular risk factors. Medical treatment at discharge was also similar. BNP levels-guided therapy patients had significantly lower levels of BNP during follow-up (14 ± 20 vs $111 \pm 218\text{ pg/ml}$ at 18 months, $p<0.01$). Nevertheless, the Framingham score was similar in both groups (0.42 ± 0.33 vs 0.39 ± 0.38 at 18 months, $p=NS$) as was the incidence of cardiovascular events. Survival at 18 months was similar (83% and 86%, respectively) and the readmission free survival rate (59 vs 56%, $p=NS$).

Conclusions: BNP levels-guided therapy approach for heart failure patients does not differ from standard clinical monitoring. Mortality and incidence of readmissions for heart failure was similar in both groups.

P1417 Race and dender do not influence the usefulness of amino-terminal proBrain natriuretic peptide (NT-proBNP) testing in dyspneic subjects



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Introduction: Amino-terminal pro-brain natriuretic peptide (NT-proBNP) is useful for the diagnosis and exclusion of acute heart failure (HF). Little is known about the effect of race on NT-proBNP concentrations. Also, NT-proBNP levels may be higher in apparently-well women, but the effect of gender on NT-proBNP concentrations in dyspneic patients is not known.

Methods: NT-proBNP was measured in 599 dyspneic patients in a prospective study. Of these, 44 were Black; 295 were female. NT-proBNP levels were examined according to race and gender in patients with and without acute HF using analysis of covariance. Receiver operating characteristic (ROC) curves assessed NT-proBNP by race and gender. Cut-points for diagnosis (450, 900 and 1800 pg/ml for ages <50, 50-75, and >75 years) and exclusion (300 pg/ml) were examined in Black and female subjects.

Results: There was no difference in the rates of acute HF between Black and non-Black (30% vs 35%, $p=0.44$) or male and female (35% vs 35%, $p=0.86$) subjects. In subjects with HF, there was no difference in median NT-proBNP concentrations between Blacks and non-Blacks (6196 vs 3597 pg/ml, $p=0.37$). In subjects without HF, unadjusted NT-proBNP levels were lower in Black subjects than in non-Black subjects (68 vs 148 pg/ml, $p<0.03$), however, when adjusted for factors known to influence NT-proBNP concentrations (age, prior HF, creatinine clearance, atrial fibrillation and body-mass index), race no longer significantly affected NT-proBNP concentrations. There was no statistical difference in median NT-proBNP concentrations between male and female subjects with (4686 vs 3622 pg/ml, $p=0.53$) or without HF (116 pg/ml vs 150 pg/ml, $p=0.62$). Among Blacks

NT-proBNP had an area under the ROC for acute HF of 0.96 ($p < 0.0001$), and at optimal cut points, had a sensitivity of 100% and a specificity of 90%. Among females NT-proBNP had an area under the ROC for acute HF of 0.95 ($p < 0.0001$), and had a sensitivity of 89% and a specificity of 88%; 300 pg/ml had negative predictive value of 100% in Blacks and females.

Conclusions: NT-proBNP is useful for the diagnosis and exclusion of acute HF in dyspneic subjects, irrespective of race or gender.

P1418 Clinical significance of N-Terminal ProBrain natriuretic peptide in hypertrophic cardiomyopathy

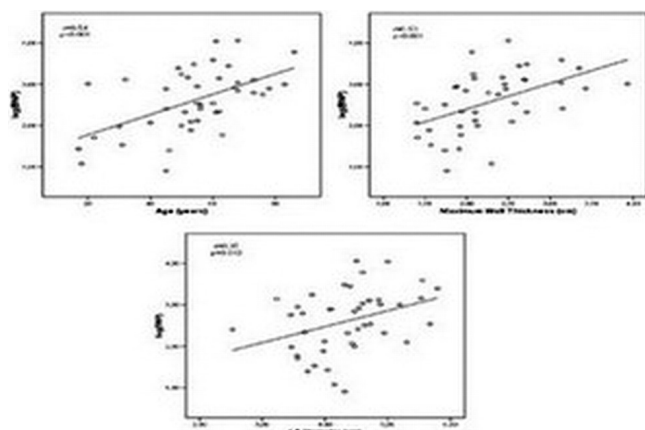


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Background: N-terminal-proBrain Natriuretic Peptide (NT-proBNP) plasma levels are elevated in patients with congestive heart failure. Published data concerning the utility of NT-proBNP in Hypertrophic Cardiomyopathy (HCM) are lacking.

Purpose: To evaluate the clinical significance of NT-proBNP in patients with HCM. **Methods:** A blood sample was collected for plasma NT-proBNP measurement from 43 consecutive patients with documented HCM. NT-proBNP was measured using a chemiluminiscence immunoassay kit (RocheDiagnostics) on an Elecsys 2010 analyser.

Results: Median value of NT-proBNP was 219 pg/ml (8 to 3045 pg/ml) in NYHA class I patients, 698 pg/ml (125 to 2463 pg/ml) in NYHA class II patients, and 2683 pg/ml (131 to 11542 pg/ml) in NYHA class III and IV patients. NT-proBNP plasma levels were significantly greater across the severity of functional limitation (ie, NYHA class classification) ($p = 0.002$). NT-proBNP levels were statistically significant greater in female vs male gender ($p = 0.034$), in referral vs non-referral patients ($p = 0.004$), in symptomatic vs asymptomatic patients ($p = 0.020$), in patients with basal subaortic gradient ≥ 30 mmHg ($p = 0.001$) and in the patients who were on cardioactive medication ($p = 0.010$). In univariate analysis NT-proBNP was significantly correlated with age ($p < 0.001$), left ventricular maximum wall thickness ($p = 0.001$), and left atrium size ($p = 0.019$). In multivariate regression analysis, age ($p < 0.001$) and maximum wall thickness ($p = 0.007$) were independently associated with NT-proBNP levels.



Conclusions: Our data support a potential role of NT-proBNP in assessing the clinical status of patients with HCM, although maximum wall thickness and age must be taken into account in clinical practice.

P1419 Androgen receptor blockade increases N-terminal fraction of BNP (NT-proBNP) in men with prostate cancer



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Background: Anti-androgens are widely used in prostate cancer. They may have adverse cardiovascular effects, as testosterone appears to be cardioprotective in men. In vitro studies suggest B-type natriuretic peptide (BNP) stimulates testicular testosterone secretion. The reverse, i.e. androgen effect on BNP is not known.

Methods and results: In a randomised trial, 43 men with prostate cancer received either goserelin (a Luteinising Hormone-Releasing Hormone analogue) or bicalutamide (an androgen-receptor blocker) for 6 months. A cohort of 20 men with a history of prostate cancer on no treatment, were studied in parallel. Mean age was 70.7 $\pm$ 6.2 years. N-terminal fraction of BNP (NT-pro-BNP) levels were assayed at baseline, 3 and 6 months. Left ventricular systolic and diastolic function were measured at baseline and 6 months. Mean change in testosterone and oestradiol levels from baseline to 6 months were -88% and -46% respectively in the goserelin group, +50% and +44% in the bicalutamide group, and -1% and -9% in 'no-treatment' group. Bicalutamide significantly increased NT-

pro-BNP (mean change $\pm$ SEM: +31.4 $\pm$ 13.4 and +106.6 $\pm$ 47.9 ng/L after 3 and 6 months ($p \leq 0.024$ for change from baseline) respectively; whereas goserelin changes were non-significant (+16.1 $\pm$ 34.9, -4.8 $\pm$ 37.5 after 3 and 6 months respectively, $p = \text{NS}$). No significant changes were seen in the 'no-treatment' cohort (-0.3 $\pm$ 4.4 and -14.1 $\pm$ 9.2 after 3 and 6 months respectively, $p = \text{NS}$). Blood pressure, left ventricular systolic or diastolic function changes did not account for the increase with bicalutamide.

Conclusion: Androgen receptor-blockade but not suppression therapy increases NT-pro-BNP, without significant changes in LV function. This may imply an adverse cardiovascular effect.

MORE ON REPERFUSION STRATEGY

P1420 Primary angioplasty performed out-of-hours has the same outcomes as for patients treated in-hours



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Background: Many hospitals have started a primary percutaneous coronary intervention (PPCI) service for patients presenting with AMI. Some centres use PPCI during standard working hours and thrombolysis out-of-hours. Some centres have reported worse outcomes with PPCI for patients treated out-of-hours. This might relate to inherent delays in activating an on-call team. We compared the characteristics of patients and their outcomes depending on the time of treatment.

Methods: We studied 299 patients undergoing PPCI or facilitated PCI within 12 hours of symptom onset for ST elevation MI from August 2003 to October 2005.

Results: 116 (39%) patients presented in-hours (Gp1) and 183 (61%) presented out-of-hours (Gp2). There were no differences in baseline characteristics except there were more women (32% vs 21%; $p = 0.04$) in Gp2. Target and multi vessel disease were similar in both groups. PCI success, complication rates, treatment delays and 30-day mortality rates were similar in both groups. In multivariate analysis, age (OR 1.08, 95% CI 1.01 to 1.17), diabetes (OR 19.9, CI 3.5 to 114), hypercholesterolemia (OR 4.2, CI 1.08 to 16.4), shock (OR 59.7, CI 11.9 to 300), LAD territory infarct (OR 4.9, CI 1.2 to 20.4) were independent predictors but out-of-hours PCI was not an independent predictor of 30-day mortality. Gp2 patients had a longer length of stay during the index hospitalisation.

Results

Baseline characteristics	Group 1	Group 2	p value
Symptom-admission (hours $\pm$ SD)	2.9 $\pm$ 2.5	2.9 $\pm$ 2.8	0.94
Admission to 1st balloon time (hours $\pm$ SD)	1.5 $\pm$ 1.6	1.9 $\pm$ 1.8	0.12
TIMI 3 pre procedure n (%)	9 (8)	25 (14)	0.2
TIMI 3 post procedure n (%)	100 (86)	160 (87)	0.9
Failed angioplasty without complications n (%)	4 (3)	8 (4)	0.8
Failed angioplasty with complications n (%)	1 (1)	2 (1)	1
Length of stay (days $\pm$ SD)	5.4 $\pm$ 3.8	8 $\pm$ 13	0.04
30 day total mortality n (%)	10 (9)	8 (4)	0.2
30 day mortality excluding pts in shock n (%)	5 (4)	3 (2)	0.3

Conclusions: Patients treated out of working hours stayed longer during the index hospitalisation but clinical outcomes were similar to those for patients treated in-hours. Patients presenting out-of-hours at experienced centers should be routinely offered PPCI.

P1421 Wireless prehospital 12-lead electrocardiographic transmission and direct referral for primary percutaneous coronary intervention (PCI) to reduce treatment delay in patients with STEMI



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Background: Early diagnosis and reperfusion is crucial for outcome in patients (pts) with ST elevation myocardial infarction (STEMI). Primary PCI is the best therapy, but majority of pts present to hospitals without PCI facilities. Rerouting pts to PCI center may cause unacceptable delays. Wireless prehospital 12-lead ECG transmission and direct transfer to interventional centre may reduce treatment delay.

Methods: STEMI pts were included into the study (01-12.2005). Prehospital clinical diagnosis was established by ambulance physician. Prehospital ECG was transmitted by wireless technology to invasive hospital. Based on typical symptoms of STEMI, interventional cardiologist in our PCI center decided on direct transfer for primary PCI. Time intervals for symptom onset, first medical contact, hospital arrival, and primary PCI were obtained. Corresponding intervals were compared with controls from database of our previous study on transfer STEMI pts for primary PCI via referring hospitals. As a first medical contact we regarded time of ECG transmission in study group and time of ambulance on-scene arrival in control group. In control group interval "first medical contact-invasive center" includes time of transfer and evaluation in ER of referring hospital and transfer to PCI hospital. Controls were matched according to the place of living.

Results: ECG transmission was performed in 113 pts. Of these, 74 pts (65,5%) were STEMI pts and directed to our PCI center. In all pts diagnosis of STEMI was confirmed and all patients had coronarography. Primary PCI was performed in 72 pts (97,3%), 1 pt was treated with CABG and 1 pt conservatively. Mean distance of transfer was $25,3 \pm 27,4$ km in study group. Relevant time intervals are shown in table.

Time intervals (min)	Study group n=74	Controls n=221	p
MI onset - first medical contact	$189,3 \pm 162$	$154,4 \pm 131$	0,06
First medical contact - invasive center	$43,8 \pm 25$	$81,7 \pm 63$	<0,001
Door to needle	$27,7 \pm 18$	$30,8 \pm 14$	0,13
First medical contact to needle	$71,6 \pm 32$	$112,6 \pm 64$	<0,001

Conclusion: Wireless 12-lead ECG transmission is useful tool in early diagnosis of STEMI. Application of prehospital ECG transmission with direct transfer to PCI hospital result in reduction in the treatment delay compared to strategy with initial admission to referring hospital.

ACUTE CORONARY SYNDROMES: NEW AND OLD PROGNOSTIC FACTORS

P1422 Impact of renal dysfunction and glucometabolic status on one-year mortality after acute myocardial infarction



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Background: In patients with acute myocardial infarction, glucometabolic status (diabetes or stress hyperglycaemia) and chronic renal dysfunction (reduction in glomerular filtration rate) influence the mortality but also acute management. Their impact on one-year mortality, when quality of care is taken into account, is poorly documented.

Methods: Prospective study including patients with acute myocardial infarction. Quality of care was assessed by the rate of use of guidelines-recommended treatment. Patients were stratified according to glucometabolic status into G1 (normal) or G2 groups (history of diabetes and/or stress hyperglycaemia, defined as fasting glucose level ≥ 130 mg/dl) and according to the renal function (defined by the glomerular filtration rate: GFR1 >59 , GFR2 >29 and <60 , GFR3 <30 ml/min/1.73m²).

Results: A total of 724 patients were included: 55% had normal glucometabolic status, 24% had diabetes and 21% had stress hyperglycaemia. Twenty eight percent were in GFR1 group, 44% were in GFR2 and 27% in GFR3. The use of guidelines-recommended treatments was similar in groups G1 and G2, but lower in groups with impaired renal function. At one year, mortality was lower in G1 (6%) than in G2 (18%), $p<0.001$; and lower in GFR1 (2%) than in GFR2 (9%) or GFR3 (24%), $p<0.001$. Quality of care, glucometabolic status and renal function and age were independent predictors of one-year mortality.

Conclusions: In patients with acute MI, the glucometabolic status and the degree of renal dysfunction are predictors of one-year mortality, even after adjustment on the degree of use of guidelines-recommended therapies

P1423 Early S100A8/A9 protein elevation in patients with ACS



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There is increasing evidence that heterodimeric S100A8/S100A9 proteins display potent proinflammatory properties and are associated with disease activity in several inflammatory disorders. Since S100A8/A9 proteins have been recently identified in human atherosclerotic plaques we hypothesized that correspondingly, in atherosclerosis, S100A8/A9 may reflect the inflammatory status of the plaque and may therefore serve as marker of plaque instability.

Plasma levels of S100A8/A9 (double sandwich ELISA) were assessed in 30 consecutive patients with acute coronary syndromes (ACS) on admission (time 1) and 4, 8, 12, 24, and 48 hours after time 1. Compared to patients with stable coronary artery disease (64.21 ± 31.22 µg/ml), in ACS S100A8/A9 levels were significantly elevated, peaking at the arrival time 1 (360.80 ± 84.96 µg/ml) and then decreasing gradually over time not reaching control levels at 48 hours (63.0 ± 37.66 µg/ml). There was no difference in S100A8/A9 levels between ST elevation myocardial infarction (STEMI) and non STEMI. Interestingly, in comparison to other inflammatory markers, S100A8/A9 displayed an opposite time kinetics. Whereas S100A8/A9 were highest at the arrival in the emergency unit, levels of C reactive proteins (hsCrP) showed an inverse trend: 1.87 ± 1.21 mg/dl at time 6.81 $\pm$ 4.73 at time 48. IL-6 levels were peaking at time 4 (32.15 ± 27.66 pg/ml) and then decreasing.

In conclusion, S100A8/A9 serum levels were significantly increased in the periph-

eral blood of patients with ACS. These proinflammatory proteins may accordingly play a potential role in plaque destabilisation and inflammation in ACS.

P1424 Superiority of plasmatic fetuin-A Level (inhibitor of TNF) to CRP levels to predict 6 month mortality after acute myocardial infarction



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Background: Fetuin-A is an anti-inflammatory mediator which inhibits TNF production. Low plasmatic fetuin-A level was found to be predictive of cardiovascular events in patients with chronic renal failure. In acute myocardial infarction (AMI), its prognosis value has not yet been reported.

Methods: We prospectively studied 213 consecutive patients (61 ± 14 years, 82% men) with AMI (123 anterior wall) who received successful primary percutaneous coronary intervention (PCI) within 12 h from the onset of symptoms. Blood samples were collected at 48 hours to examine the serum fetuin level and CRP. Fetuin-A plasmatic level was compared to 6 months survival.

Results: Fetuin-A level in MI was lower than in normal subjects (154 ± 4 mg/L vs 212 ± 6 mg/L, $p<0.05$). In 23 patients who died during the 6 months follow-up period, fetuin-A level was lower and CRP level was higher compared to survivors (118 ± 10 mg/L vs 160 ± 4 mg/L, $p=0.002$, 68 ± 18 mg/L vs 16 ± 3 mg/L, $p<0.0001$, respectively). By multivariable logistic regression analysis adjusted to baseline characteristics, the following parameters were independently associated to death: fetuin-A below median value (OR=32 [5-228]), Killip score >1 (OR=13 [3-49]), TIMI flow 100/min (OR=8 [2-33]).

Conclusion: After MI, low plasmatic fetuin-A levels (inhibitor of TNF) is a strong predictor of 6 months death independently to CRP. These results suggested a reduced inhibition of inflammatory process involved in acute myocardial infarction.

P1425 Correlation of levels of NT-pro-BNP with ventricular function and extension of coronary disease in patients with acute coronary syndromes without ST elevation



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Objectives: To evaluate the relationship between the levels of NT-pro-BNP, ventricular function, and extension of coronary artery disease in patients with acute coronary syndromes (ACS) without ST elevation.

Methods: We included 200 consecutive patients with ACS without ST elevation. The level of NT-pro-BNP was measured at admission. Catheterization was performed in 90% of the patients. Ventricular function was analyzed by echocardiography and by ventriculography. At six months, we measured the levels of NT-pro-BNP and a new echocardiogram was performed.

Results: Patients were divided in tertiles depending on the levels of NT-pro-BNP at admission and at six months. We compared ventricular function and number of vessels between the three groups. Results are shown in Table 1.

Table 1. Correlation of NT-pro-BNP levels with ventricular function and coronary artery disease

NT-pro-BNP at admission	BNP <636 pg/ml	BNP 636-2002 pg/ml	BNP >2002 pg/ml	p
Number of vessels (mean)	1,3	1,6	2	0,007
LVEF ventriculography (mean)	67	61	55	<0,001
Reduced LVEF by echo (% of pts)	13,2	27,3	51	<0,001
Regional wall motion abnormalities (%)	41	68	73	0,009
NT-pro-BNP at six months	BNP <164 pg/ml	BNP 164-568 pg/ml	BNP >568 pg/ml	p
Reduced LVEF by echo at 6 months (% of pts)	3,4	0	40	<0,001
Regional wall motion abnormalities (%)	3,4	29	53	0,001
Number of vessels (mean)	1,06	1,64	1,87	0,006

Multivariate analysis: independent predictors of ventricular dysfunction at admission were: NT-pro-BNP at admission in upper tertiles ($p=0,003$), previous myocardial infarction ($p=0,001$) and number of vessels ($p=0,024$).

Conclusions: In patients with acute coronary syndromes without ST elevation, the levels of NT-pro-BNP are higher in those who have ventricular dysfunction, regional wall motion abnormalities and more extensive coronary disease.

A high level of NT-pro-BNP at admission is an independent predictor of ventricular dysfunction.

P1426 Elevated cardiac troponin is an independent predictor of short- and long-term mortality in the medical intensive care unit patients



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Introduction: Troponin elevations are common in critically ill patients. This study

evaluated whether troponin elevations predict short- (30 day) and long-term mortality independent of the severity of diseases as measured by the APACHE (Acute Physiology, Age and Chronic Health Evaluation) III prognostic system and after correction for cardiovascular co-morbidities and multiple risk factors such as prior myocardial infarction, prior PCI and/or CABG, heart failure, diabetes mellitus, hypertension, smoking and hyperlipidemia.

Methods: We examined the APACHE III database and cardiac troponin T (cTnT) levels of 1662 patients consecutively admitted to the MICU at the Mayo between August 2000 and December 2001. Admission cTnT ≥ 0.01 ng/mL were considered elevated. Survival analyses were performed by Kaplan-Meier curves and the groups were compared by the log-rank test. Unadjusted and adjusted hazard ratios (HRs) and 95% confidence interval (CI) for the endpoint death were calculated by Cox proportional hazard analysis. The variables for the multivariable Cox proportional hazard models were selected among the variables with $p < 0.10$ after univariate analysis. Variables already incorporated into APACHE III score were not included except for age.

Results: Admission troponin measurements were available in 929 (56%) of the 1662 patients and those represent our study population. Patients whose troponin was measured were older, had a higher proportion of cardiovascular risk factors, a higher APACHE III scores and higher in-hospital mortality. In hospital mortality, as previously reported, was increased in patients with cTnT elevations. At 30 days, there were 46 deaths among the 359 patients (12.8%) without elevated cTnT and 188 deaths among the 570 patients (32.9%) with elevated cTnT levels ($p < 0.001$). Survival at 1-, 2- and 3-year follow-up was 86.6%, 78.1% and 72.2% in patients without elevated cTnT and 67.7%, 51.5% and 40.4% in those with elevated cTnT, respectively ($p < 0.001$). Troponin elevations were an independent predictor of short- and long-term mortality (HR=2.76, 95%CI=2.00-3.81, $p < 0.001$ and HR=2.49, 95%CI=1.94-3.20, $p < 0.001$, respectively) even after adjustment for severity of illness measured by the APACHE score, cardiovascular co-morbidity and risk factors (adjusted HR= 1.53, 95%CI=1.08-2.17, $p=0.014$; adjusted HR= 1.72, 95%CI=1.30-2.28, $p=0.003$, respectively).

Conclusions: In patients admitted to MICU, admission troponin elevations are independent predictors of short- and long-term mortality even after correction for the severity of disease, cardiovascular co-morbidity and risk factors.

P1427 Comparison of white blood cell count, C-reactive protein, and neutrophil count in prediction of death in STEMI patients treated with primary PCI



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Background: Measures of non-specific inflammatory activation provide prognostic information in STEMI patients treated with primary angioplasty. There is however, ongoing debate which of the parameters poses the best predictive value. We compared three most commonly reported measures of inflammation: white blood cell (WBC) count, C-reactive protein, (CRP) and neutrophil count with respect of their risk-prediction value in STEMI patients treated with mechanical reperfusion.

Methods and results: 746 consecutive, unselected patients (mean age 60.1 ± 11.7 , 205 women) admitted for primary PCI to a tertiary cardiological centre had WBC count, CRP, neutrophil count and baseline clinical characteristics assessed prior to the coronary procedures. In-hospital death was the primary endpoint and occurred in 5.4% of patients. All the three inflammation parameters were independent predictors of death in separate multivariate analyses accounting for age and Killip class on admission. However, when multivariate analysis was performed where all the three inflammation parameters were included, only WBC count and CRP remained the independent predictors of death (OR 1.14, 95%CI: 1.06-1.22, OR 1.07, 95%CI: 1.02-1.13 respectively). Areas under the ROC-curves were used to compare the predictive value of the two independent parameters, and the difference of the area of 0.05 was regarded as significant. Following values of area under the ROC curve were obtained for WBC count and CRP respectively: 0.585, $p=0.035$, and 0.625, $p=0.002$.

Conclusions: WBC count and CRP seem equally valuable in risk prediction in STEMI patients treated with primary PCI.

P1428 The impact of anemia on in-hospital and long-term outcomes in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention



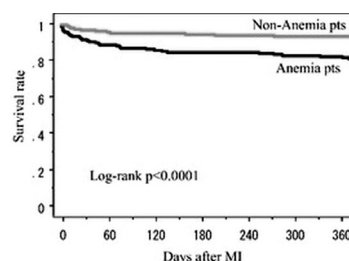
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Background: Although anemia is associated with a poor outcome in chronic heart failure patients (pts), a few data exist on outcome of pts with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (p-PCI).

Methods: We analyzed 958 pts underwent p-PCI within 72 hours onset of AMI between Jan. 1999 and Sep. 2002 at our institution and divided into two groups: 239 pts with anemia (anemia pts) and 719 pts without anemia (non-anemia pts). Anemia was defined as hemoglobin (Hb) level < 11.5 g/dl in female and < 12.5 g/dl

in male at admission. Clinical follow-up data was obtained in 98% of pts at 1-year.

Results: Mean Hb level was 13.3 ± 1.9 g/dl and female had a significantly less Hb level (female: 12.1 ± 1.9 g/dl, male: 13.8 ± 1.8 g/dl, $p < 0.0001$). 24.9% of pts had anemia (female: 35.8%, male: 21.0%). Anemia pts was significantly older (74 vs. 65 years, $p < 0.0001$), with significantly higher serum-Cre levels (1.62 mg/dl vs. 0.67 mg/dl, $p < 0.0001$) and higher rates of cardiogenic shock state (23.8% vs. 14.6%, $p < 0.001$) compared to non-anemia pts. TIMI 3 flow after p-PCI was obtained in 93.3% in anemia pts and 94.0% in non-anemia pts, $p=NS$. In-hospital and 1-year mortality rates were worse in anemia pts compared to non-anemia pts (11.3% vs. 4.6%, $p < 0.0001$, in-hospital and 18.5% vs. 6.9%, $p < 0.0001$, at 1 year).



Conclusion: Anemia pts with AMI undergoing p-PCI represented more cardiogenic shock and was associated with an increased risk of in-hospital and long-term death.

P1429 White blood count and mortality in acute myocardial infarction 48h survivors



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Introduction and Objectives: Recent studies have found a relationship between white blood count (WBC) and adverse outcomes in acute myocardial infarction (AMI). The aim of this study was to determine the predictive value of WBC in long term mortality in the survivors of the first 48h after an AMI, independently of clinical, biochemical, electrocardiographic, ecocardiographic and therapeutical variables in patients with non elevated ST AMI (NSTEMI) and with elevated ST AMI (STEMI). Patients and methods: we analyzed 1075 patients admitted consecutively in our hospital with the diagnosis of NSTEMI= 573 and STEMI= 512. The WBC was obtained from the first blood sample on admission. Cox regression models were used to determine the extent of association between WBC and total mortality for both types of AMI. The mean follow up was 12 months (7-20 months). The WBC was included in both models categorized in the following cut values: ($\times 10^3$ cells/ml): < 10 (WBC1); 10-14.9 (WBC2) and ≥ 15 (WBC3).

Results: 171 deaths were registered, 99 (17.6%) in NSTEMI and 72 (14.2%) in STEMI patients. In subjects with NSTEMI the event distribution according to each WBC group was: WBC1 44 (12.4%), WBC2 41 (23.8%) and WBC3 14 (40%) deaths, respectively ($p < 0.001$). STEMI patients had the following mortality rate distribution: WBC1 18 (8.3%), WBC2 37 (16.4%) and WBC3 17 (24.3%), ($p < 0.001$). In the multivariate analysis, after adjustment with clinical and biochemical variables, left ventricle ejection fraction, in-hospital revascularization procedures, and pharmacological therapy, in NSTEMI patients, the hazard ratios (HR) in the WBC2 and WBC3 groups compared with those in the WBC1 group were: 1.72 (1.08-2.74; $p=0.023$) and 2.08 (1.09-3.97; $p=0.026$), respectively. The corresponding figures in STEMI subjects were: 3.23 (1.75-5.95; $p < 0.001$) and 4.27 (2.02-9.02; $p < 0.001$), respectively.

Conclusions: The WBC obtained in the first hours after an AMI was independently associated with long term mortality in the first 48h survivors of an AMI, even after adjusting by confoundings such as left ventricle ejection fraction (related to the extent of necrosis), revascularization procedures and pharmacologic therapy during hospitalization, for each type of AMI.

P1430 The importance of sequential glucose dosages during hospitalization in the long-term outcome after acute myocardial infarction



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Background: Comparing baseline glucose levels with sequential glucose measurements during hospitalization, some pts show an increase in the levels, and others a decrease. There is no data in the literature comparing these two glucose profiles.

Methods: We analyzed 1158 pts with acute myocardial infarction (MI) included in a databank and followed for up to 7.48 y. (mean survival time 5.74 y.). From the global population, 482 pts (41.6%) had a decrease in glucose levels during hospitalization (GI), and the remaining 676 showed an increase in glucose levels (GII).

The two groups were compared utilizing Kaplan-Meier curves and log-rank (univariate analyses), and Cox regression (multivariable analyses). In order to avoid potential bias related to the influence of infection in glucose levels, special models were developed excluding deaths related mainly to infection disease. In the adjusted models, 18 prognostic baseline (as age, time between the pain beginning and hospital arrival, previous myocardial infarction or diabetes, for example), and in-hospital (as percutaneous coronary intervention or surgical coronary revascularization) variables were included.

Results: 1) Non-adjusted survival rates for the whole population: GI=72% $\pm$ 3.7 vs. GII=58.5% $\pm$ 3.1 (Hazard-ratio=1.7; 95% Confidence interval=1.33-2.19; $P<0.001$). Excluding infection-related deaths, the survival rates were 72.6% $\pm$ 3.7 for GI and 60.1% $\pm$ 3.2 for GII (HR=1.65; 95% CI=1.27-2.13; $P<0.001$). 2) Adjusted model for the whole population: HR=1.58; 95% CI=1.2-2.06; $P=0.003$. 3) Adjusted model excluding infection-related deaths: HR=1.52; 95% CI=1.15-2.01; $P=0.003$.

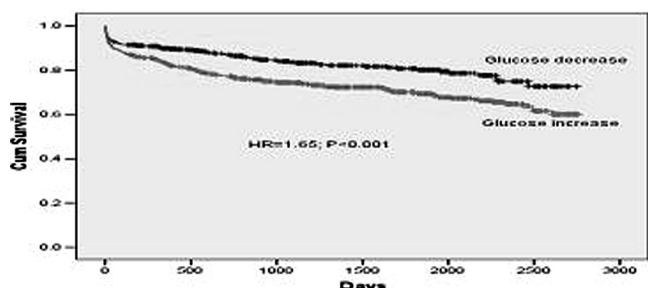


Fig. 1. Survival rates excluding infection-related deaths.

Conclusion: in the long-term post-MI, glucose level increase during hospitalization is related to a worse outcome, in comparison with glucose level decrease.

P1431 Inflammatory biomarkers and long-term prognosis in patients with ST elevation myocardial infarction



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Background: High circulating levels of C-reactive protein (CRP) have been connected to adverse long-term prognosis in patients with ST elevation myocardial infarction (STEMI). However, few studies have evaluated the long-term predictive value provided by other inflammatory biomarkers, and even fewer have examined whether other inflammatory biomarkers provide any additional predictive value over that provided by CRP, in this setting. We evaluated the predictive value of five inflammatory biomarkers including, hs CRP, serum amyloid A (SAA), fibrinogen (FIB), interleukin-6 (IL-6) and leukocyte count (WBC), for the 5-year incidence of cardiovascular death in patients with STEMI. Furthermore, whether SAA, FIB, IL-6 and WBC provide any additional predictive value over that provided by hs CRP was evaluated.

Methods: A total of 458 consecutive pts (mean age=60 $\pm$ 11yrs) with STEMI who were hospitalized in the first 12 hrs from index pain onset were studied. Circulating levels of inflammatory biomarkers were measured upon patients' presentation.

Results: By 5-year 37.3% of pts had reached the primary endpoint. All inflammatory biomarkers were significantly interrelated. By multivariate, for each biomarker, Cox analysis, in which all significant clinical variables were included, circulating levels of each inflammatory biomarker were significantly associated with the primary endpoint. In particular, hs CRP (RR=2.9; $p<0.001$), SAA (RR=1.9; $p=0.002$), FIB (RR=2.3; $p<0.001$), IL-6 (RR=2.1; $p=0.001$) and WBC (RR=3.2; $p<0.001$) provided a significant increased risk for the primary endpoint. However, by multivariate Cox analysis, in which all significant clinical variables along with inflammatory biomarkers were included, only hs CRP (RR=2.1; $p<0.001$) and WBC (RR=1.6; $p=0.009$) but not SAA (RR=1.1; $p=0.7$), FIB (RR=0.9; $p=0.9$) and IL-6 (RR=1.1; $p=0.8$) were the inflammatory biomarkers which provided independent predictive value for the primary endpoint.

Conclusions: The present results suggest that elevated circulating levels of all studied inflammatory biomarkers can provide significant predictive value for the incidence of 5-year cardiovascular death in the setting of STEMI. However, only WBC can confer additional independent prognostic information over that provided by hs CRP.

P1432 Risk stratification in diabetic patients with impaired renal function and acute myocardial infarction treated invasively



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Background: Both diabetes mellitus (DM) and impaired renal function (IRF) are

established risk factors for worse outcome in patients (pts) with acute myocardial infarction.

Aim of the study: to identify independent predictors of death in diabetic pts with IRF and AMI, who underwent percutaneous coronary intervention (PCI).

Methods: Prospective single-center study of 2172 consecutive AMI-pts admitted between 2000 - 2005 and treated with PCI was performed. 169 pts (7.8%) from the whole study population had diagnosed DM and increased serum creatinine level over 133 μ mol/L in at least one measurement during hospitalization, what was defined as IRF. Any-cause mortality during mean period of 28 months was calculated, independent risk factors of death were identified with multivariate Cox regression model.

Results: Remote mortality in diabetic patients with IRF was 41.6%. Pts who died had more frequently cardiogenic shock on admission (41.9% vs. 14.9%; $p<0.001$), anterior wall myocardial infarction (59.7% vs. 33.3%; $p<0.05$), lower ejection fraction (EF; 33.2% vs. 40.8%; $p<0.001$), higher values of uric acid (494.3 vs. 435.9 μ mol/L; $p<0.05$) and glycaemia on admission (14.6 vs. 12.3 mmol/L; $p<0.05$) in comparison with those who survived. Multivariate analysis revealed that cardiogenic shock on admission (adjusted HR 2.59; 95% CI 2.15 - 3.03; $p<0.05$) and low EF (adjusted HR 0.93; 95% CI 0.91 - 0.95; $p<0.05$) were independent predictors of any-cause death in this study population.

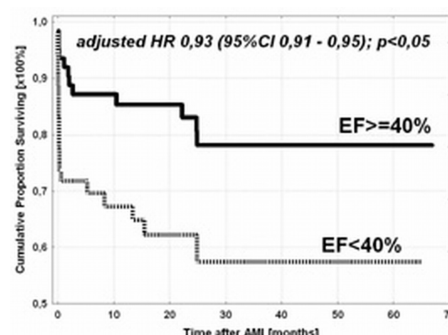


Fig. 1. Impact of EF on Survival in Study Group.

Conclusion: Presence of cardiogenic shock on admission and low ejection fraction are significantly and independently associated with increased risk of death in diabetic patients with IRF and AMI despite invasive treatment.

P1433 The prognostic value of angiogenesis markers, endoglin and vegf, in acute myocardial infarction



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Background: Recently, efforts have focused on unraveling the molecular mechanisms that underlie postinfarction neovascularization. Therefore, the identification of markers capable to reflect the formation of blood vessels should be desirable. Angiogenic markers as vascular endothelial growth factor (VEGF) have been shown to be upregulated endogenously after myocardial infarction. But there are a few data relating serum levels of these angiogenic growth factors to clinical outcome in patients with acute coronary syndromes. Endoglin (CD105) is a ischemia and hypoxia-inducible protein, abundantly expressed in angiogenic endothelial cells. Despite the description that endoglin reflects angiogenesis and endothelial dysfunction after ischemia, neither its variations in myocardial infarction (MI) and its role in predicting subsequent prognosis nor its relation with VEGF in MI have been explored.

Methods: Serum endoglin concentration was determined on arrival and 48 hours after the onset of symptoms in 183 patients (68% men, mean age $\pm$ SD = 70.6 $\pm$ 11.6 years) consecutively admitted for acute myocardial infarction. Serum VEGF on arrival was determined in 50 non-selected patients. The control group comprised 32 healthy subjects who were sex and age matched (60% men, age: 69 $\pm$ 13 years) to the patients. We tested the performance of endoglin on arrival, endoglin at 48 hours and endoglin differential (endoglin at 48 h minus endoglin on arrival) as predictors of short and long-term cardiac mortality.

Results: Patients with acute myocardial infarction had lower endoglin levels on arrival compared to sex and aged-matched healthy subjects (4.25 $\pm$ 0.99 vs. 4.86 $\pm$ 0.83 ng/mL; $p=0.001$), and lower endoglin levels at 48 hours compared to levels on arrival (3.65 $\pm$ 0.76 ng/mL vs 4.25 $\pm$ 0.99; $p<0.05$). After adjustment for confounding factors, endoglin decrease was an independent marker of cardiovascular mortality at 30 days (OR 2.7; 95% CI= 1.25-5.95; $p=0.011$) and at long term follow up (median 319 days) (OR 2.04; 95% CI= 1.04-3.98; $p=0.037$). Mean of serum VEGF on arrival was 347 $\pm$ 247 pg/mL, there was no relation with the levels of endoglin on arrival (pearson correlation $p=0.16$).

Conclusions: Endoglin differential probably reflecting endothelial dysfunction is a new major short- and long-term predictor of mortality in patients with acute myocardial infarction.

P1434 Effect of anemia on mortality in patients with acute myocardial infarction: ANAMI study

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Although prior studies have shown a relationship between anemia and outcomes in patients with heart failure and coronary artery disease, there is no data on its impact on outcome in patient with acute myocardial infarction (AMI).

The aim of this study was to evaluate the effect of anemia on outcome in patients with AMI.

Patients and methods: We examined two groups of patients (group I; anemic n= 82 patients and group II; n= 316 patients) with AMI were enrolled consecutively between January 2000 and march 2005. Patients were categorized according to the hemoglobin level on admission using the World Health Organization definition (Hb<11.0 g/dL in women and <12.0 g/dL in men). The primary end-point of the study was 30-day mortality

The baseline characteristics are presented in the table below.

Baseline characteristics

variables	Group I (n = 82)	Group II(n =316)	P
Age>65 years	52(63.4%)	93(29.4%)	0.0001
Sex(%female)	27(32.9%)	30(9.5%)	0.0001
Diabetes	25(30.5%)	101(32%)	0.79
Anterior MI	40(48.8%)	169(53.5%)	0.44
Killip class > 2	35(42.7%)	78(22.7%)	0.001
Serum creatinine > 120μmol/l	30(36.6%)	58(18.4%)	0.0001
Ischemic time > 4 hours	40(48.8%)	99(31.3%)	0.001

Results: The 30-day mortality rate was 25.6% in the anemic group versus 7% in the non anemic group (p< 0.0001). In the setting of AMI, anemia was more frequently observed in female sex patients, those older than age 65 years with serum creatinine > 120μmol/l and Killip class > 2 and with ischemic time > 4 hours.

In a multivariate regression model, anemia was an independent predictor of 30-day mortality, OR = 5.2, IC=[2.13-12.6], p<0.0001.

Conclusion : Anemia is a powerful and independent predictor of mortality in patients with AMI. A randomized clinical trial may be warranted to determine whether precise targeting of hemoglobin levels improves outcomes in patients with AMI and other acute coronary syndromes.

P1435 The role of ischemia modified albumin (IMA) as a promising ischemic marker during diagnostic and therapeutic procedures in coronary artery diseases

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Background: The utility of the standard biomarkers of myocardial necrosis for the confident exclusion of the diagnosis of myocardial ischemia at the presentation remains limited. Thus, markers for ischemia can serve an important role in diagnosis of early presenters of coronary artery diseases(CAD) and risk stratification for therapeutic aspect of those. A candidate marker for the detection of myocardial ischemia is ischemia modified albumin(IMA).

Objectives: The aim of this study was to evaluate the role of IMA in diagnosis of early ischemia and risk stratification during diagnostic and therapeutic procedures in patients with suspected CAD.

Subjects and Method: We enrolled consecutive 116 patients with CAD and suspected CAD(treadmill test; 52 patients, normal coronary angiography(CAG); 10 patients, percutaneous coronary intervention(PCI); 35 patients and coronary spasm positive study; 19 patients). Blood sampling for IMA was done in the baseline and within 1 hour after procedures.

Results: The levels of IMA were changed during diagnostic and therapeutic procedures except normal coronary angiography(pre: 91.33 ±16.69 U/mL vs. post: 94.66±18.96 U/mL, ns). IMA was decreased in the treadmill negative test(pre: 99.32 ±12.82 U/mL vs. post: 86.18±15.21 U/mL, p<0.001), IMA was decreased in the treadmill positive test with horizontal ST segment depression (pre: 102.33 ±10.37 U/mL vs. post: 93.06±16.89 U/mL, p=0.007) but elevated in treadmill positive test with ST segment elevation or downslope depression (pre: 99.33±6.81 U/mL vs. post: 114.67±9.61 U/mL, p=0.040). During other procedures, post level of IMA was increased compared to baseline(prePCI: 109.11 ±14.35 U/mL vs. post: 127.89±16.07 U/mL, p<0.001, preSpasm study: 106.84 ±11.49 U/mL vs. post: 119.68±12.64 U/mL, p<0.001).

Conclusions: IMA might serve an promising role in detection of early phase ischemia during diagnostic and therapeutic procedures of patients with acute coronary syndrome and suspected CAD.

P1436 Stress hyperglycemia is a predictor of larger infarct size and higher mortality after a myocardial infarction even in non-diabetic patients

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Background: In patients with acute myocardial infarction (AMI), glucose metabolism is modified and high blood glucose levels at admission are common phenomenon. The purpose of this study was to investigate infarct size and long-term clinical outcomes after AMI in non-diabetic patients.

Methods: This study consisted of 188 consecutive first AMI patients without diabetes mellitus, who underwent percutaneous coronary intervention (PCI) within 6 hours after chest pain onset. They were divided into two groups according to blood glucose levels at admission: low blood glucose levels (L group) (< 10 mmol/l, n = 131) and high blood glucose levels (H group) (≥ 10 mmol/l, n = 57). We analyzed incidence of major adverse cardiac events (MACE) defined as cardiovascular death or re-hospitalization for congestive heart failure after PCI as well as maximum creatine kinase and in-hospital cardiac events defined as coronary heart disease death, acute or subacute thrombosis and malignant arrhythmia.

Results: The basic characteristics of the 2 groups were similar. The angiographic data before PCI were also similar. Maximum creatine kinase levels were higher in H group (2989 ± 2185 vs. 3671 ± 3345 IU/ml, p < 0.05). In-hospital cardiac events were seen in 17.6% of L group and 31.5% of H group (p < 0.05). Upon Kaplan Meier analysis, 5 years freedom from MACE was 95.6% in L group and 74.5% in H group (hazard ratio 6.62, 95% CI 2.36-18.5; p = 0.0003).

Conclusions: Even in non-diabetic patients, who underwent PCI, stress hyperglycemia at admission is associated larger infarct size and poor outcomes after AMI. Investigations of methods improving clinical outcomes are necessary.

P1437 The prognostic value of baseline glucose is related mainly to the early phase after myocardial infarction

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Background: Little is known about the prognostic value of baseline glucose levels (GL), in the "very" long-term follow-up after acute myocardial infarction (AMI).

Methods: We analyzed 1209 pts with AMI (median age 64 y.o., 72.4% men), included prospective and consecutively in a databank and followed for up to 7.55 years (mean survival time 5.6 years). The global population was divided in quartiles, according to their GL: <98 mg/dl (Group I - GI - N=306); 98-118 mg/dl (GII, N=311); 119-160 mg/dl (GIII, N=291); >160 mg/dl (GIV, N=301). Pearson Chi-square and stepwise logistic regression were utilized for the in-hospital phase analyses; for the long-term follow-up, Kaplan-Meier curves were constructed, with Log-Rank test and Cox proportional hazards estimation applied in statistical analyses. The adjusted models included 21 baseline (as history of diabetes, time to treatment beginning and ST- or non-ST AMI), and in-hospital (as percutaneous coronary intervention and surgical revascularization) prognostic variables.

Results: (a) In-hospital phase: the mortality rates for GI, GII, GIII and GIV were, respectively, 4.57%; 9.32%; 14.77%; and 19.27% (P<0.001). In the adjusted model, GL remained significant (P<0.001) and independently correlated with mortality. (b) Long-term follow-up for the whole population: the mean survival times (95% Confidence Interval) for GI, GII, GIII and GIV were, respectively, 2231.06 (2117.84-2344.27) days (d.); 2118.76 (1996.99-2240.54) d.; 1965.61 d. (1832.84-2098.38); and 1880.25 (1741.82-2120.11) d. (P<0.001). (c) Long-term follow-up excluding in-hospital deaths: the mean survival times for GI, GII, GIII and GIV were, respectively, 2336.23 (2331.84-2440.61) d.; 2330.09 (2222.68-2437.49) d.; 2288.54 (2173.09-2403.98) d.; and 2316.63 (2199.2-2434.06) d. (P=0.93). Replacing all cause mortality as dependent variable by a composite endpoint of all-cause mortality and the need of invasive therapies (surgical coronary revascularization/percutaneous coronary intervention) or reinfarction after hospital discharge, similar results were obtained. In conclusion, the prognostic value of glucose levels is restricted to the early phase post-AMI. Our findings reinforce the hypothesis that hyperglycemia is by itself aggressor to the heart, not merely a marker of poor prognosis.

P1438 Risk stratification using multiple biomarkers in troponin positive patients with non-ST-elevation ACS identify those patients at high risk for death

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Introduction: Risk stratification with the use of biomarkers such as cardiac troponin T (cTnT), C-reactive protein (CRP), and NT-proBNP allows classification of nSTE-ACS patients into high risk, intermediate risk and low risk categories. We assessed whether troponin T positive nSTE-ACS patients can be stratified into

low risk (despite an elevated cTnT), intermediate risk and high risk categories using multiple biomarkers.

Methods and results: Baseline samples for central CRP and NT-proBNP measurements were available in 1141 nSTE-ACS patients with an elevated cTnT randomized to an early or a selective invasive strategy. Patients were divided into three categories: low risk (low NT-proBNP and low CRP), intermediate risk (elevated CRP or NT-proBNP) and high risk (elevated CRP and NT-proBNP). The incidence of the primary endpoint (the composite of death, myocardial infarction and rehospitalization for angina by one year) was 27.1 in the high risk group, 21.3% in the intermediate group and 21.1% in the low risk group; $p=0.25$. Kaplan-Meier estimates of the cumulative rate of death are shown in figure 1.

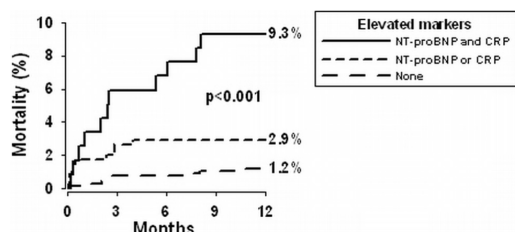


Fig. 1

Conclusions: We could not demonstrate that additional risk stratification using multiple biomarkers is able to identify those patients at high risk for the primary endpoint. However, we observed a significant higher mortality in patients with all three biomarkers elevated compared to patients with only one or two elevated biomarkers.

P1439 H-FABP vis-a-vis troponin as a predictor of long term mortality following acute coronary syndrome



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Objective: To assess the value of troponin and heart-type fatty acid binding protein (H-FABP) in predicting 30-day and long-term all-cause mortality in patients with acute coronary syndrome (ACS).

Methods: The EMMACE-2 study was a prospective observational study across 11 adjacent hospitals in West Yorkshire that recruited consecutive consenting patients validated to have ACS during a 6-month period (April 28th to October 28th 2003). H-FABP (a novel marker of myocyte necrosis) was measured in 1,449 patients. Of these, 1165 patients for whom H-FABP, TnI results and all-cause mortality status were known, were included. Median long-term follow-up was 786 days. Patients were divided into quartiles (Q1, Q2, Q3, Q4) based on the H-FABP and troponin values. Cut-offs for quartiles of H-FABP in $\mu\text{g/L}$ were 6.4, 12.1 and 34.1. Cut-offs for quartiles of troponin in $\mu\text{g/L}$ were 0.14, 1.3 and 9.6.

Results: 30-day mortality: Both troponin and H-FABP were significant predictors of 30-day all-cause mortality on univariate analysis (Troponin: Q4 vs. Q1, HR 2.94, $p<0.001$, H-FABP Q4 vs Q1, HR 20.25, $p<0.001$) and remained independent predictors after correction for age, systolic BP, heart rate, admission glucose, admission creatinine and heart failure.

Long-term mortality: H-FABP was a significant predictor of long-term all-cause mortality but not troponin (Figure 1). After correction for confounding factors (age, systolic BP, heart rate, admission creatinine, heart failure on admission, gender, previous MI, previous diabetes), H-FABP remained an independent predictor of long-term all-cause mortality across all quartiles.

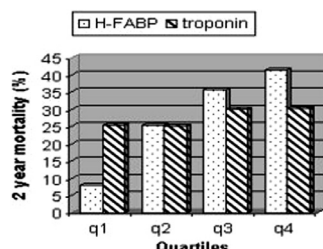


Fig. 1. Mortality in quartiles of H-FABP vs TnI

Conclusions: While both H-FABP and troponin predict 30-day mortality, only H-FABP was an independent predictor of long-term mortality in patients with acute coronary syndrome.

P1440 The new prognostic risk score in acute coronary syndromes: BANACH Score



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Many risk scores (RSs) have been proposed for the risk estimation in ST-elevation myocardial infarction (STEMI), non-STEMI and unstable angina (NSTEMI/UA) patients (pts). Aims: to identify the long-term mortality predictors in unselected acute coronary syndromes (ACS) pts treated in one centre with invasive cardiology on-site.

Methods: 601 STEMI, 330 NSTEMI/UA pts registry from 2002-03 years with 1-year follow-up, using multivariate logistic regression model. The predictive value of the model was assessed with the area under ROC curves. The models' goodness-of-fit checked by Pearson or Hosmer-Lemeshow tests. Creation of an own RS was attempted.

Results: Mean age was 63 years, 27% with previous STEMI/NSTEMI, 16% diabetes, 6% NYHA III/IV class, 3% in cardiogenic shock. 88% STEMI and 81% NSTEMI/UA pts were treated invasively. 1-year total mortality was 14.8% and 10.9% respectively. Sudden cardiac arrest at presentation (odds ratio [OR]=3.6), Killip class II-IV (OR=3.4), age >65 years (OR=3.3), bundle branch block in the first electrocardiogram (ECG) (OR=3.0), NYHA III-IV classes history (OR=2.4), any ST depression in ECG (OR=2.1), heart rate >78/min (OR=1.9), ST elevation in precordial leads (OR=1.7), elevated levels of myocardial necrosis markers at admission (OR=1.66), and ECG pathological Q wave (OR=1.65) were independent predictors of 1-year total mortality. On the contrary, systolic blood pressure on admission >130 mmHg and angina de novo <2 weeks type of chest pain decreased the this risk (respectively: OR=0.5, OR=0.4). Each risk predictor was given "1 point" and protective predictors "-1 point", as the calculated prognostic indices were between 0.50 and 1.27. The developed predictive model, called the BANACH RS (after the famous Polish mathematician), proved to offer both high goodness-of-fit and predictive value (ROC=0.85). Pts with: <1, 1, 2, 3, 4, 5 and ≥ 6 Banach points had respectively: 1.16; 3.7; 7.4; 15; 30.7; 49 and 75% total 1-year mortality.

Conclusions: BANACH RS maybe used in all ACS patients, irrespective of ACS type. It is simple and developed on the basis of ACS registry with unselected pts.

P1441 The impact of tissue plasminogen activator antigen, high sensitivity C - reactive protein and cardiac troponin I on long term-prognosis in patients with non-ST elevation acute coronary syndromes



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Background: High circulating levels of tissue plasminogen activator (tPA) antigen, high sensitivity C-reactive protein (hs CRP) and cardiac troponin I (cTnI) have been connected to adverse long-term prognosis in patients with non-ST-segment elevation acute coronary syndromes (NSTACS). However, no previous studies have simultaneously evaluated the long-term impact of all these biomarkers in this setting.

Methods: A total of 355 consecutive pts (mean age=70 $\pm$ 8 yrs, 66.4% males) with NSTACS who were hospitalized in the first 24 hrs from index pain onset were studied. Circulating levels of the study biomarkers were measured in blood samples obtained upon patients' presentation. The pts were classified according to the tertiles of the circulating levels of the study biomarkers. The incidence of 3-year cardiovascular death was the prespecified primary endpoint.

Results: By 3-year 28.8% of pts had reached the primary endpoint. Tertiles of tPA (RR=2.4; $p=0.002$ for top vs bottom tertile), hs CRP (RR=3.2; $p<0.001$ for top vs bottom tertile) and cTnI (RR=3.9; $p<0.001$ for top vs bottom tertile) were significantly associated with the primary endpoint. There was a significant gradual increased risk for the primary endpoint with increasing the number of biomarkers at the top tertile (Fig. 1).

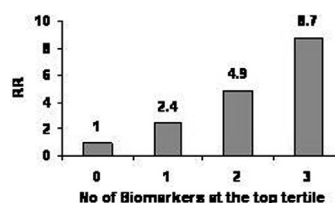


Fig. 1

Conclusions: The present results suggest that circulating levels of tPA antigen, hs CRP and cTnI can be used in combination for early risk stratification in pts NSTACS.

P1442 Inflammatory biomarkers and long term prognosis in patients with non-ST elevation acute coronary syndromes



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Background: High circulating levels of C-reactive protein (CRP) have been connected to adverse long-term prognosis in patients with non-ST-segment elevation acute coronary syndromes (NSTACS). However, few studies have evaluated the long-term predictive value provided by other inflammatory biomarkers, and even fewer have examined whether other inflammatory biomarkers provide any additional predictive value over that provided by CRP, in this setting. We evaluated the predictive value of five inflammatory biomarkers including, hs CRP, serum amyloid A (SAA), fibrinogen (FIB), interleukin-6 (IL-6) and leukocyte count (WBC), for the incidence of 5-year cardiovascular death in patients with NSTACS. Furthermore, whether SAA, FIB, IL-6 and WBC provide any additional predictive value over that provided by hs CRP was evaluated.

Methods: A total of 476 consecutive pts (mean age=70.2±8 yrs) with NSTACS who were hospitalized in the first 24 hrs from index pain onset were studied. Circulating levels of inflammatory biomarkers were measured upon patients' presentation.

Results: By 5-year 35.5% of pts had reached the primary endpoint. All inflammatory indices were significantly interrelated. By multivariate, for each biomarker, Cox analysis, in which all significant clinical variables were included, circulating levels of each inflammatory biomarker were significantly associated with the primary endpoint. In particular, hs CRP (RR=2.9; p<0.001), SAA (RR=1.8; p<0.001), FIB (RR=1.7; p<0.001), IL-6 (RR=1.9; p<0.001) and WBC (RR=3.4; p<0.001) provided a significant increased risk for the primary endpoint. However, by multivariate Cox analysis, in which all significant clinical variables along with all study inflammatory biomarkers were included, only hs CRP (RR=2.4; p<0.001) and WBC (RR=2; p<0.001) but not SAA (RR=1.1; p=0.8), FIB (RR=0.8; p=0.7) and IL-6 (RR=0.9; p=0.8) were the inflammatory biomarkers which provided independent predictive value for the primary endpoint.

Conclusions: The present results suggest that elevated circulating levels of all studied inflammatory biomarkers can provide significant predictive value for the incidence of 5-year cardiovascular death in the setting of NSTACS. However, only WBC can confer additional and independent prognostic information over that provided by hs CRP.

P1443 Prognostic role of plasma angiogenin in non-ST-elevation acute coronary syndrome



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Angiogenesis is a process necessary for regulation and repair after ischemic injury of tissue. However, angiogenesis also facilitates atheroma progression towards plaque instability and has been related with an adverse outcome. Angiogenin is a member of the ribonuclease superfamily. It has been implicated as a mitogen of endothelial cells and activator of matrix metalloproteinases and plasminogen-activated plasmin pathways. In some malignant diseases, it has been related with poor prognosis. There are no available data on angiogenin in ischemic heart disease. We hypothesised abnormal angiogenin levels in non-ST elevation acute coronary syndrome (ACS) patients, which were prognostically important.

Methods: Baseline measurements of plasma angiogenin levels [ELISA, R&D reagents] in 396 consecutive patients (mean age 67.4±15.1; 251 males) with ACS. They were compared with 44 stable coronary patients and 119 controls without vascular disease. Positive troponin T was considered ≥0.1ng/mL. The risk for major events (death, new ACS, revascularization and heart failure) at 6 months follow-up was analyzed.

Results: ACS patients had increased levels of plasma angiogenin [245ng/mL (IQR 199-333)] than stable coronary patients [148ng/mL (IQR 91-224)] and controls [152ng/mL (IQR 102-208)], p<0.001. Only ACS patients (p<0.001) and hypertension (p=0.021) were associated with angiogenin levels (linear regression). ACS patients with raised troponin T showed increased angiogenin levels (p=0.013). After adjusting for baseline characteristics, raised troponin T and electrocardiographic changes (Cox analysis), fourth quartile (≥332.6ng/mL) of angiogenin was associated with more adverse events (HR 2.54 [95%CI 1.54-4.20; p<0.001], Table.

Cox analysis

	Fourth quartile angiogenin	age >72 years	ECG changes
HR (95%CI)	2.54 (1.54-4.20)	1.96 (1.09-3.52)	2.01 (1.21-3.33)
p value	<0.001	0.025	0.007

Conclusions: For the first time, we show that plasma angiogenin levels are raised in ACS and associated with hypertension and raised troponin T levels. Importantly,

the highest angiogenin was independently prognostic for adverse events in ACS.

P1444 A new leukocyte activity marker adds to prediction of cardiovascular risk in patients with severe angina pectoris



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Purpose: Leukocyte/monocyte activation has been demonstrated to be involved in the onset and course of unstable angina. However, easy evaluable markers of this activation have not been available to evaluate for possible predictive value. We have developed a new assay for elastase damage of circulating fibrinogen and studied whether this proteolytic footprint of activity of leukocyte/monocytes was of importance for predicting outcome in a well defined study population of consecutive patients admitted with unstable angina.

Methods: In blood of 211 consecutive patients with severe unstable angina we measured with the new plasma assay the elastase damaged fibrinogen (Fibrinogen Elastase Damage Product: FgEDP) on admission and evaluated whether it was related to the in-hospital course. In addition, markers of inflammation, coagulation activation and endothelial cell function were evaluated.

Results: FgEDP (p=0.006, Mann Whitney) levels were significantly higher in patients with refractory unstable angina pectoris, when compared with patients who had an uneventful clinical course. There was no correlation between FgEDP and D-dimer. The adjusted odds ratio (95% CI) for patients in the highest quartile compared with those in the lowest quartile of FgEDP was 3.84 (1.44 - 10.30). For other markers the ORs were: 1.92 (0.76 - 4.83) for C-reactive protein (CRP); 2.98 (1.19 - 7.46) for fibrinogen. Adjustment was made for age, sex, body mass index, smoking behaviour, cholesterol and leukocyte count. It was further observed that individuals with combined elevations of specifically FgEDP and CRP showed a super-additive OR.

Conclusions: In a clinically well-defined study population of patients with severe unstable angina, with a proinflammatory state as an important and independent determinant of short-term outcome, we found that a marker of the involvement of leukocyte/monocyte proteolysis is an important predictor. In addition the predictor adds to CRP to identify very high risk patients. It supports the importance of participation of the inflammatory cells in precipitating events in this syndrome.

P1445 Which bedside assessment best predicts mortality risk in acute coronary syndromes?

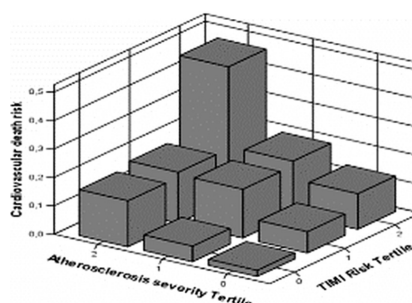


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Bedside assessment of event risk is critical in acute coronary syndromes to focus invasive therapy to those who might profit most of it. We hypothesised that echocardiographic assessment of atherosclerotic burden (Ab) could represent a new, strong parameter to assess individual event risk.

Methods: In a prospective study of 267 consecutive patients with ACS (age 66±13y, females 70, STEMI in 105, Troponin + in 207), conventional risk stratification was complemented by measurement of Ab at the bedside using a validated echo method described in detail in <http://www.koronarsyndrom.ch>. Follow-up to two years was assessed using telephone interviews and chart review. Cardiovascular death was the primary endpoint.

Results: Follow-up information was available in all patients. Death occurred in 43, cardiovascular death in 40 patients. Besides the expected value of conventional risk predictors including ST elevation (p=0.02), Troponin (p=0.03), BNP, Creatinine, TIMI score and age (all p<0.001), we found that Ab was a strong predictor (p<0.001) of outcome in univariate analysis. Multivariate Cox regression analysis documented that atherosclerotic burden remained Ab an incremental value to conventional risk factors. Strategies for improved risk assessment were therefore evaluated by their ability to improve diagnostic reliability, measured as area under the curve (AUC) in the receiver operating curve: Best prediction was achieved by combining Ab with either the TIMI score (figure) or with LVEF and Creatinine level (increase of AUC from 0.75 to 0.85).



Conclusion: State-of-the art risk assessment in acute coronary syndromes can further be improved by early bedside determination of atherosclerotic burden, further enhancing the clinical benefit of early echo these patients.

P1446 Renal insufficiency is a strong and independent risk factor associated with higher mortality in Non ST-segment Elevation Acute Coronary Syndromes regardless of TIMI Risk Score

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Background: The TIMI Risk Score is a widely accepted scale to predict mortality in Non ST-segment Elevation Acute Coronary Syndrome (NSTEMI ACS) patients. However, other comorbidities not included in the scale may influence outcome independently. The aim of this study was to assess creatinine clearance as an independent factor from the TIMI Risk Score in predicting mortality among NSTEMI ACS.

Methods: 29 non PCI centers participated in the Registry of Acute Coronary Syndromes. Data on 870 patients with ACS were gathered. Creatinine clearance (CrCl) was calculated according to the Cockcroft-Gault formula. Impaired renal function was defined as CrCl less than 60 ml/min. Patients were divided according to TIMI Risk Score.

Results: 295 patients were assigned to group with CrCl < 60 ml/min, whereas 575 (66%) of patients had preserved renal function. Patients with impaired renal function were more often older (79±9 vs 62.9±9 p<0.001) and women (55% vs 35% p<0.0001) with past medical history of myocardial infarction (45% vs 32% p<0.001), diabetes mellitus (30% vs 22% p=0.01) and stroke (8% vs 4% p=0.04). Patients with CrCl<60 ml/min received less aggressive pharmacotherapy in terms of thienopyridines (46% vs 54% p=0.009) and statins (64% vs 74% p=0.01). In-hospital mortality rate in all TIMI Risk Score groups was significantly higher among patients with renal insufficiency (Table 1). Logistic regression of multivariate analysis revealed one independent risk factors for death CrCl<60 ml/min OR 6.0 (95%CI 1.5 - 22.5), p=0.03.

Table 1. In-hospital mortality in NSTEMI ACS

TIMI Risk Score	CrCL<60 ml/min	CrCL>60 ml/min	P=
0 - 2	3.6%	0%	<0.001
3 - 4	4.1%	1.4%	NS
5 - 7	7.3%	2.4%	0.03

CrCl - creatinine clearance

Conclusions: TIMI Risk Score does not contain renal insufficiency which is a strong and independent risk factor of mortality in NSTEMI ACS. Creatinine clearance should be taken into consideration prior to planning invasive therapy in NSTEMI ACS patients.

P1447 Quantitative troponin predicts cardiogenic shock, sustained ventricular arrhythmias, cardiac arrest and reinfarction in non-ST elevation acute coronary syndromes. The GRACE registry

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Background: Limited information is available about the relation between quantitative troponin and outcomes in patients with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS). There are conflicting data on whether the amount of troponin elevation imparts a prognostic gradient of risk.

Methods: Data were analysed from 9657 patients with NSTEMI ACS enrolled in the GRACE registry. Patients were divided into tertiles of troponin level (expressed as a multiple of the local hospital's upper limit of normal) measured ≤24 h from admission.

Results: Patients in the highest tertile were less likely than those in the other tertiles to be on aspirin, beta-blockers, angiotensin-converting enzyme inhibitors or statins before their event, and had higher rates of ST depression and/or Q waves at presentation. Elevated troponin was associated with increasing rates of in-hospital and 6-month mortality and in-hospital (re)myocardial infarction, ventricular tachycardia (VT), ventricular fibrillation (VF), and cardiogenic shock (Table).

Event rates according to troponin level

In-hospital events (%)	Negative troponin (n=3,921)	Positive troponin			P value
		Lowest tertile (n=1,912)	Intermediate tertile (n=1,912)	Highest tertile (n=1,912)	
Mortality	0.9	2.3	3.4	4.8	<0.0001
Myocardial (re)infarction	1.7	3.3	4.8	5.3	<0.0001
Cardiogenic shock	0.6	1.6	2.1	3.2	<0.0001
Sustained VT/VF or cardiac arrest	1.3	2.8	3.3	6.6	<0.0001
Mortality from discharge to 6 months (%)	2.4	7.3	7.4	8.4	<0.0001

In a multivariable analysis adjusting for other variables, low, intermediate, and high elevations of troponin were associated with increased in-hospital (odds ratio 1.95, 95% confidence interval 1.19-3.19; 1.99, 1.23-3.21; and 2.78, 1.76-4.37, respectively) and 6-month mortality (hazard ratio 2.40, 95% CI 1.66-3.46; 2.12, 1.47-3.06, and 2.82, 1.96-4.05, respectively) (vs negative troponin).

Conclusion: The quantitative increase of troponin elevation in patients with NSTEMI ACS is associated with an increase in in-hospital adverse events as well as 6-month mortality.

P1448 White blood cell count increases the prognostic value of the TIMI risk score in acute coronary syndromes

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Background: TIMI risk score (TIMI) has been used in the stratification of the risk of acute coronary syndrome (ACS). The inclusion of a simple inflammatory marker such as white blood cells count (WBC) could improve the ability to identify the patients at risk.

Objective: To study the additional value of WBC in the risk stratification of ACS. **Methods:** 486 patients admitted with non ST elevation ACS were analyzed. WBC count and TIMI risk score were determined at admission and in-hospital events were registered. Composed endpoint of in-hospital death, recurrent angina and emergency revascularization was defined. The variables of the TIMI were incorporated in stepwise logistic regression model. A second model add WBC to previous variables. Both models included a random sample of 70% of the population, the remained 30% was used for validation.

The probability of occurrence of the composed endpoint was plotted in a ROC curve, the area under curve (AUC) for both models was thus compared as an indicator of the ability of each model to correctly predict the occurrence of the endpoint.

Results: The mean age was 66±13 years, 66.5% male. 43% had TIMI > 3 at admission. The mean WBC was 9466 ± 4349 (range 3800-64600). The troponin I was positive in 53% of patients (>0.1 ng/mL). In-hospital mortality was 2.4%. The occurrence of the composed endpoint was 13%.

The troponin I and WBC showed a strong association with the occurrence of the composed endpoint (Spearman Rho 0.13, p= 0.01 y 0.15, p=0.001, respectively). A positive troponin was related to the in-hospital mortality (rho 0.12, p = 0.01). The TIMI predicted the occurrence of the endpoint in 87.1% of the cases, AUC 0.64 (IC 0.55-0.72; asymptotic significance p=0.04). After WBC count was added the accuracy of the model increased, allowing the correct identification of 91.2% of events in the validation sample, AUC 0.67 (IC 0.58-0.75; asymptotic significance p<0.001). WBC ≥ a 10000/mm was associated for the occurrence of the composed endpoint, OR 1.43 (1.33 - 1.72, p= 0.02).

Conclusion: WBC count increases the prognostic value of the TIMI risk score in ACS. This finding suggests that inflammatory markers could be incorporated in the evaluation of risk.

P1449 Reperfusion arrhythmia immediately following primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction predicts short and long-term survival

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Background: Despite early recanalization of an occluded infarct related artery (IRA) during primary percutaneous coronary intervention (PPCI) for ST-segment elevation myocardial infarction (STEMI), impaired myocardial reperfusion carries adverse prognosis. Reperfusion arrhythmias occurring immediately following restoration of coronary flow may indicate successful tissue level reperfusion.

Methods: We prospectively collected data on consecutive acute STEMI patients undergoing PPCI from April 2002 until December 2005. Patients with an impaired epicardial flow (TIMI flow grade < 3) at the end of the procedure were excluded. Reperfusion arrhythmia(RA) occurring immediately following recanalization of the IRA was documented by the operator. Median follow up was 466 days and mortality data was extracted from the national register.

Results: Of the 688 patients, 22% were women. Mean (±SD) age of the cohort was 61 (+14) years and frequent co-morbidities included diabetes mellitus (25%), dyslipidemia (55%), hypertension (43%) and smoking (41%). The IRA was the left anterior descending in 49%, circumflex in 13% and right coronary in 38%. RA was recorded in 200 patients (29%) and included mainly accelerated idioventricular rhythm (71% of all RA). Patients with RA had lower rates of diabetes (16% vs 30%, p<0.01) and hypertension (48% vs. 62%, p<0.01) and had significantly shorter median pain to balloon time (201 vs. 234 minutes, p<0.01) than patients without RA. Thirty-day mortality was 3.7% and 8.3% for patients with and without RA, respectively (p=0.04). After controlling for age, gender and pain to balloon time the hazard ratio for mortality for patients with RA during the follow up period was 0.46 (95%CI=0.23-0.92).

Conclusions: the occurrence of RA immediately following PPCI for acute STEMI is associated with better clinical characteristics, especially shorter pain to balloon time. In patients who achieve TIMI grade 3 flow after PPCI, RA identifies a subgroup with a particularly favorable prognosis.

P1450 Plasma NT-proBNP can predicts perioperative cardiac events in patients undergoing noncardiac surgery

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Background: Perioperative cardiac complication is a major cause of morbidity after noncardiac surgery. The utility of plasma NT-proBNP for preoperative cardiac risk evaluation has not been evaluated. We hypothesized that plasma NT-proBNP has an additional value in predicting perioperative cardiac complications.

Methods: A cohort of 1002 patients referred for cardiac consultation before elective noncardiac surgery was enrolled prospectively. The level of NT-proBNP was measured within 2 weeks before surgery. Various preoperative clinical variables and laboratory results such as hsCRP and serum creatinine were also evaluated. Perioperative cardiac event (POCE) was defined as acute myocardial infarction, congestive heart failure including acute pulmonary edema or primary cardiac death within 5 days after surgery.

Results: POCEs occurred in 73 (7.9%) of the 1002 patients. Using receiver operating characteristic analysis, the optimal cut-off value of NT-proBNP was determined. In multivariable logistic regression analyses, three independent predictors of POCEs were identified: preoperative high NT-proBNP (≥ 340 pg/ml), vascular surgery, and ischemic heart disease. Single measurement of preoperative NT-proBNP ≥ 340 pg/ml demonstrated high sensitivity (81.0%) and specificity (80.0%) for predicting POCE. Next, we compared the performance of predicting POCEs by comparing the area under receiver operating characteristic (ROC) curves. The area under ROC curve was 0.714 for the Revised Cardiac Risk Index. When a high preoperative NT-proBNP (≥ 340 pg/ml) was combined with the Revised Cardiac Risk Index, the prediction power has significantly strengthened (area under ROC curve; 0.822 versus 0.714, $p = 0.0001$, table).

Comparing the areas under ROC curves for predicting POCE using the technique of Hanley and McNeil

	Area under curve	Standard error	95% CI		p
			Lower	Upper	
Revised Cardiac Risk Index	0.714	0.031	0.654	0.775	0.0001
Combined with NT-proBNP	0.822	0.021	0.781	0.863	

Conclusions: A high preoperative NT-proBNP (≥ 340 pg/ml) is a strong and independent predictor of POCE and may have an additional role in preoperative cardiac risk index development.

P1451 Acute coronary syndrome as a manifestation of global atherosclerosis: impact of combination evidence-based therapy on mortality and morbidity in acute coronary syndrome. The GRACE registry

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Background: Acute coronary syndrome (ACS) is potentially a manifestation of global atherosclerosis and may be associated with atherosclerosis at other arterial sites. The impact of combining antiplatelets, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and lipid-lowering drugs in ACS patients with peripheral arterial disease (PAD) or stroke is not well known.

Methods: Patients (n=32,735) presenting with ACS were stratified into those with prior PAD, stroke, both or neither. Based on discharge use of evidence-based therapies, we created a composite appropriateness score depending on the number of the drugs used divided by the number indicated for each patient. The impact of the composite score on 6-month mortality and morbidity was analysed using risk-adjusted logistic regression models, including ACS subtype; age; presenting pulse, systolic blood pressure, positive biomarker, ST depression, serum creatinine; prior myocardial infarction (MI); prior and admission heart failure; in-hospital coronary artery bypass grafting, percutaneous coronary intervention; in-hospital renal failure (death model only) or congestive heart failure/pulmonary edema (composite only).

Results: Appropriateness level III-IV (75-100% of indicated medications used) versus appropriateness level 0-II (0-67% of indicated medications used) had a lower odds ratio for either outcome (Table). The interaction between appropriateness level and ACS subtype was not significant, suggesting that these therapies were equally effective among ACS subgroups.

Table 1

	OR for death (95% CI)	OR for death/MI/stroke (95% CI)
Prior stroke only	1.41 (1.17-1.70)	1.62 (1.38-1.89)
Prior PAD only	1.49 (1.25-1.77)	1.46 (1.26-1.70)
Prior stroke and PAD	1.79 (1.34-2.39)	1.95 (1.50-2.53)
Appropriateness level III-IV vs 0-II	0.81 (0.72-0.91)	0.88 (0.79-0.98)

Adjusted odds ratios (ORs) for 6-month death, and death/MI/stroke. CI=confidence interval

Conclusions: Use of combination evidence-based therapies was independently and strongly associated with lower 6-month mortality and morbidity in patients

with an ACS. Such therapies appear to offer a marked advantage when compared with patients in whom they are omitted.

ACUTE HEART FAILURE

P1452 Type of acute heart failure significantly affects the costs of hospitalization

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Background: Heart failure (HF) is a chronic progressive disease accounting for substantial economic burden to the health care system. Hospitalizations constitute up to 75% of all treatment related costs. Objective: To evaluate the costs of hospitalization in different types of acute HF (AHF).

Method: Patients (N=620) hospitalized for AHF in a multicenter study were divided in to five clinical subgroups (Table 1). Duration of index hospitalization episode was recorded including uninterrupted rehabilitation periods. Total number of hospital days during 6 months was accomplished from the National Discharge Registry. Costs were calculated taking into account the number of days at intensive care (1576€/day), CCU (970€/day) and normal ward (340€/day). ANOVA was used, results given as mean (SD).

Results: On average, patients were hospitalized during 6 months for 27.0 (30.2) days resulting in mean costs of 11414 (12153) €/patient. The mean duration of index episode was 15.5 (19.3) days and the mean costs, 6760 (8295) €/stay, represented 59% of the total hospitalization costs. Overall, 320 (52%) patients had at least one readmission. Subgroup results are presented in Table 1. Patients with cardiogenic shock had a significantly longer index episode, spent more time in ICU/CCU, and thus incurred the highest costs. Although the length of index episode was not significantly longer in patients with pulmonary oedema (compared to groups 3,4,5), the costs of index episode and of total 6-month period were significantly higher (due to higher need for ICU/CCU care).

Table 1.

Group (n)	Length of index episode (days)	Costs of index episode (€)	Total 6-month hospitalization (days)	Costs of total 6-month hospitalization (€)
(1) Cardiogenic shock (14)	36.1 (32.9)*	24058 (17594)*	42.1 (33.9)	28146 (18741)*
(2) Pulmonary oedema (163)	18.1 (20.8)	8706 (9051)**	30.7 (32.0)	14226 (13335)**
(3) Decompensated HF (394)	13.7 (18.1)	5493 (6872)	25.4 (29.9)	9984 (11084)
(4) Hypertensive crisis (19)	12.9 (11.9)	5440 (4714)	18.7 (18.7)	8230 (8265)
(5) Right ventricular failure (30)	16.3 (15.7)	5605 (5337)	26.6 (25.4)	9118 (8631)

The mean duration (days) of index episode, total number of hospital days during 6 months, and hospitalization costs (€) for each AHF group. * $p < 0.05$ group 1 vs 2,3,4,5; ** $p < 0.05$ group 2 vs 3

Conclusion: Overall, the hospitalization costs related to acute HF are high and readmissions common. Any treatment that substantially reduces readmissions and length of stay in hospital is likely to be cost-effective in these patient groups.

P1453 Are patients with acute heart failure who present to secondary care being missed?

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In addition to its role as a "rule out" strategy, N Terminal pro B-type BNP (NT proBNP) may be used to "rule in" patients likely to have heart failure (HF). The PRIDE study found that adjusted for age, the NT proBNP level identified 3 groups: Low Level = no HF; Intermediate Level = possible HF; High Level = HF likely. In a pilot study, NT proBNP was measured in patients admitted to an admissions unit with breathlessness/oedema if the differential diagnosis included HF. Patients with known heart failure we excluded. If >300 pg/ml the laboratory report recommended echocardiography. We found no increase in new HF diagnoses but no echo had been requested in nearly one third of the patients. This paper examines the potential for missed HF diagnoses in this group.

Over 7 months there were 283 admissions where NT proBNP was measured. Despite an elevated level, 78 patients (28%) did not have an echo. The case records were available for 71 patients who form the basis of this report. Age range was 63-101 (mean 83 years) and 50 were women. The initial clinical diagnosis was HF (+/- other diagnoses) in 44 patients whereas 27 were considered to have an alternative cause.

Why no echo performed? 14 patients died rapidly before investigation, and 18 patients had major co-morbidities but no reason was apparent in the remaining 39. 24/71 died during admission. Of the 47 discharged, 26 were readmitted within 3 months with 12 further deaths (3 month mortality 36/71 = 51%). Discharge diagnosis was HF in only 22 of the 47 patients.

Could the NT proBNP level have helped improve care?

On admission 52 of the 71 had a High Level NT proBNP, the remaining 19 being Intermediate. Of the 27 patients considered to have a diagnosis other than HF,

14 had a High level NT proBNP level suggesting that HF was likely and of these 5 died in hospital, 9 were discharged and 5 were readmitted with 4 subsequent deaths. Of the 13 with an intermediate NT proBNP level, 2 died in hospital and of the 11 discharged, 3 were readmitted although there were no further deaths.

Conclusion: Nearly a third of patients presenting with breathlessness and raised NT proBNP did not have an echo. This group included some very sick and frail patients who died in hospital. More than half the survivors were not diagnosed or treated as HF and were at high risk of readmission and death. The diagnosis of HF was missed in the majority of these patients. Reporting the level of NT proBNP as High would have identified 9 of the 11 deaths. Using NT proBNP to "rule in" HF could have improved the use of disease modifying treatments and improved outcome.

ACUTE CORONARY SYNDROMES: PATHOGENETIC MECHANISMS

P1454 Serum glucose levels upon presentation associated with biomarkers of inflammation and myocardial necrosis in non-diabetics with acute coronary syndromes



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Objectives: Serum glucose levels upon presentation confer incremental predictive value for no-diabetics (and diabetics) with an acute coronary syndrome. However the precise pathophysiologic mechanisms for this effect are not well known. We sought to investigate the possible association of serum glucose levels upon presentation with serum levels of biomarkers of both inflammation and myocardial necrosis in non-diabetics with either ST elevation myocardial infarction (STEMI) or non-ST-segment elevation acute coronary syndromes (NSTACS).

Methods: A total of 848 STEMI and 666 NSTACS consecutive pts, without previous history of diabetes, who presented in the first 12 and 24 hours of index pain respectively, were studied. Serum glucose levels upon presentation and during hospitalization was ≤ 11 mmol/L in all pts. Each cohort was divided into 3 groups according to the serum glucose levels upon presentation: Group A with <6.1 mmol/L, Group B with 6.1-7 mmol/L and Group C with 7-11 mmol/L. Serum levels of hsCRP, interleukin-6 (IL-6), fibrinogen (FIB), leukocyte count (WBC) and cardiac troponin I, were the measured biomarkers.

Results: There was a significant gradual increase of serum levels of hsCRP ($p<0.001$ and $p<0.001$ for STEMI and NSTACS pts respectively), IL-6 ($p<0.001$ and $p<0.001$ for STEMI and NSTACS pts respectively), FIB ($p=0.02$ and $p=0.01$ for STEMI and NSTACS pts respectively), WBC ($p<0.001$ and $p=0.001$ for STEMI and NSTACS pts respectively) and cTnI ($p=0.007$ and $p<0.001$ for STEMI and NSTACS pts respectively) from Group A through Group C in each cohort.

Conclusions: According to the present results serum glucose levels upon presentation are strongly associated with the degree of inflammatory response and myocardial necrosis in non-diabetics with acute coronary syndromes. This may at least partially explain the, observed by other studies, significant association of serum glucose levels upon presentation and adverse outcome in non-diabetics with acute coronary syndromes.

P1455 C-reactive protein elevation in acute coronary syndrome: extension of myocardial damage or inflammatory process?



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Evidence shows that inflammation is crucial in the pathogenesis of atherosclerosis. High-sensitivity C-reactive protein (hs-CRP), an unspecific inflammation marker, has been accepted as a risk stratifier in the clinical setting of acute coronary syndromes (ACS). However, its release and seric elevation may be a response to myocardial necrosis, for which troponin-T is a specific marker, or an independent indicator of the inflammatory process that occurs in this acute setting. Aim. To evaluate the correlation between hs-CRP with myocardial necrosis markers and with inflammatory markers, in the ACS context. Population and methods. We studied 285 consecutive patients (66% male, mean age 64 ± 13 years, 55% hypertensive, 40% dyslipidemic, 34% smokers, 21% diabetic), admitted for ACS in the first semester of 2005 (57% with ST-elevation ACS, 13% in Killip Class $\geq II$, 79% underwent coronary angiography and 50% underwent angioplasty). The following parameters were assessed: hs-CRP, leukocyte count and fibrinogen plasma levels at baseline, maximum troponin T, CK and CK-MB. In-hospital mortality was considered the major outcome event.

Results: There is a positive correlation between hs-CRP and leukocytosis ($r=0.2$; $p<0.005$) and with fibrinogen ($r=0.4$; $p<0.0001$). There is no correlation between hs-CRP and the studied myocardial necrosis markers.

Conclusion: In this ACS population, hs-CRP is correlated with inflammatory markers but not with myocardial necrosis markers.

P1456 Association of chronic microinflammation, progression of atherosclerosis and outcome in maintenance hemodialysis (hd): long term effect of dialytic membranes



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Cardiovascular disease (CVD) is the main cause of morbidity and mortality in HD patients. An increasing body of evidence suggest that chronic inflammation may cause CVD. Bioincompatibility of HD membranes is strictly associated with an increased production of pro-inflammatory mediators and may explain the persistent low grade inflammation observed in HD pts. The aim of the study was to investigate whether the long term use of more biocompatible synthetic (S) (polysulphon, polyamide or EVAL) or less biocompatible cellulosic (C) (cellulose acetate, hemophan) membranes may modulate the progression of ATS lesions and influence the cardiovascular morbidity and mortality rate in HD pts. We enrolled in a perspective, observational study, 170 uremic pts stably treated for at least 1 year with the same S (130 pts, mean age 62.2 years; dialytic age 53.1 months) or C (40 pts, mean age 64.3 years; dialytic age 58.7 months) membranes. The pts were followed for 24 months. High sensitive C-reactive protein (hsCRP), brachial-ankle pulse wave velocity (PWV) and carotid intima-media thickness (cIMT) were measured at the beginning (T0) and at the end of the observational period (T2). At T0 significantly ($p=0.004$) higher CRP levels were found in C (1.04 ± 0.3) than in S (0.8 ± 0.4), without any significant variation at T2. At T2, C-treated pts showed an increased PWV values as compared to S-treated pts (PWV T2-T0: C 1.4 ± 0.5 ; S 0.1 ± 0.3 mm, $p<0.01$). In addition, after 24 months, cIMT values, normalized for baseline values, were significantly higher in C- (1.1 ± 0.2 mm) than in S-treated pts (1.03 ± 0.2 mm, $p<0.001$). Interestingly, hsCRP at T0 was directly correlated with PWV ($p<0.05$) and cIMT ($p<0.02$) measured at T2. In a multiple regression model, T2 arterial stiffness was independently correlated with the long term use of cellulosic membranes, whereas T2 cIMT was independently correlated with T0 hsCRP and age. During the follow-up the average time of hospitalization was higher in C- (2.06 ± 0.8 days) than in S-treated pts (0.6 ± 0.2 days, $p<0.02$). Similarly, a higher cardiovascular mortality rate was observed in the C (12%) than in the S group (1.8%, $p<0.02$). The use of C membranes was associated with an increased relative risk (HR 1.74, $p=0.04$) for cardiovascular mortality as assessed by Cox analysis in a model adjusted for anagraphic and dialytic age. The long term use of bioincompatible dialytic membranes (BM) may worsen inflammatory status and the burden of ATS in HD pts, whereas the use of BM may contribute to reduce the cardiovascular morbidity and mortality in these pts.

P1457 Graded association between arterial stiffness and diverse inflammatory markers in newly diagnosed essential hypertensive subjects: linking proinflammatory mechanisms with vascular dysfunction



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Purpose: Increased arterial stiffness and low-grade inflammation are both associated with atherosclerosis progression. In this study we examined the possible correlations between large artery stiffening and plasma inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a) and E-selectin plasma levels in essential hypertensive patients.

Methods: Our population of 148 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [98 men, aged 49 years, office blood pressure (BP)=150/97 mmHg] was divided into three groups according to carotid to femoral pulse wave velocity (PWV) values, by means of a computerized method (Complior SP): Group A (PWV < 7.8 m/sec), group B (PWV $= 7.9-8.7$ m/sec) and group C (PWV > 8.7 m/sec). Moreover, venous blood samples were drawn for estimation of lipid profile and inflammatory markers levels.

Results: Patients in group A ($n=55$) compared to subjects in group B ($n=54$) and C ($n=39$) had lower office systolic BP (146 ± 11 vs 150 ± 14 vs 157 ± 14 mmHg, respectively; $p<0.05$ for all) and left ventricular mass index ($102 \pm 16 \pm 12$ vs 114.7 ± 16 vs 102 ± 16 121.7 ± 12 g/m², respectively; $p<0.0001$ for all), while did not differ regarding metabolic profile ($p=NS$). In the total population, PWV was correlated with office systolic BP ($r=0.221$, $p<0.05$) and TNF-a ($r=0.189$, $p<0.05$), while IL-6 was associated with body mass index ($r=0.175$, $p<0.05$) and office systolic BP ($r=0.226$, $p<0.005$). Moreover, TNF-a and E-selectin were related to body mass index ($r=0.314$ and $r=0.274$, respectively; $p<0.05$ for both cases). Patients in group C exhibited higher levels of IL-6 compared to group B and A (1.8 ± 0.1 vs 1.3 ± 0.5 vs 0.8 ± 0.3 pg/ml, respectively; $p<0.005$ for all), TNF-a (3.5 ± 0.07 vs 2.5 ± 0.1 vs 1.2 ± 0.3 pg/ml, respectively; $p<0.0001$ for all) and E-selectin (55.3 ± 2.1 vs 48.7 ± 2.4 vs 43.1 ± 1.7 ng/ml, respectively; $p<0.05$ for all). Analysis of covariance revealed that inflammatory markers values remained significantly different between groups after adjustment for confounding factors ($p<0.05$).

Conclusions: In newly diagnosed essential hypertension, there is an augmentation in IL-6, TNF-a and E-selectin values throughout increasing PWV tertiles. These findings suggest that arterial stiffening is closely related to subclinical inflammatory processes, in this setting.

P1458 Implantation of paclitaxel-eluting stents is associated with reduction of sCD40L and hsCRP levels in patients with stable CAD undergoing elective PTCA



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Background: Increased levels of inflammatory markers (sCD40 ligand, hsCRP) are predictors of short and long-term adverse cardiac events as well as restenosis in patients undergoing PTCA. Use of drug eluting stents (DES) delivering paclitaxel significantly lowered the risk of restenosis and need for repeat revascularization, moreover paclitaxel is a potent antiproliferative agent, but it can also modulate the activity of immune cells leading to altered levels in systemic inflammatory markers. We hypothesized that in patients with stable CAD undergoing the elective PTCA the implantation of DES leads to suppression of procedure-associated increase of sCD40L, hsCRP and TNF-alpha levels in comparison to bare metal stents (BMS).

Patients and methods: 28 patients undergoing elective one-vessel PTCA with DES implantation (paclitaxel) and 22 with implantation of BMS were enrolled. Plasma samples were drawn at baseline (before PTCA), 24 to 48 hours after PTCA and on ambulatory basis after 4 weeks. Patients with acute myocardial infarction within 2 months prior to PTCA were excluded. ELISA kits were used to measure the plasma levels of sCD40 ligand (sCD40L), tumor necrosis factor-alpha (TNF-alpha) and hsCRP.

Results: Implantation of BMS is associated with significant increase of sCD40L after 24-48 hrs post PTCA, however no changes were seen in DES group. CD40L levels decreased after 1 month (4.88 vs. 2.51 ng/mL; $p < 0.03$) to baseline levels in both groups. TNF-alpha and hsCRP levels remained at comparable levels throughout follow-up in both groups. After stratification according to baseline sCD40L levels (high: > 2 ng/mL) and hsCRP levels (high: > 2.0 mg/L) in patients with high baseline sCD40L and hsCRP levels DES implantation was associated with more significant reduction of both markers of inflammation after 24-48 hrs and 1 month in comparison to baseline (sCD40L: 6.1 (0-19) vs. 2.9 (0-13.1) $p < 0.05$; and 2.0 (0.05-6.4) $p < 0.003$; hsCRP: 2.35 (0.3-50) vs. 1.4 (0.1-24) $p < 0.05$ and 0.9 (0.2-6) $p < 0.03$).

Conclusions: Implantation of DES delivering paclitaxel prevents the procedure-related increase of sCD40L. DES implantation is associated with significant reduction of sCD40L and hsCRP levels after 24-48 hours and 1 month in patients with high pre-procedural levels of these inflammatory markers.

P1459 Carotid Artery Remodeling in Acute Coronary Syndromes: Correlation with high sensitivity C-reactive Protein levels



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Background: The carotid intima-media thickness (IMT) may be a marker of advanced coronary artery disease. Inflammation might promote the development of atherosclerosis, & high levels of C-reactive protein (CRP) are associated with an increased risk of acute coronary events (ACE).

Objectives: To investigate the relationship between ultrasonographic features of carotid arteries (CA), levels of high sensitivity (hs)-CRP & the angiographic features of coronary plaques in acute coronary syndromes (ACS).

Methods: The study enrolled 150 patients with ACS. Within one week of the ACE, the common CA were examined using B-mode ultrasonography. The IMT, interadventitial diameter (IAD) & luminal diameter (LD) were measured. Carotid plaques were assessed. Ultrasensitive immunoassay was used to measure serum levels of hs-CRP. All patients underwent coronary angiography & according to the presence or absence & number of complex coronary plaques (CCP), patients were divided into 3 groups (G), simple plaque G (I), solitary complex plaque G (II) & multiple complex plaque G (III). Positive carotid remodeling (PCR) was defined as $IMT > 1.1$ mm & $IAD > 8$ mm.

Results: No significant difference was detected between GI & G II as regard IMT, IAD & hs-CRP levels (0.92 ± 0.19 mm vs. 0.93 ± 0.21 mm, 7.75 ± 0.49 mm vs. 7.88 ± 0.5 mm, 6.72 ± 1.5 mg/L vs. 7.1 ± 1.68 mg/L respectively, $p > 0.05$ for all.) while these variables were significantly higher in G III when compared to those of G I (1.1 ± 0.2 mm vs. 0.92 ± 0.19 mm, 8.1 ± 0.48 mm vs. 7.75 ± 0.49 mm, 9.97 ± 3.02 mg/L vs. 6.72 ± 1.5 mg/L respectively, $p < 0.001$ for all.) & those of G II (1.1 ± 0.2 mm vs. 0.93 ± 0.21 mm, 8.1 ± 0.48 mm vs. 7.88 ± 0.5 mm, 9.97 ± 3.02 mg/L vs. 7.1 ± 1.68 mg/L respectively, $p < 0.001$ for all.) Strong positive correlations detected between IMT & IAD ($r = .67$ in G I, $r = .77$ in G II, $r = .86$ in G III), also between IMT & hs-CRP levels ($r = .61$ in G I, $r = .57$ in G II, $r = .88$ in G III), $p < 0.001$ for all. The prevalence of PCR was significantly higher in G III (50.74%) when compared to G I (15.38%) or G II (15.9%), $p < 0.001$. In multivariate analysis, multiple CCP, dyslipidemia & Diabetes Mellitus were the strongest independent predictors of PCR (OR 3.87, 2.92, 2.86 & 95% CI [1.65-9.07], [1.83, 4.77], [1.61, 3.21], respectively).

Conclusions: In ACS, multiple CCP are associated with more evident inflammatory process with higher hs-CRP levels, and PCR suggesting that plaque vulnerability may be a systemic phenomenon.

P1460 Serum levels of high-sensitivity C-reactive protein predicts progression of obstructive lesions than late restenosis in patients with unstable angina undergoing coronary artery stenting



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Background: This study tested a hypothesis that high-sensitivity C-reactive protein (hs-CRP) levels may reflect significantly serial changes in unstable angina (UAP) patients and that elevation of hs-CRP may involve in a progressively obstructive lesion rather than late restenosis in patients with UAP undergoing coronary stenting.

Methods and Results: Serum levels of hs-CRP in 168 patients with UAP undergoing coronary stenting for a new obstructive lesion were prospective measured (at pre-procedure, and on days 21, 90, and 180 post-procedure). The hs-CRP levels were also evaluated in 30 at-risk control and 50 healthy volunteers. Moderately obstructive lesion of non-culprit vessels (defined as $\geq 50\%$ $< 70\%$ of stenosis) which did not treated by coronary angioplasty was found in 63.7% (107) patients. The hs-CRP level was significantly higher at pre-procedure in study patients than in both at-risk control and healthy control subjects (all p values < 0.0001) and markedly declined after the procedure ($p < 0.0001$). Both pre-procedure ($p = 0.799$) and post-procedure hs-CRP levels (all p values > 0.1) did not differ between restenotic and non-restenotic patients. However, at pre-procedure or on day 180 level of hs-CRP was independently associated with progressively obstructive lesions of non-culprit vessels which required coronary angioplasty (both p values < 0.05).

Conclusion: The hs-CRP level was significantly higher at pre-procedure and declined substantially thereafter in patients with UAP following coronary stenting. There was no evidence of a positive association between an elevated hs-CRP level and late restenosis. However, both at pre-procedure and on day 180 levels of hs-CRP were strongly associated with the progression of moderately obstructive lesions in non-culprit vessels.

P1461 Impact of lipids and their oxidative products on dendritic cell activation



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The interaction of lipids and their oxidative products with plaque inflammatory cells like macrophages and dendritic cells (DCs) is a central event in the pathogenesis of atherosclerosis. We analysed the impact of LDL and oxLDL on 1) DC adhesion on endothelial cells (ECs), 2) Expression of DC-adhesion, -costimulatory/-endocytotic molecules, 3) Phagocytosis capacity, 4) Intracellular protein-expression, 5) DC-cytokine secretion, 6) DC-differentiation.

Methods: DC-EC adhesion (murine DC 2.4/autologous aortal ECs) in response to oxLDL (10-100 μ g/ml, 24h) was quantified by fluorescent assays. Human monocyte derived DCs were incubated for 24h with LDL and oxLDL (10-100 μ g/ml). Expression of the adhesion- (CD54, CD11a, CD209), costimulatory- (CD83) and endocytotic molecules (DEC205) on DCs was detected using FACS-analysis. Endocytosis capacity of FITC-Dextran and Lucifer-yellow were used as marker of phagocytosis. An intracellular protein-array (human DCs) for the detection of IL-4, LIGHT, Osteoprotegerin, VE-Cadherin, VEGF, Oncostatin-M, was performed after a 24h incubation with oxLDL (10 μ g/ml). IL-6, IL-12 and IL-10 cytokine-secretion from DCs ($\pm$ oxLDL) was measured by ELISA. Using FACS-analysis the DC-differentiation (BDCA-1/-BDCA-2-expression) and maturation (CD83 expression) was analysed.

Results: DC-adhesion was increased by oxLDL (100 μ g/ml, +15%; 10 μ g/ml, +20% $p < 0.05$). The extracellular expression of CD11a was enhanced (oxLDL +50%/LDL +30%, $p < 0.05$). LDL and oxLDL (each 100 μ g/ml, $p < 0.01$) significantly induced the maturation of DCs (CD83-expression by LDL+500%/oxLDL+800% $p < 0.005$). In line with the maturation a differentiation of the DCs in myeloid (BDCA-1 +250%, $p < 0.01$) and plasmacytoid DCs (BDCA-2 +1100%, $p < 0.01$) was induced. Simultaneously, we found a decrease of the endocytotic capacity of Dextran/Lucifer-yellow by oxLDL (-50%/-50%, $p < 0.05$) and LDL (-20%/-35% $p < 0.01$). These results correlated particularly with the extracellular downregulation of the Mannose-receptors (-38%/-18% $p < 0.001$). The endocytosis-molecule DEC205 was upregulated by oxLDL and LDL (100%/90%; $p < 0.005$). The protein-array uncovered that oxLDL (10 μ g/ml) induces osteoprotegerin-expression. The IL-10 cytokine secretion was completely suppressed and the IL-6 secretion was increased by oxLDL.

Conclusion: LDL and especially oxLDL induce a maturation and differentiation of DCs. Because of the inhibition of the IL-10-secretion, a Th1-dominant T-cell-answer is supported. Our results underscore the importance of the intravascular lipid-deposits for immunomodulation and plaque progression.

P1462 Percutaneous coronary intervention is associated with overproduction of cysteinyl leukotrienes



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Background: There is growing evidence that cysteinyl-leukotrienes (LT) might play an important role in development and progression of atherosclerosis. An increased urinary level of leukotriene E₄ (LTE₄), believed to reflect global LT production, was reported in patients with unstable angina or myocardial infarction. Release of urinary LTE₄ following coronary intervention in patients with stable angina has not been studied yet.

Methods: We measured urinary excretion of LTE₄ in 19 patients with stable coronary artery disease who developed signs of myocardial ischemia (chest pain and ST segment changes) during percutaneous coronary intervention (PCI). The control group consisted of 19 patients undergoing diagnostic angiography without PCI. LTE₄ was assessed by immunoassay from urine samples obtained two hours before and two and four hours after the intervention.

Results: Mean urinary LTE₄ levels did not differ at baseline in both groups (414 pg/mg creatinine; PCI group vs 320 pg/mg creatinine; control group, *p*=NS). Two hours after PCI LTE₄ levels increased significantly (813 pg/mg creatinine, *p*=0.005) and then decreased in the next two hours (725 pg/mg creatinine). Such changes were not observed in the control group (414 pg/mg creatinine; after 2 hours, *p*=0.11 and 415 pg/mg creatinine; after 4 hours, *p*=0.49).

Conclusions: Myocardial ischemia triggered by PCI in patients with stable angina is associated with increased cysteinyl-leukotrienes release.

P1463 Is there a correlation between soluble CD40 ligand levels, CRP and the extent of coronary artery disease in chronic stable angina?



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Background: CD40 ligand is a trimeric, transmembrane protein of the tumor necrosis factor family and, together with its receptor CD40, is an important contributor to the inflammatory processes that lead to atherosclerosis and thrombosis. Raised soluble CD40 ligand (sCD40L) levels are associated with adverse outcomes in patients with acute coronary syndromes. It is still not known whether or not the same is true for patients with chronic stable angina.

Methods: We measured serum sCD40L levels in 198 consecutive patients who were undergoing elective coronary angiography for chronic stable angina. Risk factors, medications and angiographic coronary vessel score (0=normal, 1=single, 2=double, 3=triple vessel disease) were analysed in relation to sCD40L levels using univariate analysis.

Results: 142 patients (72%) were male; mean age was 58.3 years (range 32-82) and mean body mass index was 27.3 (range 19.2-42.7). 123 (62%) were past smokers and 27 (14%) were actively smoking. 24 (12%) were diabetic, 82 (41%) were hypertensive and 100 (50%) had positive family history for ischaemic heart disease. Aspirin, statin, betablocker and ACE inhibitor were taken by 165 (83%), 114 (58%), 109 (55%) and 34 (17%) respectively. Coronary angiography revealed triple vessel disease in 52 (26%), two vessel disease in 45 (23%), single vessel disease in 49 (25%) and no lesions were found in 52 (26%). sCD40L levels were between 0.05 to 6.1 µg per litre with a mean of 1.17 and standard deviation of 0.84. There was no significant correlation between sCD40L levels and vessel score (*p*=0.886). No significant correlation was also noted between sCD40L levels and a previous history of acute coronary syndromes (*p*=0.454) or serum CRP levels (*p*=0.71). A weak correlation was observed between sCD40L levels and a history of smoking (*p*=0.063) but there was no correlation with any of the other traditional risk factors for development of coronary disease.

Conclusion: Serum sCD40L levels were not found to correlate with traditional coronary artery disease risk factors, serum CRP levels or the extent of coronary artery disease on angiography in patients with chronic stable angina. Our data suggests that measurement of serum sCD40L levels is of little utility in the investigation and management of stable angina.

P1464 Mechanisms of contrast-induced nephropathy: possible role of inflammation



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Background: The pathogenesis of contrast-induced nephropathy (CIN) is poorly understood and the possible role of inflammation remains to be investigated.

Objectives: To evaluate the predictive factors and incidence of CIN in a patient population receiving the low osmolar non-ionic contrast medium (CM) iomeprol.

Methods: 971 patients (699 men, mean age: 65.5±10.4; 272 women; mean age: 67.2±9.6) referred for coronary angiography/PTCA were evaluated. The following variables were analysed: basal and post-procedural serum creatinine, basal creatinine clearance (ClCr; ml/min) calculated according to the Cockcroft-

Gault formula, volume (ml) of CM administered, mean arterial pressure (mmHg), age (years), body mass index (BMI), left ventricular ejection fraction (LVEF; %), plasma osmolality (OSM; mosm/L), total protein (g/dL), total cholesterol (mg/dL), LDL cholesterol (mg/dL), fibrinogen (mg/dL), sex, arterial hypertension, diabetes mellitus, hypercholesterolemia, and smoking. Analysis of variance (ANOVA) and multivariate (stepwise and logistic regression) analyses were performed. CIN was defined as a post-procedural (48h) increase of serum creatinine (ΔCr) of ≥ 0.5 mg/dL relative to basal creatinine (Cr).

Results: In overall population mean basal Cr was 1.08±0.35 mg/dl; mean post-procedural Cr was 1.15±0.45mg/dl and mean ΔCr resulted 0.07±0.24 mg/dl. CIN occurred in 29/971 (3.0%) patients, of whom 4/971 (0.5%) had ΔCr of >1 mg/dl, only one patient had a renal damage requiring dialysis. Significantly increased incidences of CIN were observed in patients with basal Cr >1.2 mg/dl (8.2% vs 1.5%; *p*<0.0001), basal ClCr <60 ml/min (7.3% vs 1.4%; *p*<0.0001), age >70 years (5.8% vs 0.4%; *p*=0.0002), LVEF <50% (5.2% vs 1.6%; *p*=0.002) and diabetes mellitus (7.0% vs 2.1%; *p*=0.0003). The independent variables considered predictive of post-procedural variations in creatinine (ΔCr) (stepwise analysis) were basal Cr (*P*<0.0001) and OSM (*P*=0.003). Conversely, variables predictive of CIN (logistic regression analysis) resulted basal Cr (*p*<0.02) and plasma concentration of fibrinogen (*p*<0.02).

Conclusions: Non-ionic iomeprol was associated with a very low incidence of CIN (3.0%). The independent predictors of CIN were pre-existing renal insufficiency and inflammatory system activation (elevated plasma fibrinogen). Pre-procedural plasma osmolality correlated with variations (negative and positive) in post-procedural creatininemia but was not predictive of CIN.

P1465 The acute and long-term effect of drug-eluting stent and statin treatment on serum levels of inflammatory and cardiac necrosis markers in patients undergoing percutaneous coronary intervention



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Background: Inflammatory and immune mechanisms are involved in the pathophysiology of atheromatous plaque disruption. We evaluated the serial changes of serum levels of inflammatory and cardiac necrosis markers in coronary artery disease patients (pts) undergoing percutaneous coronary intervention (PCI).

Methods: Serum levels of high-sensitivity C-reactive protein (h-CRP), metalloproteinase 9 (MMP-9), tissue inhibitor of metalloproteinases 1 (TIMP-1), neopterin (NEO), as well as creatine kinase (CK), its CK-MB fraction and troponin-I (Tn-I) were measured in 120 consecutive pts (male 103, mean age 62 ± 10) with stable angina undergoing PCI. Diabetes mellitus was present in 23%, and hypercholesterolemia in 87% of pts [69% of them were receiving statin treatment (ST)]. Blood samples were taken pre-, 24-h post-PCI and at 13.8 ± 3.5 months later [follow-up (FU)].

Results: PCI was attempted in 140 vessels to treat 185 lesions, using sirolimus-eluting (SES, *n*=78 pts) or bare metal (BS, *n*=42 pts) stents. There were no differences in demographics, risk factors profile, clinical symptoms, or angiographic characteristic of stenosis between two groups. Cardiac necrosis markers measurements post-PCI showed no differences in patients treated with SES compared to those treated with BS; no differences were observed according to ST. In pts receiving ST pre-PCI serum levels of h-CRP (3.99 ± 5.98 mg/L vs 5.13 ± 6.58 mg/L, *p*=0.02) and NEO (10.94 ± 10.0 nmol/L vs 12.26 ± 5.7 nmol/L, *p*=0.03) were lower compared to pts without treatment. Serum levels of h-CRP, MMP-9, and TIMP-1 increased 24-h post-PCI both in pts treated with SES and BS (*p*<0.001); these changes were not affected by ST. However 24-h post-PCI MMP-9 levels were lower in pts treated with SES (*p*<0.01). During FU (99% of pts were on ST, 61% on combined antiplatelet treatment) a significant decrease was observed in h-CRP, MMP-9, and TIMP-1 serum levels (*p*<0.001, ANOVA for repeated measurements); these changes were not different between SES and BS pts.

Conclusion: ST pre-PCI is associated with a significant reduction in specific inflammatory markers, suggesting the interrelationship between inflammation and statin use. There were no differences in serum levels changes of inflammatory markers 24h post-PCI, and at long-term FU in pts treated with SES or BS. The greater increase in MMP-9 observed with BS 24 hours post-PCI might be due to greater tissue damage.

P1466 Is there any correlation between hsCRP and natriuretic peptides in elderly patients with suspected heart failure in a primary care setting?



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Background: High sensitivity CRP (hsCRP) is a risk marker for cardiovascular diseases. The natriuretic peptides (NT-proBNP, ANP, BNP) are markers for heart failure with different reference levels according to age and gender. There is limited knowledge of the association between hsCRP, natriuretic peptides, underlying diseases and treatment.

Aim: The main purpose of this study was to investigate if there were any correlations between hsCRP and natriuretic peptides (NT-proBNP, ANP and BNP) in patients with suspected heart failure in primary health care (PHC) taking gender

into consideration. A second aim was to explore relationships between hsCRP, natriuretic peptides and underlying cardiovascular diseases, diabetes and statin treatment.

Method: A general practitioner examined 170 patients (120 women, 49 men, mean age 78 and 75 years, respectively) who had clinical symptoms of suspected heart failure. A pre-specified heart failure record was filled in. All patients were referred for echocardiography and cardiac consultation where the diagnosis of heart failure was principally established or refuted according to the criteria proposed by the European Society of Cardiology. Blood samples were taken and stored frozen in 157 patients. HsCRP and the peptides were logtransformed. Of all examined patients, 45% had a verified diagnosis of heart failure and remaining patients were used as a control group.

Results: In all patients there were significant correlations between hsCRP and NtproBNP ($r=0.28$; $p<0.001$) ANP ($r=0.24$; $p=0.002$) and BNP ($r=0.18$; $p=0.028$). However, these correlations were significant only in women (hsCRP and NtproBNP ($r=0.34$; $p<0.001$) ANP ($r=0.29$; $p=0.002$) and BNP ($r=0.26$; $p=0.007$)) and were independent of the presence/absence of heart failure. In multivariate regression analysis of all patients the associations between hsCRP and NtproBNP ($p<0.001$), ANP ($p=0.023$) remained significant, but not for BNP when adjusted for underlying cardiovascular diseases, diabetes and statin treatment.

Conclusion: We found a significant correlation between hsCRP and natriuretic peptides in women independent of age or the presence/absence of heart failure. High levels of hsCRP may be one explanation why women have higher levels of natriuretic peptides than men, especially for NtproBNP.

P1467 PCI-induced plaque disruption activates the immuno-inflammatory cascade



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Background and Aim: There is growing evidence that coronary intervention (PCI) leads to the release of inflammatory mediators. The aim of this study was to evaluate whether "active" coronary plaque disruption during PCI in coronary artery disease (CAD) patients, with either stable or unstable angina, provokes further inflammatory responses.

Methods: 20 patients with CAD (CNTR), who were not candidates for PCI after coronary arteriography, were compared with 60 patients (PCI), who were subjected to single vessel ad hoc PCI with stent implantation.

Pro-inflammatory cytokines IL-6 and IP-10, chemokine MCP-1, adhesion molecules ICAM-1 and VCAM-1, metalloproteinase MMP-9 and its inhibitor TIMP, were assessed before (BL), 12 hours and 36 hours after either coronary arteriography or PCI respectively. Values are expressed as mean $\pm$ 1SE (pg/ml).

Results: see Table 1.

Table 1

	ICAM			VCAM		
	CNTR	PCI	p	CNTR	PCI	p
BL	656 $\pm$ 20	731 $\pm$ 32	NS	934 $\pm$ 69	998 $\pm$ 44	NS
12h	608 $\pm$ 33	747 $\pm$ 31	0.03	861 $\pm$ 60	1153 $\pm$ 45	0.002
36h	598 $\pm$ 31	740 $\pm$ 31	0.03	987 $\pm$ 67	1088 $\pm$ 45	NS

	MMP-9			IL-6		
	CNTR	PCI	p	CNTR	PCI	p
BL	647 $\pm$ 71	473 $\pm$ 38	NS	6.2 $\pm$ 1.9	6.2 $\pm$ 2.7	NS
12h	605 $\pm$ 78	844 $\pm$ 57	0.09	12.5 $\pm$ 2.3	14.8 $\pm$ 7.8	NS
36h	790 $\pm$ 96	732 $\pm$ 59	NS	13.3 $\pm$ 2.6	21.3 $\pm$ 12.8	0.06

a) At 12 hours post PCI, levels of ICAM-1, VCAM-1, and MMP-9 were significantly higher compared to the CNTR group.

b) At 36 hours post PCI, levels of ICAM-1 and IL-6 were significantly higher compared to the CNTR group.

Conclusions: a) "Active" coronary plaque disruption during PCI seems to provoke further inflammatory activation in CAD patients.

b) PCI probably triggers a broad spectrum of immuno-inflammatory responses as indicated by the intervention-induced elevation of mediators representing various stages of the inflammatory cascade.

P1468 Immunomodulating effects of the endogenous NO Synthase inhibitor ADMA



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Atherosclerosis is a chronic disease triggered by endothelial injury and sustained by inflammation. Dendritic cells (DCs) are critical for the cell-mediated arm of an immune response and are known to initiate inflammatory immunity. The aim of our study was to describe the impact of the endogenous competitive nitric oxide synthase (NOS) inhibitor asymmetric dimethylarginine (ADMA) for the activation of DCs. Human monocyte derived DCs were isolated from healthy donors and immature DCs were incubated for 24 h with different concentrations (1-10 μ M) of ADMA. The expression of adhesion- (ICAM-1, LFA-1, DC-SIGN), costimulatory- (CD80, CD83), and endocytotic molecules (Dec205, mannose-receptor) was investigated by FACS-analysis. DC phagocytotic capac-

ity was analyzed by FITC- Dextran endocytosis (receptor-mediated phagocytosis) and Lucifer yellow (macropinocytosis). To identify the mechanisms responsible for efficient antigen capture the mannose receptor mediated phagocytosis was blocked with Mannan (0.1-10 mg/ml) and the macropinocytosis was inhibited with 100 μ M p-chloromercuribenzenesulphonate (pCMBS). Protein expression of DC-adhesion-, costimulatory, and endocytotic molecules, chemokines and cytokines were characterized using protein arrays.

Results: DC-adhesion and transmigration was concentration-dependently enhanced by ADMA ($p<0.01$), associated with a 23 $\pm$ 12% increase in LFA-1 expression. DC phagocytosis capacity was blocked with Mannan (-46%; $p<0.01$), but was unchanged by inhibiting macropinocytosis using CMBS. ADMA 10 μ M reduced DC phagocytosis by -30% ($p<0.05$), associated with a downregulation of the mannose receptor ($p<0.05$). VEGF, IL-12, MMP-2 and E-Selectin protein expression was upregulated by ADMA, whereas IL-10 release from DCs was not altered. IP-10, LIGHT and VE-cadherin were downregulated by ADMA. Finally, ADMA (5-10 μ M) induced a DC-maturation with enhanced expression of CD83 (+21%; $p<0.01$).

In summary, vascular invasion of DCs, as well as DC-activation and maturation is stimulated by ADMA. Receptor mediated phagocytosis but not macropinocytosis was increased by ADMA. Regulating vascular DC invasion and activation by modulating the NO-pathway may have relevance to atherogenesis.

P1469 Iberiotoxin-sensible potassium channels are involved in IL-1 β -induced adhesion of monocytes to endothelium



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Purpose: Potassium channels control the membrane potential (MP) of endothelium and modulate signaltransduction of inflammatory processes. Adhesion of monocytes to endothelium is important for the formation of atherosclerotic plaques. Cytokines like IL-1 β enhance adhesion and promote atherosclerosis. Aim of our study was to examine whether iberiotoxin-sensible potassium channels like BK_{Ca} modulate IL-1 β -induced adhesion.

Methods: Measurement of MP, calcium-influx and reactive oxygen species (ROS) were performed using the fluorescence-dyes DiBAC, Fura-2AM and DCF. Adhesion of U-937 cells to HUVEC was analyzed by 3H-thymidin- and BCECF-fluorescence adhesion assays. Expression of ICAM-1 and VCAM-1 was assessed by FACS.

Results: IL-1 β induced a hyperpolarisation of HUVEC that was inhibited by iberiotoxin, an inhibitor of BK_{Ca}. Hyperpolarisation was followed by an increase of intracellular calcium and of ROS-generation that was also inhibited by IBX. ROS-generation was also inhibited by the calcium-chelator BAPTA and inhibition of NAD(P)H-oxidase using Diphenyleneiodonium (DPI). IL-1 β -induced adhesion of U-937 cells to HUVEC was reduced by IBX, DPI and BAPTA.

Conclusion: IL-1 β induces a hyperpolarisation of HUVEC via modulation of BK_{Ca}. This is followed by an increase of intracellular calcium, activation of NAD(P)H-oxidase and enhanced ROS-generation. ROS-synthesis then promotes adhesion of U-937 cells to HUVEC.

P1470 Time-course of tissue factor plasma level in patients with acute coronary syndrome



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Background: Inappropriate expression of tissue factor (TF) may result in thrombosis contributing to acute clinical consequences of coronary artery disease. Several studies demonstrated elevated plasma levels of TF as well as high sensitivity CRP (hsCRP) in patients with acute coronary syndrome (ACS). The aim of our study was to compare the concentrations of TF in coronary sinus (CS) and peripheral blood and its relations to hsCRP levels.

Methods: TF and hsCRP plasma levels were measured in the blood drawn from CS, AO and PV. Time course of the TF and hsCRP peripheral blood plasma levels was followed on day 1 and day 7 after index event of ACS and was compared to day 0 values. No heparin was given prior to the blood sampling.

Results: Twenty-nine patients in the ACS group (age 63.9 $\pm$ 11.0 years, 20 males, 9 females and 24 patients with SCAD (age 62.3 $\pm$ 8.1 years, 21 males, 3 females)

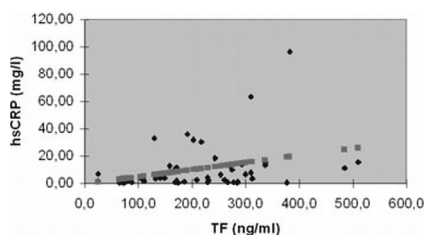


Fig. 1

were examined. TF plasma level was significantly higher in patients with ACS then in those with SCAD (239.0 ± 99.3 ng/ml vs 164.3 ± 114.2 ng/ml; $p=0.016$). There was no difference in TF plasma levels in CS, AO and PV (253.7 ± 131.5 ng/ml vs 239.0 ± 99.3 ng/ml vs 250.6 ± 116.4 ng/ml, respectively). TF plasma levels tended to decrease only non-significantly on the day 7 (224.4 ± 109.8 ng/ml). hsCRP levels were also significantly higher in ACS group then in SCAD (14.7 ± 20.9 ng/ml vs 3.99 ± 7.05 ng/ml; $p=0.013$) and tended to increase non significantly on day 1 (20.9 ± 26.6 ng/ml) and day 7 (24.4 ± 42.7 ng/ml). Significant linear correlation between TF and hsCRP levels on day 0 was found (Fig. 1).

Conclusion: TF plasma levels are elevated in patients with ACS not only locally in CS but also in systematic circulation. Our data support the relationship between TF production and proinflammatory mediators.

P1471 Successful reperfusion with PCI reduces both pro- and anti-inflammatory upregulation during the acute phase of STEMI



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Some detailed issues concerning enhanced immunologic activation in ST elevation myocardial infarction (STEMI) still await to be resolved.

Aim: To investigate the effect of primary PCI on markers of pro- and anti-inflammatory activation in pts with STEMI.

Material and methods: Studied group: 30 consecutive patients, 19 male (63%), aged 57.3 ± 11.2 yrs with STEMI, treated with PCI. Single-vessel disease was diagnosed in 22 pts whereas multivessel disease in 8. Each patient underwent triple evaluation of plasma levels of pro- and anti-inflammatory cytokines, ie. interleukin 6 (IL-6) and interleukin 10 (IL-10), respectively, as well as the assessment of other inflammatory, platelet and endothelial dysfunction and myocardial performance indices: high-sensitive C-reactive Protein (hsCRP), fibrinogen (FIB), soluble CD40 ligand and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP): at baseline - within the first 24 hours of STEMI, 7 days and 6 months after STEMI.

Results: All of the parameters evaluated, including IL-10 presented peak values at baseline or 7 days after STEMI (FIB) with subsequent significant decrease during follow-up (table). The ratio IL-6/IL-10 did not change during the observation. Peak IL-10 value strongly correlated with peak values of IL-6 ($R=0.41$, $p<0.03$), hsCRP ($R=0.37$, $p<0.04$), FIB ($R=0.41$, $p<0.03$) as well as peak NT-proBNP ($R=0.39$, $p<0.04$).

Inflammatory markers during follow-up

	baseline	7 days after STEMI	6 months after STEMI
IL-6 (pg/mL)	19.7 ± 16.1	$4.1 \pm 3.8^*$	$3.9 \pm 3.8^{**}$
IL-10 (pg/mL)	4.6 ± 3.6	$2.1 \pm 2.0^*$	$2.4 \pm 2.2^*$
hsCRP (mg/L)	27.6 ± 26.4	$18.5 \pm 13.1^*$	$5.6 \pm 5.1^{**}$
FIB (mg%)	452.7 ± 129.8	536.0 ± 132.6	$365.0 \pm 79.5^{***}$
NTproBNP (pg/mL)	79.8 ± 62.7	$49.6 \pm 45.4^{**}$	$48.5 \pm 38.6^{**}$

* - $p<0.04$ vs baseline; ** - $p<0.01$ vs baseline; *** - $p<0.04$ vs 7 days after STEMI

Conclusions: In pts with STEMI (1) successful myocardial reperfusion with PCI diminishes both pro- and anti-inflammatory upregulation, (2) parallel course as well as relationships between pro- and anti-inflammatory markers reflect interdependence and counterbalance between both components of immunoinflammatory activation, (3) successful treatment of STEMI and downregulation of proinflammatory activation is not associated with significant additional long-term enhancement of anti-inflammatory component.

P1472 Multiple bead array assays to detect elevations of inflammatory markers at the site of plaque rupture in acute myocardial infarction



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Background: The mechanisms leading to plaque rupture and thrombosis in acute myocardial infarction (AMI) are still not completely identified. In particular, the role of local and systemic inflammation needs to be further clarified. We hypothesized that the comparison of levels of inflammatory mediators from blood samples taken at the site of coronary occlusion with those in the systemic circulation can reveal additional factors with local impact.

Methods: In 32 consecutive patients undergoing primary percutaneous coronary intervention (PCI) for AMI, systemic blood samples were taken from the aorta. In 17 of them, an additional blood sample from a closed compartment surrounding the ruptured plaque was obtained using distal protection (PercuSurge GuardWire System) in order to compare local and systemic levels of inflammatory markers. Samples were analyzed by multiple bead array assays (Luminex), which allowed parallel measurement of 32 different inflammatory markers. Statistical differences between local and systemic values were identified by effect size as well as univariate (Wilcoxon signed ranks test) and multivariate (chi-squared statistics) analysis.

Results: Of the 32 patients with AMI, 25 presented clinically with STEMI and 7 with NSTEMI. The average time from the onset of symptoms to PCI was 428 ± 418 min. In the 17 patients with additional sampling at the site of plaque rupture, the local milieu was preserved as evidenced by an angiographic total occlusion in 94% and no relevant collaterals ($< \text{Rentrop } 1-2$) in 88% of the cases. The following cytokines were locally elevated as compared to aortic levels: IL-12, MIP-1alpha, MCP-1, MIF, INF-alpha, IL-6, tPAI, IL-1Ra, IL-8, IP-10, GM-CSF, Eotaxin, and IL-17 (all $p<0.05$). All of these markers, except for tPAI, IL-17 and IP-10, also showed a medium to large effect size (0.53-0.81). Furthermore multivariate (chi-squared statistics) allowed the classification of aortic and local samples with only 5 markers (IL-12, MIF, INF-gamma, MIP-1alpha and IL-8) in 100% of the cases demonstrating different inflammatory processes at the site of plaque rupture. No gradients in serum levels could be detected for other important inflammatory markers such as CRP, TNF-alpha, IL-10, sICAM, and sVCAM.

Conclusion: The elevation of specific inflammatory mediators at the site of plaque rupture compared with systemic levels in AMI points to an early and local role of these factors independent from the systemic inflammatory reaction.

P1473 Interaction between tumour necrosis factor-related apoptosis inducing ligand & osteoprotegerin in acute coronary syndromes



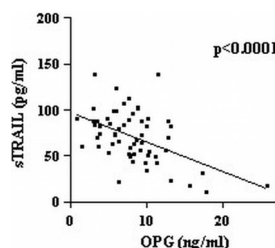
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Purpose: TRAIL, a member of the TNF ligand superfamily, is expressed on inflammatory cells, induces apoptosis of human endothelial cells & is present in atherosclerotic plaques. Osteoprotegerin (OPG) is a soluble TRAIL receptor which is raised in coronary artery disease (CAD). Recent studies have identified a role for OPG in preventing TRAIL-induced apoptosis of endothelial cells. We investigated the possibility of an interaction between soluble TRAIL (sTRAIL) & OPG in CAD.

Methods: Plasma was collected from patients with stable CAD ($n=76$), & patients with ACS, 24 & 48 hrs after admission ($n=62$). Soluble TRAIL, OPG, C-reactive protein (CRP) & Troponin T (TnT) were measured & correlations assessed.

Results: sTRAIL was significantly lower in the ACS group at 24 hours vs patients with stable disease, but sTRAIL levels then increased at 48 hrs ($p<0.0001$). There was no significant difference in mean OPG between stable CAD and ACS patients at 24 hrs, but there was a marked fall in OPG between 24 & 48 hrs in the ACS group ($p<0.001$). In addition, there was a strong inverse correlation between sTRAIL & OPG in the ACS patients at both 24 hrs ($p<0.0001$) & 48 hrs ($p<0.001$). In the same patients at both time points, there was a significant positive correlation between OPG & both CRP & TnT, & a significant negative correlation between sTRAIL & both CRP & TnT.



TRAIL & OPG in Unstable Angina at 24 hrs

Conclusions: We report for the first time a significant inverse correlation between sTRAIL and OPG in ACS patients. Taken together, these results suggest a possible interaction between systemic TRAIL and OPG in acute coronary syndromes which warrants further investigation.

P1474 Telomerase activity in plaque neutrophils of patients with acute coronary syndromes



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Background: Systemic activation and delayed apoptosis of polymorphonuclear neutrophils (PMN) has been demonstrated in acute coronary syndromes (ACS), however little is known on PMN activation status at the unstable plaque level. These inflammatory cells have a finite lifespan with a low or absent activity of telomerase, a polymerase that extends repetitive DNA tracts at the ends of chromosomes essential for cell aging. Therefore we investigated telomerase activity in circulating PMN of patients with ACS, assessing telomerase activity also in PMN isolated directly from atherosclerotic plaque during percutaneous coronary intervention (PCI).

Methods: We studied 6 patients with Braunwald's class IIIB unstable angina (IIIB-UA), 11 patients with IIB unstable angina (IIB-UA) and 5 patients with chronic

stable angina (SA). Circulating PMN were isolated from venous and arterial blood. Plaque PMN were isolated directly from washing medium of angioplasty balloons by density gradient centrifugation. Telomerase activity was detected in cellular extracts by telomere repeat amplification protocol.

Results: The median telomerase activity calculated as a ratio between plaque and venous PMN was higher in IIIB UA group (56.25, range 9.2-135) than IIB UA and SA group (respectively: 1, range 0.9-1.4; $p=0.001$ and 1 range 0.5-1.1; $p=0.006$). There was no difference between the median telomerase activity in IIIB UA and SA patients ($p=0.51$). The median telomerase activity calculated as a ratio between plaque and arterial PMN was higher in IIIB UA patients (17.2, range 4-94) than in IIB UA and in SA patients (respectively: 1.1, range 0.8-1.9; $p=0.001$ and 1 range 0.4-1.2; $p=0.006$). There was no difference between the median telomerase activity in IIB UA and SA patients ($p=0.29$). Cardiovascular risk factor, medical therapy, angiographic type of coronary lesions were similar in telomerase positive and negative patients.

Conclusions: We have developed a novel approach which allows to collect inflammatory cells directly from coronary plaques treated by PCI. In patients with IIIB UA, but not in patients with IIB UA and SA telomerase activity was detected in plaque but not in circulating PMN, suggesting a specific and local mechanism of PMN survival at the plaque level that may play an important role in UA pathogenesis.

P1475 Nuclear Factor- κ B and complex lesions in patients with Acute Coronary Syndroms



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Purpose: Nuclear Factor- κ B (NF- κ B) is a transcription factor which plays a coordinating role in the genesis of the inflammatory response and it is thought to be involved in the pathogenesis of atherosclerosis. However, the role that NF- κ B plays in acute coronary syndromes (ACS) is not well defined. We sought to assess the relation between NF- κ B level and complex coronary stenosis in patients with SCA.

Methods: We studied 66 consecutive patients (50 men; 62 ± 13 years) with ACS (17 patients with unstable angina, 24 with non-Q-wave myocardial infarction and 25 with Q-wave myocardial infarction) who underwent coronary angiography. Coronary stenoses with $> 30\%$ diameter reduction were assessed and classified as complex (irregular borders, ulceration or filling defects suggesting thrombi) or smooth (without complex features). Angiographic thrombus was graded from 0 to 4. Sullivan's scoring system was used to assess the extension of atherosclerotic disease. Venous blood samples were obtained within 24 h of the ischemic event and NF- κ B activation was determined by electromobility shift assay.

Results: the number of complex lesions per patient was 2.3 ± 1.4 . NF- κ B level was 1.84 ± 0.93 units. A significant correlation was observed between NF- κ B level and the presence of complex coronary lesions ($r=0.46$, $p<0.001$), and between NF- κ B level and the thrombus score ($r=0.53$, $p<0.001$). NF- κ B was not significantly associated with disease extent and severity, as assessed by Sullivan's score.

Conclusion: NF- κ B activity was associated with the presence of angiographically complex lesions and thrombus in patients with ACS. These data suggest a role for NF- κ B in the pathogenesis of ACS.

P1476 Low-grade inflammation expressed by white blood cell count is a better marker of arterial wave reflections than C-reactive protein



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Purpose: Increased white blood cell count (WBC-C), a marker of low-grade inflammation, is associated with cardiovascular events and subclinical atherosclerosis. Arterial wave reflections are determinants of cardiovascular performance and predictors of the corresponding risk. We investigated the relationship of augmentation index (AIx), a composite measure of arterial stiffness and wave reflections, with WBC-C in healthy adults and we evaluated the importance of WBC-C compared with C-reactive protein (CRP), an established inflammatory risk predictor.

Methods: WBC-C and level of high-sensitivity CRP (hsCRP) were measured in 261 apparently healthy individuals (mean age 41 years, 174 men and 87 women) who had not any cardiovascular disease or risk factor except for smoking. AIx of the central (aortic) waveform was assessed using a validated system (Sphygmocor) that employs high-fidelity applanation tonometry of the radial artery and pulse wave analysis to synthesize the aortic waveform. AIx reflects the afterload the left ventricle must cope with due to reflected wave. hsCRP was log-transformed because of non-Gaussian distribution.

Results: AIx correlated with both WBC-C and hsCRP ($r=0.16$, $P<0.05$ and $r=0.15$, $P<0.05$ respectively). In multivariate linear regression analysis (AIx: dependent variable), WBC-C and hsCRP were independently associated with AIx when analyzed in separate models that adjusted for confounders such as age, gender, blood pressure, heart rate, smoking, height and total cholesterol (WBC-

C: standardized beta coefficient 0.14, $P<0.01$; hsCRP: beta 0.11, $P<0.05$). In these models, WBC-C accounted for almost a double amount of AIx variability compared with hsCRP. Interestingly, when both WBC-C and hsCRP were forced into the same model, only the association of WBC-C with AIx remained significant (WBC-C: beta 0.12, $P<0.05$; hsCRP: beta 0.09, $P=NS$).

Conclusion: WBC-C, an inexpensive, readily available and widely used test, is a marker of wave reflections, which is an important determinant of cardiovascular risk. Prospective studies are needed in order to determine the role of WBC-C as a cardiovascular risk predictor in asymptomatic populations.

P1477 The regulatory chemokine eotaxin-3 is a novel predictor of cardiovascular outcome in patients with coronary artery disease



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Background: Inflammatory indexes have been linked to adverse prognosis in patients with coronary artery disease. The eotaxin family comprises three distinct peptides (eotaxin, eotaxin-2 and eotaxin-3) which have been implicated in eosinophilic inflammation. In vitro and clinical studies suggest that eotaxins could play a role in vascular inflammation, but no data are available on their prognostic significance on cardiovascular events in patients with angiographically confirmed coronary artery disease.

Methods: We obtained baseline samples from a total of 1014 Italian patients with angiographically documented coronary artery disease. Circulating levels of eotaxin, eotaxin-2 and eotaxin-3 were determined in plasma. We tested the predictive effect of markers of eosinophilic inflammation and C-reactive protein on death from cardiovascular causes and nonfatal myocardial infarction over a follow-up period of 2.7 years (maximum 4.1 years).

Results: During follow-up 105 patients had a cardiovascular adverse event. Lower eotaxin-3 concentrations were observed in patients with adverse cardiovascular events, whereas both eotaxin and eotaxin-2 showed no associations with risk. After adjustment for classic risk factors, clinical, and therapeutic features, patients in the upper quartile of eotaxin-3 levels had a hazard ratio of 0.42 (95% CI, 0.29 to 0.61, $P<0.001$) for future cardiovascular events as compared with subjects in the lowest quartile. A strong inverse correlation between plasma eotaxin-3 concentrations and CRP was evident ($r=-0.293$, $P<0.001$). To test the hypothesis that eotaxin-3 and CRP have an incremental prognostic value in CAD patients, subjects were stratified into 4 groups according to the combinations of high or low eotaxin-3 ($>$ or ≤ 25 th percentile, i.e. 32.93 pg per milliliter) and CRP ($>$ or ≤ 75 th percentile, i.e. 1.20 mg per deciliter) levels. The event-free rate in patients with combined elevated CRP and reduced eotaxin-3 was lower than that of subjects with raised CRP alone (Log rank: 4.40, $P=0.03$).

Conclusions: Low levels of the regulatory chemokine eotaxin-3 are an independent predictor of future adverse cardiovascular events in patients with coronary artery disease and may be useful for risk stratification.

P1478 The effect of Interleukin-1 receptor antagonist on restenosis - continued suppression of neointima at 90 days



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Background: Interleukin-1 (IL-1) is involved in the pathogenesis of restenosis. IL-1 receptor antagonist (IL-1ra) blocks IL-1 signalling via the Type 1 IL-1 receptor and previous work (using a porcine model of restenosis) has shown that at 28-days, IL-1ra inhibits restenosis following stenting. Although initial results with Sirolimus and Paclitaxel in the pig at 28 days were impressive, when a longer time-point of 90 days was studied, in both cases the effect of the drug seemed to have worn off with no difference in neointima formation between drug and placebo.

Aim: The aim of this work is to determine whether 28 days of IL-1ra therapy is enough to maintain inhibition of neointima formation at a 90 day time-point and if so, to determine whether IL-1ra in combination with a polymer can still bind to its receptor, thus allowing local delivery.

Methods: IL-1ra was given by an intravenous bolus of 0.5mg/kg followed by a 28 day continuous subcutaneous infusion of 2mg/kg/24h. 8 pigs underwent coronary stenting (balloon/artery ratio 1.25:1) of the left anterior descending (LAD) and the right coronary artery (RCA) with a BiodivYsioTM Phosphorylcholine (PC) coated 3.5mm stent and were randomised to receive either IL-1ra or placebo. Injured vessels were harvested at 90 days. Histomorphometric analysis of all injured vessels was performed. Human IL-1ra was attached to a novel polymer and bound to a stent. Surface plasmon resonance was used to determine whether the combination following elution from the stent was still able to bind to the human Type 1 IL-1 receptor.

Results: For the same amount of injury, IL-1ra resulted in a 41% decrease in neointima formation (0.13 ± 0.01 vs. 0.22 ± 0.01 ; $p = 0.000001$) and a 21%

increase in lumen area (3.00 ± 0.01 vs. 3.76 ± 0.18 ; $p = 0.005$). after stenting. When bound to a novel polymer and coated on a stent, IL-1ra is still able to bind to its receptor implying biological activity.

Conclusions: In pig coronary arteries, IL-1ra is associated with a reduction in neointima formation when vessels undergo coronary stenting. Unlike Sirolimus and Paclitaxel, inhibition in neointima formation by IL-1ra is maintained at 90 days. We have shown that when combined with a polymer its biological activity is maintained and thus its potential for use as another agent against restenosis is promising.

P1479 Anti-inflammatory effects of clopidogrel



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Aspirin are known to reduce several pro-inflammatory markers in patients with coronary heart disease (CHD), while limited data exists with clopidogrel.

Objective: The aim of the present study was to assess the influence of clopidogrel as compared to aspirin on selected circulating inflammatory markers in patients with stable angiographically verified CHD.

Methods: 206 patients participating in the Aspirin non-responsiveness and clopidogrel clinical endpoint trial (ASCET)* were consecutively randomised to either aspirin 160 mg (n=105) or clopidogrel 75 mg (n=101). All patients were treated with aspirin 160 mg for at least 7 days before randomisation. Fasting blood samples were drawn at baseline and after 1 year treatment for determination of high sensitivity CRP, tumor necrosis factor alpha (TNF alpha), interleukin 6, monocyte chemoattractant protein 1(MCP-1), CD40L, P-selectin, interleukin 10 and transforming growth factor beta. As most variables were skewed distributed non-parametric statistics were used.

Results: The two groups were similar regarding demographic variables. At baseline and after 1 year there were no differences in any variables including changes from baseline to 1 year between the groups. However, in the aspirin group there were significantly lower levels of TNF alpha and MCP-1 after 1 year; 1.00 vs 1.16 pg/ml ($p < 0.001$) and 245 vs 261 pg/ml ($p < 0.001$), respectively. Likewise, in the clopidogrel group the level of TNF alpha was significantly reduced after 1 year; 0.99 vs 1.19 pg/ml ($p < 0.001$).

Conclusion: In patients with CHD we found no between group differences in circulating markers of inflammation after 1 year treatment with clopidogrel 75 mg compared to aspirin 160 mg. In both groups lower levels of TNF alpha were obtained, indicating similar anti-inflammatory effects of the two drugs.

* Pettersen et al. The ASCET design. *Scand Cardiovasc J* 2004;38:353-6.

P1480 Difference between acute coronary syndrome and stable angina: Relationship between plasma adiponectin, high sensitive C-reactive protein and coronary plaque components

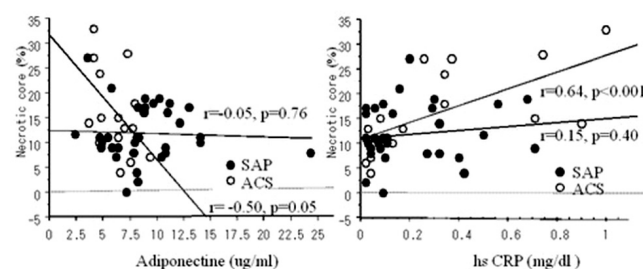


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Background: Acute coronary syndrome (ACS) may associate with plaque vulnerability, which may not exist in stable angina (SAP). We assessed the coronary plaque components using intravascular ultrasound (IVUS) derived virtual histology (VH™, Volcano) in relation to plasma levels of antiatherogenic adiponectin and high sensitive CRP (hs-CRP) in both ACS and SAP.

Methods: Total of 50 patients (ACS: 16, SAP: 34) was measured plasma adiponectin and hs-CRP levels before catheterization, and VH™ was performed at culprit lesion (>75% diameter stenosis) and at non-culprit lesions (<50% diameter stenosis). Coronary plaque components were classified into fibrotic, fibrofatty, dense calcium, and necrotic core (NC).

Results: The plasma adiponectin concentrations were significantly lower, and the plasma hs-CRP levels were significantly higher in ACS than those in SAP (adiponectin: 6.01 ± 0.44 μ g/ml vs. 8.76 ± 0.72 μ g/ml, $p = 0.02$; hs-CRP: 0.33 ± 0.08 mg/dl vs. 0.19 ± 0.03 mg/dl, $p = 0.05$). The ratio of NC to total plaque volume (%NC) of the culprit lesions was significantly higher in ACS than that in SAP ($16.6 \pm 2.2\%$ vs. $11.9 \pm 0.9\%$, $p = 0.03$). In ACS, a significant inverse correlation was observed between the plasma adiponectin levels and %NC of culprit lesions, and plasma hs-CRP levels showed positive good correlation with %NC of culprit lesion (figure). Furthermore, in ACS, %NC of non-culprit lesions were also positively corre-



lated with the plasma hs-CRP levels ($r = 0.58$, $p = 0.04$). In SAP, these two indices weren't correlated with any components.

Conclusions: The reciprocal association of adiponectin and hs-CRP levels with specific plaque components may reflect the precise mechanisms in the development of vulnerable plaques, predisposing to ACS.

P1481 Toll-like receptor induced TNF-alpha production predicts outcome of Fractional Flow Reserve measurement in patients undergoing percutaneous coronary intervention



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Background: Toll-like receptors (TLRs) are key players in innate immunity and are causally related to atherosclerosis, arterial remodeling and neointima formation. Ligand binding of TLRs results in the production of pro-inflammatory cytokines like TNF- α . Negative modulation of TLRs after cerebral ischemia has been described previously, but not following myocardial ischemia. Fractional Flow Reserve (FFR) measurement is routinely performed during percutaneous coronary intervention (PCI) to determine the functional severity of coronary artery stenosis and reflects myocardial ischemia during maximal hyperemia. We hypothesized that episodes of myocardial ischemia due to significant coronary artery stenosis modulates Toll-like receptor induced TNF- α production.

Methods: In 13 patients eligible for FFR measurement, a blood sample was drawn immediately following sheath insertion. These whole blood samples were incubated overnight with TLR2 and TLR4 ligands Pam3Cys (50, 500 and 5000 ng/ml) and lipopolysaccharide (LPS) (1, 10 and 100 ng/ml). TNF- α levels were measured with an enzyme linked immunosorbent assay. FFR was considered significant at a value ≤ 0.75 and non-significant at a value ≥ 0.80 . TNF- α levels were compared with binary FFR outcome. A p value < 0.05 was considered statistically significant.

Results: In 7 patients the FFR outcome was ≤ 0.75 , in 6 patients the FFR outcome was ≥ 0.80 . Pam3Cys and LPS induced TNF- α levels were significantly higher when FFR was ≤ 0.75 compared to FFR > 0.80 ($p = 0.014$, 0.008 and 0.035). The results are summarized in table 1.

Table 1

TLR ligand	FFR ≤ 0.75	FFR ≥ 0.80	p
Pam3Cys 5000 ng/ml	321 (± 148)	12 (± 10)	0.014
Pam3Cys 500 ng/ml	121 (± 46)	3 (± 1.7)	0.014
Pam3Cys 50 ng/ml	66 (± 23)	0 (± 0)	0.008
LPS 100 ng/ml	4853 (± 1910)	1062 (± 757)	0.073
LPS 10 ng/ml	2506 (± 968)	659 (± 202)	0.014
LPS 1 ng/ml	1871 (± 776)	348 (± 156)	0.035

Mean ($\pm$ SEM) TNF- α levels after stimulation with LPS and Pam3Cys in patients with FFR ≤ 0.75 and ≥ 0.80 .

Conclusion: Patients with significant coronary lesions have enhanced production of TNF- α following TLR2 and TLR4 ligand binding. This observation might be explained by episodes of myocardial ischemia prior to catheterization.

INTERVENTION AND PERIPHERAL CIRCULATION

P1482 Femoral artery ultrasonographic imaging better than carotid predicts extent and severity of CHD



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Background: Carotid and more rare femoral intima-media thickness (IMT), as well as atherosclerotic plaques have been confirmed as markers for coronary artery disease (CAD).

Purpose: The aim of the study was to evaluate the diagnostic importance of non-invasive peripheral atherosclerosis measurement for severity of CAD detection.

Methods: In 410 patients with suspected CAD, (73.2% men), aged 30-70 years

Risk factor	OR	95% CI	p
One vessel disease			
myocardial infarction	22.3	4.0-122.9	0.0004
right femoral IMT	5.0	1.4-18.4	<0.02
typical angina	6.4	1.2-34.2	<0.04
ex-smoking	5.6	1.1-28.7	<0.04
pulse pressure	1.8	1.0-3.2	<0.05
Multi-vessel disease			
myocardial infarction	3.7	1.8-7.5	0.0004
typical angina	3.3	1.7-6.5	0.0006
age	1.05	1.01-1.08	<0.01
number of cigarettes per week	0.8	0.6-1.0	<0.02
total cholesterol level	1.1	1.0-1.2	<0.03
left femoral atherosclerotic plaque	1.4	1.0-2.0	<0.05

(mean 56.0 ± 9.5 y), clinical examination, laboratory tests, carotid and femoral arteries ultrasonic imaging, and coronary angiography were performed. IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall. Atherosclerotic plaque in extracoronary artery was defined as a distinct area with an IMT $>50\%$ thicker than neighbouring sites. Significant CAD was defined as stenosis $>50\%$ of at least one major branch of the coronary artery. Severity of CAD was coded as one vessel disease, and multi-vessel disease, regardless to the number of atherosclerotic plaques.

Results: Using multiple stepwise regression analysis, the following parameters were found to be independent predictors of the one- and multivessel CHD (table).

Conclusion: Femoral IMT is an independent marker of one vessel disease, but femoral atherosclerotic plaque presence indicates severe CAD.

P1483 Femoral artery intima media thickness is an independent predictor of premature coronary artery disease



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Intima media thickness (IMT) of carotid artery and other peripheral vessels is a well established marker for coronary artery disease (CAD), especially in older individuals. In young CAD patients, smoking habits is a common feature and femoral IMT is closely related to smoking. How femoral IMT is related to premature CAD (<45) remains unknown.

The primary aim of this study was to determine whether carotid and femoral artery IMT had the same power to predict premature CAD.

Consecutive young patients (<45) admitted for acute coronary syndromes were matched for age, sex and smoking habits with young healthy controls participating to a primary prevention program of atherothrombosis. Carotid and femoral artery IMT were measured by B mode Doppler study as well as the presence of significant plaques ($>50\%$ of IMT in width).

A total 117 patients were matched with 234 controls for age, gender and smoking habits. Baseline characteristics were comparable in both groups. However, patients had a significant higher smoking intake ($<.0001$), were more likely to have a familial history of CAD (38.5% vs 29.5% , $p<0.0001$), were more likely to be HIV+ (17.1% vs 2.6% , $p<0.0001$), but were less likely to have a known dyslipidemia (58.1% vs 75.6% , $p=0.0013$) as compared to controls. As expected, plasma concentrations of total cholesterol, LDL-cholesterol, APO-B, Lp(a) and fibrinogen were found to be significantly higher in patients as compared to controls ($p<0.001$ for all). Carotid IMT was significantly higher than femoral IMT ($p<0.01$). Mean carotid and femoral IMT were higher in patients compared to controls (0.62 ± 0.17 vs 0.54 ± 0.09 and 0.87 ± 0.41 vs 0.36 ± 0.16 mm, respectively, $p<0.001$). Similarly, the prevalence of significant carotid and femoral arterial plaque was higher in patients with CAD (48.5% vs 18.9% and 54.5% vs 22.4% , respectively, $p<0.001$). Dyslipidemia, fibrinogen level, IMT and presence of plaque in carotids and femoral arteries were strongly associated with CAD on univariate analysis. After multivariate logistic regression analysis, femoral IMT (OR, 6.04; 95% CI, 3.9-9.5) and presence of plaque in the femoral artery (OR, 1.94; 95% CI 1.2-3.1) were the only factors found to be associated with the presence of CAD. Femoral IMT and presence of significant femoral plaque are independent predictors of premature CAD. Prospective investigations of these parameters in young healthy controls with smoking habits are now warranted.

P1484(W) The difference of early brain damage in diabetic and non-diabetic hypertensive patients



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Background - It is known that diabetes mellitus (DM) is independent risk factor for stroke, however early structural changes of a brain at these patients are insufficiently investigated. The aim of this study was to compare early brain damage in diabetic and non-diabetic hypertensive patients.

Methods - 31 patients with arterial hypertension (AH) and DM type 2 (AH+DM group - 10 males and 21 females, aged 40 to 61 y.o.) and 152 hypertensive patients without DM (AH group) matched for age and sex, participated in this study. 24-hours ambulatory blood pressure monitoring and MRI of brain were performed in all patients.

Results - Brain MRI detected liquorodynamics disturbances (increase of sub-arachnoidal species -100% in the AH+DM group vs 50% in the AH group, $p<0.001$, expansion of lateral ventricles - 97% in the AH+DM group vs 38% in the AH group, $p<0.001$), intracranial hypertension (87% in the AH+DM group vs 57% in the AH group, $p<0.01$), including widening of sulci (84% in the AH+DM group vs 36% in the AH group, $p<0.001$), focal white matter lesions (90% in the AH+DM group vs 66% in the AH group, $p<0.01$). The frequency of periventricular leucoaraiosis had no difference between two groups (41% in the AH+DM group vs 56% in the AH group). More than 2 forms of brain damage were revealed at all patients with AH+DM, and at 50% hypertensive patients without DM ($p<0.001$), despite of lower level of systolic and diastolic blood pressure in the AH+DM group

than in the AH group (156 ± 17 mmHg vs 178 ± 21 mmHg, $p<0.01$, and 92 ± 11 mmHg vs 111 ± 11 mmHg, $p<0.01$, respectively), and lower duration of AH (10 ± 8 y. in the AH+DM group vs 12 ± 7 y. in the AH group, $p<0.05$).

Conclusion - The results of this study indicated that hypertensive patients with DM have more expressed early structural changes of a brain than non-diabetic hypertensive patients and require more aggressive treatment for the prevention of stroke.

P1485 The prevalence of coronary atherosclerosis in patients with stroke



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Background: Cardiac death is the leading cause of long-term mortality in stroke patients, but the prevalence of coronary atherosclerosis in these patients is unknown.

Methods: Using an autopsy data bank, we studied the prevalence of coronary plaques and coronary stenoses greater than 50 percent in 811 consecutive autopsies of neurological patients.

Results: Coronary plaques and stenoses were present in 72 and 37 percent of the 347 patients with cerebrovascular disease and 27 and 10 percent of the 464 patients with other neurological diseases ($P<0.001$). Two thirds of myocardial infarction were unexpected autopsy findings. After adjusting for age, gender and heart weight, the odds ratio (95 percent confidence interval) of presence of coronary plaques, coronary stenosis and myocardial infarction were 3.65 (2.54 to 5.24), 2.60 (1.71 to 3.94) and 2.30 (1.55 to 3.42) respectively. Frequency of coronary atherosclerosis and myocardial infarction was similar between stroke subtypes. The prevalence of coronary plaques, coronary stenosis and myocardial infarction was 79, 46 and 46 percent in the presence of plaques in any segment of extra- and intracranial brain arteries, and 51, 17 and 23 percent in the absence of plaques, respectively (adjusted p-values <0.01). Coronary atherosclerosis was also related to the severity of atherosclerosis in any segment of cerebral arteries (adjusted p-values for linear trend <0.003). Similar results were observed in relation to internal-carotid-artery atherosclerosis.

Conclusions: Coronary atherosclerosis is highly prevalent in stroke patients regardless of the etiology, and more prevalent when atherosclerosis is present in carotid and cerebral arteries

P1486 A history of stroke or peripheral arterial disease is common in patients with acute myocardial infarction and is associated with less aggressive therapy and worse in-hospital outcome



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Purpose: Extracardiac vascular disease (EVD) (stroke/transient ischemic attack and peripheral arterial disease) and acute myocardial infarction (AMI) share common risk factors and formation processes. However, patients with EVD are generally excluded from AMI trials. We aimed to analyse the impact of EVD on prognosis on population-based AMI survey.

Methods and results: From the RICO survey database, we analysed all the consecutive patients hospitalised for AMI in the 6 cardiologic units from one region of eastern France between 1st January 2001 and 31st August 2005. Prior EVD was reported in 479 (12%) of the 3925 patients, including 168 (4%) with stroke/TIA, 280 (7%) with peripheral arterial disease and 31(1%) with both. Patients with EVD were 7 years older than those without prior EVD ($74(65-82)$ vs $67(54-77)$ y, $p<0.0001$). They were more likely to have diabetes, hypertension, prior MI, and renal insufficiency. However, the frequency of left ventricular dysfunction and anterior wall location were similar to those in patients without EVD. Necrosis size as assessed by peak plasma CK level was also similar among the groups. In the acute phase, patients with EVD were less frequently acutely treated with b-blocker (64 vs 77%, $p<0.001$), GpIIb/IIIa receptor blocker (26 vs 32%, $p=0.018$) and LMWH (39 vs 53%, $p<0.001$). In-hospital mortality (7 vs 4%, $p=0.005$), stroke (3 vs 1%, $p<0.001$) and heart failure (46 vs 28%, $p<0.001$) rates were higher in EVD patients. On multivariate analysis, prior EVD was independently associated with a higher risk of death or heart failure during the hospital stay (OR(95% CI), 1.45(1.13-1.88), $p=0.004$).

Conclusion: Patients with prior EVD constituted 12% of our non-selected AMI population and had high risk factors features, but similar clinical characteristics. Prior EVD was independently associated with worse in-hospital outcomes even after adjustment for potential confounders. Our data support the hypothesis that a history of stroke/TIA or peripheral arterial disease could be a marker of extensive atherosclerotic processes, and that EVD shares common risk factors with acute MI yet undetermined and suggest that in such patients, more aggressive therapy is warranted.

P1487 A new strategy to detect paroxysmal atrial fibrillation in patients with stroke



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Background: Up to 20% of acute ischemic strokes may be embolic events secondary to paroxysmal atrial fibrillation (PAF), and 24 hr-ECG recordings have a low yield to detect asymptomatic PAF. However, abnormal pulmonary vein activity potentially triggering PAF can be detected in 24 hr-ECG. We hypothesised that repetitive atrial premature contractions (APC) was associated with an increased prevalence of PAF, and that PAF can be detected by prolonged cardiac monitoring in a subgroup of patients with stroke.

Methods: 130 patients with stroke and without known PAF were enrolled in a prospective study, and were stratified according to the number of APC/24 hr (<70 or >70 APC/24hr according to a previous retrospective study). They underwent an echocardiography and three 7-day-Event-Recorder monitorings at 0, 3 and 6 months. Episodes of AF were correlated with the presence of repetitive APC in the ambulatory ECG. A logistic regression analysis for possible cofounders was conducted.

Results: 127 patients could be analysed. Patients with > 70 APCs (n=50) were significantly older, had more often hypertension, and had a higher LV-mass-index, than the patients without frequent APC (see table). PAF was documented more often in patients with frequent APC (26% vs. 6.5%, p=0.0021). In the multivariate analysis the presence of frequent APC in the initial ambulatory-ECG was the only independent risk factor for documented PAF during the follow-up (odds-ratio 5.06; 95% CI 1.7-15.3; p=0.004).

	< 70 PACs (n=77)	> 70 PACs (n=50)	p
Age, yr	56 ± 14	70 ± 9	< 0.0001
Male sex, n (%)	46 (60%)	32 (64%)	n.s.
Hypertension, n (%)	45 (58%)	41 (82%)	0.0055
Left atrial enlargement, n (%)	20 (26%)	22 (44%)	0.035
LV-mass-index, g/m ² (SD)	104 ± 36	121 ± 40	0.028
LV ejection fraction, % (SD)	63 ± 7	59 ± 10	0.021
Paroxysmal AF, n (%)	5 (6.5%)	13 (26%)	0.0021

Conclusion: In patients with ischemic stroke, repetitive APC (>70/24hr) identifies a subgroup at risk to present PAF. In this subgroup, PAF can be documented using repetitive long-term ECG recordings.

P1488 Effects of Aggrenox and telmisartan versus clopidogrel and aspirin in combinations on platelet activation and major receptor expression in diabetic patients: Relevance to the PROFESS trial



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Background: Chronic use of antiplatelet agents represents an independent avenue to improve outcomes and reduce the incidence of second stroke in these high-risk populations. Aggrenox (Ag) + telmisartan (T), or clopidogrel (C) + aspirin (ASA) are widely used in post-stroke regimens, and are currently tested in a mega trial with the survival endpoint (PROFESS). We determined antiplatelet properties of the same regimens in diabetic patients.

Methods: Forty patients were assigned to Ag (twice daily)+T (80mg) or C (75mg)+ASA (325mg) groups according to randomization codes. All patients received ASA for at least one month prior to screening. Other antithrombotic agents, ACE inhibitors, and angiotensin receptor blockers were not allowed. Platelet function biomarkers were assessed at baseline, Days 15, and Day 30 by conventional aggregometry, flow cytometry and rapid cartridge-based analyzers.

Results: There were no differences in the baseline clinical and platelet characteristics between Ag+T and C+ASA groups. C+ASA provided fast (Day 15) and sustained inhibition of ADP-induced (p=0.0003), and later (Day 30) collagen-induced (p=0.002) aggregation, prolongation of the closure time with PFA-100 analyzer (p=0.01), and reduction of the platelet activation units with the Ultegra device (p=0.003). Expression of PECAM-1 (p=0.02), GP IIb/IIIa activity (p=0.03), and reduced formation of platelet-leukocyte microparticles (p=0.01) were also significantly reduced already at Day 15 in the C+ASA treated patients. In contrast, Ag+T therapy has been associated with the delayed (mostly at Day 30) reduction of platelet receptor expression (GP IIb/IIIa activity (p=0.04), GP Ib (p=0.002), vitronectin receptor (p=0.01), P-selectin (p=0.007), lysosome-associated membrane protein (p=0.009), CD40-ligand (p=0.02), as well as inhibition of PAR-1 intact (p=0.01) and cleaved (p=0.01) thrombin receptor epitopes. Expression of GP IIb/IIIa antigen and CD63 was not affected by both regimens.

Conclusion: In the randomized trial of small sample size, the patterns of platelet inhibition were entirely different when patients are treated with Ag+T versus C+ASA. While the antiplatelet potency of C+ASA was stronger, and occur faster, the Ag+T regimen produced delayed, delicate downregulation of multiple major activation-dependent platelet receptors. Which strategy represents a therapeutic advantage is currently being tested in the PROFESS trial. These data also suggest that addition of clopidogrel to Aggrenox and angiotensin receptor blocker may be well justified due to their complementary effects on platelets.

P1489 Distal embolic protection devices, high intensity transient signals and neurological outcomes during carotid artery stenting



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A major limitation of percutaneous carotid artery stenting (CAS) is the occurrence of distal embolization during the procedure. Transcranial Doppler (TCD) performed during CAS with the detection of high intensity transient signals (HITS) indicate that distal embolization is a universal finding. Yet the clinical correlation between HITS, distal embolic protection devices and neurologic events has not been clearly established. We assessed the incidence and clinical impact of HITS in high-risk pts undergoing CAS with different embolic protection devices. A total of 154 consecutive high-risk pts underwent CAS, 78 had restenosis following carotid endarterectomy (CEA) and 76 had de novo lesions. Three different types of filters for distal cerebral embolic protection were used: E.P.I. FilterWire[®], Angioguard[®] and Spider[®]. The total number of HITS is presented. The mean age was 71±8 years, 37% were female, 40% had diabetes, 81% hypertension and 58% coronary disease. An optimal window for TCD was available in 47 post-CEA pts and 42 pts with de novo lesions. A filter was used in 22 pts and in 30 pts, respectively. Six pts had a cerebrovascular accident (CVA), three in pts treated without filters (0, 63 and 63 HITS), 2 with the Angioguard[®] (0 HITS and 277 HITS) and 1 with the Spider[®] filter (0 HITS). Six pts had a transient ischemic event (TIA), 2 with the Angioguard[®] (15 and 90 HITS), 2 without filter, 1 with the FilterWire[®] and 1 with the Spider[®], these 3 pts did not have an appropriate window for TCD. One patient died, he was treated without filter and had 72 HITS. The average number of pts, events and HITS are shown in the Table.

	No Filter	Angioguard [®]	FilterWire [®]	Spider [®]	Other
S/P CEA (n=47)	25	7	11	2	2
De Novo (n=42)	12	11	10	8	1
S/P CEA and HITS	120	145	185	128	92
De Novo and HITS	136	142	198	161	21
CVA	3	2	0	1	0
TIA	2	2	1	1	0

Conclusions: HITS are a very common event during CAS and are present during different stages of the procedure. Neither lesion type (post CEA or de novo) nor filter type seem to influence on the number of HITS or neurological events or viceversa.

P1490 Results after percutaneous intervention of pelvic artery lesions according to TASC- A-D



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Background: The TASC consensus paper defined 1999 the types (A - D) of pelvic artery lesions depending on their extensions and therapeutic feasibility. According to these the treatment of choice is for less severe type A and B lesions the percutaneous intervention, whereas for the severe type C and D lesions the surgical approach is indicated.

Aim of the study: We hypothesised, that type C and D lesions can be treated as well successful nowadays with an endovascular approach than type A and B lesions.

Method: Between 1996 and 2001 we performed 436 pelvic interventions in 373 patients on indication (74% stenosis, 26% occlusions). The periprocedural success rate and the long-term outcome after 36 months were prospectively analysed according to their TASC classification. Indication for intervention was a) claudication (Rutherford 1-3) 87.1% b) critical limb ischemia, rest-pain or necrosis (Rutherford 4-6) 12.4% and c) groin access for percutaneous interventions for patients with coronary heart disease (0.5%). Stentimplantation was performed in 83% and intraarterial lyses in 1.1%. Mean lesions length was 48 mm, mean stent-length 51 mm.

Results: The primary success rate and long-term outcome, improvement of the TBQ and Rutherford classification after 36 months are shown in table 1.

	n	Primary success	Restenosis 36 months	Re-occlusion after 36 months
TASC A	117	99.1%	12.8%	0%
TASC B	163	96.7%	11.6%	0.6%
TASC C	99	92.9%	11.1%	1%
TASC D	57	100%	10.5%	7%

	TBQ preintervention	TBQ after 36 months	Rutherford preintervention	Rutherford after 36 months
TASC A	117	99.1%	2.9	1.8
TASC B	163	96.7%	2.8	1.9
TASC C	99	92.9%	2.9	1.7
TASC D	57	100%	3.1	2.0

TBQ= Tibio-brachial quotient

Conclusion: The percutaneous approach is not only feasible with an acceptable

outcome for less severe (type A and B) but also for severe (type C and D) pelvic artery lesions.

P1491 Femoral artery pseudoaneurysms: a trend for minimally invasive treatment modalities, including ultrasound guided thrombin injection



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Background: Femoral pseudoaneurysms are a well-recognized complication following cardiac catheterization via transfemoral approach. Standard treatment options included surgery or manual compression. More recently, selective injection of thrombin has been proposed as an alternative.

Methods: We retrospectively analyzed data from 6800 patients who received cardiac catheterization at our institute from 1/2005 until 2/2006.

Results: At day 1 after the procedure, approximately 10% of the patients were examined with duplex sonography for clinical suspicion of a groin complication by the presence of hematoma, pain or palpable bruise. In 205 patients (3.0%), a pseudoaneurysm of the femoral artery was diagnosed. All patients underwent manual compression or compression with a femostop device at the day of diagnosis. 159 (77%) of the aneurysms could be successfully closed by compression therapy within 2 additional days. Most of the remaining 43 aneurysms had a maximal diameter of more than 2cm (range 1.5-7.3cm). 42 of these patients underwent ultrasound and biopsy-line guided thrombin injection (Baxter Tissucol Duo®) into the aneurysm cavity. This resulted in a successful occlusion in 41 cases. There were no complications during or following thrombin injection such as allergic reaction, venous or arterial thrombosis. On average, 0.45 ml containing 225IE thrombin were injected. In one case, an initially successfully occluded aneurysm was found to be reperforated at the following day. After a second successful thrombin injection, there was, again, a reopening of the aneurysm at control. The patient was then referred to surgery. All other patients continued to have complete occlusion at duplex control. Three patients did not receive thrombin because of a wide connection of the aneurysm with the artery and were revised surgically.

Conclusion: Femoral pseudoaneurysms with a size smaller than 2cm can generally be treated with compression therapy. Larger pseudoaneurysms can successfully be occluded by thrombin injection with a very low complication rate. Only wide necked aneurysms should be sent to surgery since the risk of arterial occlusion following thrombin injection cannot be excluded.

P1492 Hybrid interventions in complex aortic aneurysms and dissections: the frozen elephant trunk



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Background: The treatment of complex aortic aneurysms and dissections involving the aortic arch as well as the descending aorta remains one of most challenging issues for the surgeon as well as the interventionalist. The "elephant trunk" procedure, a two-step approach, and its variations, the "reversed-" and "bi-directional elephant trunk" became the treatment of choice for combined aortic arch and descending aortic aneurysms.

Aim: Aim of this study was to determine if the use of a hybridprosthesis ("frozen elephant trunk"), combining the "elephant trunk" technique and an endovascular approach is feasible and reduces the risk normally associated with a two-step approach.

Patients and Methods: The device used in our series is an E-vita Open hybridprosthesis (Jotec, Hechingen, Germany) made out of a woven polyester tube graft and a selfexpandable nitinol stentgraft available in sizes 24 to 40 mm. Performance of this device was demonstrated in two patients in need of complex aortic surgery. Patient #1 presented with an aneurysm of the ascending aorta, the aortic arch and the proximal descending aorta of about 65mm. The aortic root was severely dilated and the patient had severe aortic valve insufficiency. Patient #2 presented with a 50mm dilatation of the remaining part of the ascending aorta, the aortic arch and the proximal part of the descending aorta 8 years after implantation of a composite graft. Operations were performed in deep hypothermic circulatory arrest with selective antegrade cerebral perfusion via the right subclavian artery and stentgraft placement under x-ray control.

Results: We experienced no problems in placing the stentgraft. Exclusion of the aneurysm could be achieved in all cases. Both patients had an uneventful postoperative hospital course and were discharged on the 10th postoperative day. The 6 month follow-up using CT scans showed excellent postoperative results.

Conclusion: The use of the new E-vita Open hybridprosthesis is a safe and efficient option in the treatment of complex aortic pathologies and effectively combines surgical and interventional technologies. Compared to a two-step "elephant trunk" procedure, the "frozen elephant trunk" technique provides access to the complete thoracic aorta combined with an acceptable perioperative risk.

P1493 MRI guided balloon angioplasty of coarctation of the aorta: assessment of feasibility and first clinical results



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Purpose: Balloon angioplasty of coarctation of the aorta (CoA) is currently performed under x-ray angiography. MRI guidance of this procedure would be desirable to enable continuous visualization of function and morphology and to eliminate x-ray exposure. The aim of this study was (1) to assess the suitability of an iron oxide based contrast medium for MRI guided balloon angioplasty and (2) subsequently to apply this MRI technique to patients with CoA.

Methods: Catheter tracking was based on interactive real-time MRI (irMRI). The concentration of iron oxide based contrast medium (Resovist, Schering) that produced optimal signal contrast between the balloon catheter and its background anatomy was determined in-vitro and in pigs (n=4). After experimental evaluation the method was applied to patients with native CoA (n=5). To assess the stenosis a whole-heart isotropic 3D scan was performed prior to and immediately after intervention. IrMRI guided balloon angioplasty was realized with Resovist filled catheters and invasive pressures were determined online during the procedure. All hemodynamic and morphologic data were confirmed during conventional x-ray angiography performed before and after MRI.

Results: In the in-vitro and in animal experiments optimal signal contrast between the balloon catheter and its anatomical background was noted during irMRI at concentrations of 1.25% Resovist. In the patients MRI enabled us to assess the site of stenosis prior to intervention, to safely perform balloon angioplasty and to determine the degree of stenosis after the procedure. In all patients balloon dilation resulted in significant widening of the stenosis and a decrease in pressure gradients. There was excellent agreement between pressure and angiographic data as determined with MRI and conventional x-ray fluoroscopy.

Conclusion: Resovist MR contrast medium is well suited to safely perform MRI-guided balloon angioplasty of CoA. This interventional MRI method represents a potential alternative to conventional x-ray fluoroscopy for catheter based treatment of patients with CoA.

P1494 Intraluminal two-dimensional and Doppler ultrasonography depicts detailed pathology in type B aortic dissection and safely guides emergency fenestration



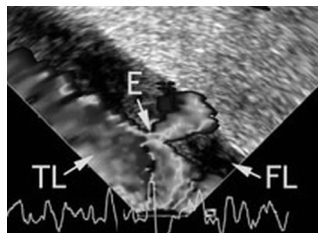
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Purpose: To evaluate the diagnostic value of intraluminal phased-array imaging (IPAI) in type B aortic dissection. Prospective, quadruple-blinded comparison of IPAI with intravascular ultrasound (IVUS), transoesophageal echocardiography (TEE), and angiography was performed.

Methods: Twenty-three patients (mean age 62 ± 13 years) with acute (n=6) or chronic (n=17) type B aortic dissection were included. After completion of TEE, two other examiners carried out angiography and positioned an AcuNav-catheter inside the true lumen (TL). An IVUS-catheter was then introduced into the TL by a fourth examiner. All examiners were blinded to each other. Two additional patients with type B aortic dissection developed peripheral malperfusion due to true lumen collapse. In these individuals, an AcuNav-catheter was inserted into the inferior vena cava in order to guide emergency fenestration of the intimal flap.

Results: The ability of IPAI to depict TL and false lumen (FL), to localize which abdominal arteries (left and right renal artery, superior and inferior mesenteric artery, and coeliac trunk) originate from the TL and FL, and to identify all entries and reentries was tested. TL and FL could be equally well identified by all diagnostic methods. IPAI detected more entries than IVUS (3.0 ± 1.2 vs. 0.8 ± 0.5 ; $p < 0.001$) and thoracic IPAI depicted more entries than TEE (1.8 ± 1.0 vs. 1.2 ± 0.5 ; $p < 0.001$). Both IPAI and IVUS showed $> 90\%$ of the abdominal side branches. In both patients with peripheral malperfusion, successful emergency intimal flap fenestration was safely guided by IPAI.



Conclusions: In the detailed diagnostic evaluation of type B aortic dissection,

IPAI is superior to IVUS and TEE. IPAI is also very useful for guiding emergency intimal flap fenestration.

P1495 Long-term follow up of 100 patients after percutaneous intervention of the subclavian artery



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Background: Percutaneous intervention of peripheral arteries is a well accepted approach for treatment of peripheral lesions. However there are only few data about long-term follow up of a percutaneous approach of subclavian artery stenosis/occlusions.

Aim of the study: Assessment of relevant restenosis after endovascular revascularisation of the subclavian artery.

Method: Between September 1996 and October 2004 we assessed non-invasively target vessel restenosis after percutaneous intervention of the subclavian artery or brachiocephalic trunk.

Results: We included 100 in most cases symptomatic (82%) patients (male 51%; mean age 65 ± 10.6) with a high risk profile (dyslipidemia 83%, arterial hypertension 72%, nicotine 55%, diabetes mellitus 26% and stenosis (>70%) or occlusion of the left (82%) subclavian artery or the brachiocephalic trunk (18%). With exception of one case revascularisation with stentangioplasty (76%), balloon-angioplasty (20%) or atherectomy (3%) was successful with a low complication rate (2 false aneurysms). The results of the patients seen in our clinic are shown below (table 1). To complete the missing date ambulatory follow up was initiated.

Table 1

Follow up	Restenosis>50%	In-Stent	TLR	BP-Delta syst.	p
Post-intervention	1 (1,2%)	0	0	12 ± 17	<0,001
6 months n= 51	14 (27,4%)	10	5 *	26 ± 32	0,110
1 year n= 45	4 (8,8%)	1	4 **	21 ± 25	0,006
2 years n= 26	0	0	3 ***	20 ± 28	0,032
3 years n= 19	0	0	1 ****	27 ± 38	0,256
4 years n= 10	2 (20%)	2	1 *****	15 ± 12	0,092
5 years n= 6	1 (16,7%)	0	1 *****	14 ± 11	0,006
7 years n= 4	0	0		14 ± 11	0,028

TLR= Target Lesion Revascularisation; * 1xTEA-Patch, 4x stent, 1xPTA, 1x PTFE-bypass; ** 3x stent, 1x cutting; ***1xPTA, 1x Re-PTA, 1x bypass; **** 1xstent; ***** 1 x PTA; ***** 1 x stent

Conclusion: Percutaneous intervention is a save and efficient approach for acute/chronic lesions of the subclavian artery or the brachiocephalic trunk.

P1496 Transplantation of embryonic stem cell derived endothelial cells promotes functional recovery after transient cerebral ischemia



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Background: Stroke is a leading cause of death and disability. But despite intensive research, few treatment options exist. Cell therapy, such as cells from stem cells, immortalized cell lines, bone marrow and umbilical cord blood cells as implant sources which have been investigated in preclinical trials. Preliminary observations suggest that cell transplantation may be a viable stroke therapy. Few studies have assessed the behavior of ESC-derived endothelial cells (ECs) transplantation. It is important to determine how these ESC-derived ECs respond to the ischemic brain and to mobilize, integrate, and reconstitute the complex and widespread neuronal-endothelial interrelationships through revascularization and angiogenesis.

Methods: Mouse ESCs were genetically modified that stably expresses the EC specific promoter for VE-Cadherin driving a GFP reporter gene, as well as reporter genes for bioluminescence and PET. Endothelial cell lineage were induced by sequential culture and purification steps of differentiation of ESCs. The purified EC progenitors were further cultured for expansion and proliferation. Endothelial lineage was examined using antibodies against endothelial specific markers. Adult male Sprague-Dawley rats (n=30) were anesthetized and focal cerebral ischemia were induced using suture-induced middle cerebral artery occlusion (MCAO). Two hours after occlusion, 5X 10⁵ ESC derived ECs were injected through common carotid artery. Bioluminescence imaging were performed using the Xenogen In Vivo Imaging System after cell transplantation. Immunohistochemistry was performed.

Results: 1, 3, 7, and 14 days after cell transplantation, we observed bioluminescence in the region of the lesion when cells were injected through common carotid artery. Intriguingly, we did not observe any signal in uninjured contra-lateral cortex region. Furthermore, we observed GFP positive cells in the luminal lining of some small vessels in the ischemic area by immunohistochemistry 14 days after cell transplantation. We observed improved blood flow and oxygen uptake with PET and neurological evaluation.

Conclusion: ESC derived endothelial cells were able to mobilize, integrate into cerebral ischemic injury region, contribute to revascularization and promote functional recovery.

P1497 Dose and regimen effects of intramuscular NV1FGF in patients with critical limb ischemia: a randomized, double-blind, placebo controlled study



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Purpose: Peripheral arterial disease (PAD) is a major health care problem and critical limb ischemia (CLI) is the most severe form of PAD. Patients with CLI are at major risk for limb amputation and death with limited treatment options beyond revascularization. NV1FGF is a pCOR[®] plasmid for expression of fibroblast growth factor-1 (FGF-1) to promote therapeutic angiogenesis.

Methods: Conducted in United States, PM202 was a phase II randomized, multicenter double-blind, placebo-controlled, dose and regimen finding study, in patients with CLI. Patients were randomized to placebo, or 1 of 5 treatment regimens of 2 to 16 mg, delivered via 8 intramuscular injections in the affected leg every 2 weeks for 4 sessions. The primary endpoint was change in TcPO₂. Secondary measures included changes in toe or ankle pressure, ulcer healing, incidence of amputation and death, and PK.

Results: 71 patients were randomized. There was an increase in TcPO₂ and hemodynamic parameters in all 6 groups, but there were no differences between groups. In addition, there were no statistically significant differences between individual groups for other main secondary efficacy parameters. Safety measures were similar across the groups.

Conclusions: This study and a parallel study performed in Europe which led to a reduction in death and amputation, provide the first data from placebo-controlled gene transfer studies in patients with CLI. Intramuscular delivery of up to 16 mg of NV1FGF is safe and well tolerated. Results from this placebo-controlled study provide valuable insight into the potential utility of NV1FGF in CLI.

P1498 Safety and feasibility of intra-arterial autologous bone marrow mononuclear cells transplantation in acute ischemic stroke



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Purpose: In animal models, stem cells enhanced functional recovery after stroke. Furthermore, recent publications indicate that the intracoronary injection of autologous bone marrow mononuclear cells (BMMC) in humans is safe. We hypothesized that intra-arterial autologous BMMC transplantation is safe and feasible in acute ischemic stroke.

Methods: This open label phase I trial was designed to include 10 patients and 5 controls with ischemic stroke involving the territory of the middle cerebral artery (MCA) with a NIH stroke scale score (NIHSS) between 4 and 20 and confirmed patency of the MCA by transcranial Doppler (TCD) and magnetic resonance angiography. Between the third and the fifth day after stroke onset, bone marrow cells were harvested from the posterior iliac crest. BMMC were through Ficoll gradient and diluted in saline for injection. On the same day, 30 million BMMC were injected into the MCA via catheter angiography. The procedure was monitored by TCD and electroencephalography. Baseline and 4 month follow-up brain perfusion with 99mTc-ECD SPECT; PWI/DWI-MRI and brain PET-FDG were performed and clinical assessment was quantified by the NIHSS, Barthel Index (BI) and the modified Rankin Scale (mRS).

Results: We report the results of the first 6 patients of the active group (49.8 ± 7.8 y/o; 4 male). No EEG abnormalities or significant micro-embolic signals were observed during BMMC injection. Median NIHSS; mRS and BI were 10.9 ± 4.5 ; 3.4 ± 1.1 and 59.2 ± 47 at baseline; 8 ± 5.5 ; 2.1 ± 1.5 and 57 ± 44 at 1 week and 6.8 ± 4.4 ; 2.5 ± 1 and 75 ± 31.6 at 1 month; 3.8 ± 3.4 ; 2 ± 1 ; 87.5 ± 10.3 at 4 month after procedure, respectively. One of the patients assigned to the treatment group had a stroke at the beginning of the procedure and did not undergo to cell injection. No complications were found up to 4 month follow-up in any patient submitted to BMMC injection.

Conclusions: These initial data suggest that intra-arterial injection of autologous BMMC in the MCA is feasible and safe after an acute ischemic stroke. Further studies are required to assess the efficacy of this procedure.

CORONARY AORTIC INTERVENTION

P1499 Long-term results of percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism using the Amplatzer PFO Occluder



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Background: Patent foramen ovale (PFO) has been associated with cryptogenic stroke. Percutaneous PFO closure has been shown safe and feasible using a wide variety of devices, and its clinical efficacy appeared favorable compared with medical treatment. However, all closure devices are not alike, and in our experience, the Amplatzer PFO Occluder was associated with the lowest risk for complications and the highest rates of complete closure.

Methods: Between Nov. 1998 and Nov. 2004, 390 patients (age 51±12 years; 56% male) with both PFO and at least one ischemic stroke, transient ischemic attack (TIA), or peripheral embolic event presumably due to paradoxical embolism underwent percutaneous PFO closure without echocardiographic guidance, using the Amplatzer PFO Occluder. An 18 mm device was used in 47 patients, a 25 mm device in 288 patients, and a 35 mm device in 55 patients. The mean number of clinically apparent embolic events prior to the intervention was 1.6, and 132 patients (34%) had more than one event. An atrial septal aneurysm was present in addition to the PFO in 120 patients (31%). All patients were followed prospectively for up to 6 years.

Results: The implantation procedure was successful in all patients (100%). There was only 1 procedural complication (0.3%; AV fistula requiring elective surgical correction), without any long-term sequelae. Contrast transesophageal echocardiography after Valsalva maneuver at 6 months showed complete abolition of right-to-left shunt via PFO in 90% of patients, whereas a minimal, moderate, or large residual shunt persisted in 7%, 2%, and 1%, respectively. During a mean follow-up period of 2.2±1.4 years (median 1.9 years; total 808 patient-years), 2 deaths (1 road traffic accident, 1 cancer), 1 ischemic stroke, 2 TIAs, and no peripheral emboli were reported. Survival free from recurrent ischemic stroke, TIA, or peripheral embolism was 99% at 1 year, 99% at 2 years, and 98% at 5 years.

Conclusions: The present study attests to safety, feasibility and long-term efficacy of percutaneous PFO closure using the Amplatzer PFO Occluder for secondary prevention of paradoxical embolism in a large cohort of patients.

P1500 Transcatheter PFO closure mitigates aura migraine headaches abolishing spontaneous right-to-left shunting



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Background: patent foramen ovale (PFO) has been implicated in the etiology of migraine headache with aura (MHA) but the mechanisms that link right-to-left shunt to MHA are unclear and the reports on the efficacy of transcatheter PFO closure on MHA prevention are scarce.

Methods: we reviewed the clinical records of 131 consecutive patients underwent successful transcatheter PFO closure at our institution at a mean age of 45±13 years because of cryptogenic stroke. 35 out of the 131 patients (27%) had a diagnosis of MHA made by the primary care physician or the referring neurologist. MHA incidence and severity were assessed by using migraine disability assessment questionnaire (MIDAS). Presence and magnitude of right-to-left shunt was assessed in all patients by means of transesophageal echocardiography and also by means of transcranial Doppler (TCD) in the last 50 patients (38%).

Results: Patients with MHA had a higher prevalence of thrombophilia (p=0.007), a more complex atrial septal anatomy (p=0.001) and they also had higher prevalence of spontaneous right-to-left shunt and of spontaneous large shunt, both at transesophageal echocardiography (p=0.015, and p=0.028 respectively) and at TCD (p=0.036, and p=0.038 respectively). After the procedure 32/35 patients (91%) had either complete resolution or significant improvement in their MHA. At a mean follow-up of 1.7±1.3 years, MHA disappeared completely in 29/35 patients (83%). Of the remaining 6 patients, 3 patients (8%) had an improvement of ≥ 2 grades in the incidence and severity of MHA, 2 patients did not show any improvement of their MHA, whereas 1 patient reported a severe relapse of MHA about 1 year after the procedure.

Conclusions: in patients with PFO, MHA is associated with spontaneous large right-to-left shunt and thrombophilic conditions. Transcatheter defect closure seems to be an effective and safe mean to treat MHA in patients with PFO.

P1501 Intracardiac echocardiography in percutaneous closure of patent foramen ovale: a faisability study



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Background: Transoesophageal echocardiography (TEE) has been successfully used for guiding transcatheter device closure of atrial septal defect and patent foramen ovale (PFO). However, TEE is uncomfortable for the patient and requires often general anesthesia. Experience with intracardiac echocardiography (ICE) guidance is still limited so far.

Methods: We prospectively collected data of 44 consecutive patients (pts) (F: 19, age: 27-73 y.) referred for percutaneous closure of PFO after cryptogenic stroke (65%), transient ischaemic attack (29%), paradoxical embolism (2%), migraine (2%) or platypnea-orthodeoxia syndrome (2%). All pts underwent trans-thoracic and TEE during work-up. Interatrial septal aneurysm (> 11 mm excursion in TM mode) was present in 86% of the pts. PFO closure with Starflex occluder in 43 pts (NMT Medical Inc, Boston, MA) and Amplatzer PFO-occluder in 1 patient (AGA Med Corp, USA) was achieved under fluoroscopy and systematic intracardiac ultrasound AcuNav catheter (Acuson-Siemens Co, Mountain View, CA) guidance in all pts.

Results: All pts had successful device placement. They were all awake. The ICE catheter was moved forward under fluoroscopy control from the left femoral vein through a 10 F sheath. ICE provided adequate views of the PFO and surrounding structures at the various stages of device deployment. The importance of right to left shunt and interatrial septal aneurysm was concordant with the TEE measurements obtained before intervention. There was no complication related to the use of AcuNav catheter, and adequate evaluation of the size and deployment of the device was achieved in all pts. The median fluoroscopy time was 9.2 minutes (range 5-21 min). Mean in hospital stay was 1 day less in the ICE group of pts than in the TEE group we treated before the ICE era, thanks to the absence of general anesthesia.

Conclusion: ICE provides excellent images of the PFO and surrounding structures and is a safe alternative to TEE-guided percutaneous PFO closure. ICE improves the safety of this percutaneous technique, without the disagreement and risk of general anesthesia required by TEE guidance. Finally, it tends to reduce in hospital stay.

P1502 Percutaneous septal ablation after previous myectomy in hypertrophic obstructive cardiomyopathy



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Purpose: Surgical myectomy (SMY) is considered the standard therapy for patients (pts.) with highly symptomatic obstructive hypertrophic cardiomyopathy (HOCM). Septal ablation (PTSM) has emerged as an alternative during the last decade. We report on the acute and 12-months follow-up results in those pts. who had a PTSM procedure for recurrent left ventricular outflow obstruction (LVOTO) after previous (2-10 years) SMY.

Results: Recurrent LVOTO after SMY was present in 10 out of 401 pts. (3% of our PTSM cohort). On echocardiography, LVOTO was caused by an insufficient subaortic trough in all these cases, in one pt., marked mitral leaflet elongation was additionally involved. A permanent pacemaker (DDD-PM) had been implanted after SMY in 2 pts. All PTSM procedures were guided by intra-procedural echocardiography; there was no in-hospital mortality. Mean CK rise was 633±427 U/l after injection of 4±3 (1-6) ml of ethanol. The resting gradient acutely dropped from 76±23 to 10±8, the post-extrasystolic gradient from 132±50 to 43±24 mm Hg (p<0.0001, resp.). With a pre-existing left bundle branch block (LBBB) in 5, and a bifascicular (RBBB + left anterior hemiblock) in 2 pts., a permanent DDD-PM was necessary in 2 additional pts. (20%). After 12 months, all pts. reported significant clinical improvement (NYHA class: from 3.0±0.5 to 1.7±0.9; p<0.0001). Exercise capacity improved from 87±42 to 113±33 watts (p<0.01). Echocardiography showed a sustained reduction of LVOTO (at rest: 5±9, with stress: 10±12 mm Hg) and left atrial size (from 55±9 to 48±7 mm; p<0.0001, resp., vs. baseline).

Conclusion: LVOTO recurrence occasionally does occur after SMY. In these cases, echo-guided PTSM is a valuable treatment option leading to LVOTO elimination and marked clinical improvement. Due to conduction abnormalities induced by the previous SMY including LBBB, the rate of DDD-PM implantations is relatively high in this pt. subset.

P1503 Transcatheter restriction of left ventricular cavity in piglets



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Purpose: To offer an alternative to surgery in eliminating post-infarction left ventricular (LV) aneurysms in high risk patients. Transcatheter restriction of LV

aneurysms could improve morbidity and mortality associating with surgery, maintaining the benefits of improved ejection fraction and wall tension.

Methods: The procedure was performed in 12 piglets, 12-16 kg, after ketamine anesthesia. A transcatheter patch/balloon device was introduced in the left ventricle, through a 12F sheath after sub-xiphoid apical needle puncture. The device consists of a balloon catheter, with a sleeve type polyurethane patch mounted on the balloon and a floppy disk attached on the tail of the patch. The patch was inflated in diameters of 15-20 mm using normal saline or whole blood and contrast; it was pulled to the apex of the LV, with the tail of the patch occluding the residual myocardial hole and the floppy disk immobilizing the patch on the epicardium. Fluoroscopy and echocardiography were used for the device placement and the animal were followed for periods of 4 days to 3 months, when they were euthanized and had autopsies.

Results: All devices were successfully placed, restricting the left ventricular apical region. There was no significant change on the EKG or the blood pressure during the procedure. There was no case of tamponade. On follow-up all animals, except for two who develop severe infection did well. In autopsy the LV apical region was restricted although most balloons lost part of their initial volume. The residual balloon size was larger if it was inflated with whole blood. The patches were fully endothelialized within 2 weeks. They were free of thrombus.

Conclusion: Percutaneous restriction of the left ventricular apical region is feasible, simple and relatively safe in piglets. The method could be applicable in high risk patients. Feasibility clinical studies are justified.

P1504 Transcatheter mitral valve in piglets; a ball valve without a cage



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Purpose: To develop an easily placed and potentially retrievable mitral valve for temporary or long term use; the valve is based on a proximally attached balloon moving in the natural valve orifice.

Methods: Two types of valves were tested; a detachable balloon valve (DBV) attached by a cable from the groin (femoral vein) and a nitinol ball valve (NBV) covered by elastomere attached on the atrial septum. Ten DBV and 5 NBV were implanted in piglets 10-15 kg. The devices were introduced through 9-12F transeptal sheaths. The ball diameters varied between 10-15 mm. The optimal length of the attaching cable should allow forward movement of the ball in diastole and backward movement in systole eliminating any mitral insufficiency. Thirteen of the fifteen devices were released over normal valves and two over valves with insufficiency. Follow up was performed in periods from one day to one month; no anticoagulation was used.

Results: All devices were easily deployed. The valves were functional, did not cause mitral insufficiency; they improved the existing mitral insufficiency in two cases. There was one death from ascending aorta embolization and one from ventricular fibrillation (short cable). One DBV was retrieved because of leakage. In autopsy there was mild leaflet thickening with longer use, without major thrombus. One case with mitral stenosis was associated with large left atrium.

Conclusion: The ball valves can be placed easily transeptally and they are potentially retrievable; they can be potentially useful in high risk for surgery patients. The NBV is more convenient, but requires accurate septal to mitral valve length measurements. Most complications can be prevented with technical improvements.

P1505 Percutaneous closure of atrial septal defects in adults: role of intracardiac echocardiography



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Transesophageal echocardiography (TEE) has been routinely used for diagnosis and during percutaneous closure of atrial septal defects (ASD) before the deployment of specific devices. However, intracardiac echocardiography (ICE) may simplify the procedure and make it more comfortable for the patient, avoiding general anesthesia and orotracheal intubation. We describe our experience with the Amplatzer® device during ASD closure in adult patients, with the exclusive use of ICE to select device size and guide the intervention.

Methods: Forty patients (69% female, 39±12 years) with documented ASD underwent percutaneous closure with the Amplatzer® devices. ICE (Ultra ICE 9F-9MHz, Boston Scientific) was used in all cases. Bilateral femoral venous access was obtained under local anesthesia, and all patients received heparin (1 mg/kg) plus aspirin or clopidogrel. Transthoracic echocardiography (TTE) was performed the day after the intervention and at 6 months.

Results: The procedure was successful in 98% of the patients. The mean diameter of the device was 23 mm (14-34 mm). The position and size of the defect was adequately measured with ICE in all cases, and there was no need to use the sizing balloon or TEE before the implant. Mean duration of the procedure was 51±17 minutes (radiation time 9.4±6 minutes). All patients were discharged the next day after a TTE showed stable position of the device. Clinical and echocardiographic follow-up for 15±7 months was uneventful but for 2 episodes of paroxysmal atrial

fibrillation. No intracardiac shunts, embolic events, vascular complications or device embolizations were described.

Conclusions: ICE is useful and safe during percutaneous closure of ASD in adult patients, with a high success rate and very low complications. ICE can avoid the use of TEE and anesthesia during the intervention, thus making the procedure shorter and more comfortable for the patient.

P1506 Left atrial appendage occlusion in patients with atrial fibrillation and high risk of thromboembolic complications



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Background: Thromboembolic stroke is the most serious complication in the patients with nonvalvular atrial fibrillation (Afib). Long term anticoagulation therapy which significantly decrease the risk of thromboembolic complication is in general practise underused, not always tolerated by patients and sometimes is contraindicated. Recently was proved 91% of all thromboses coming from left atrial appendage (LAA) and mechanical occlusion seems to be promising method how to decrease the risk of stroke in these patients. The purpose of this study was to validate ICE to guide occlusion of LAA.

Methods and patient group: In one year we performed mechanical catheter occlusion of LAA for 32 patients in Afib with high risk stroke (CHADS₂). Up to date there are two transcatheter occluders approved in Europe for clinical use (PLAATO - ev3 Inc. and Watchman - Atritech Inc). There are several sizes of occluders for both systems. Procedure is based on transeptal puncture with guiding long sheath into LAA cavity and deploying occluders within the orifice to seal it completely. For guiding the procedure we used two ultrasound systems - transesophageal (TEE) and intracardiac (ICE) echocardiography. Before deployment we checked the size of LAA also by contrast injection. Half of the patients was sedated and for other half we used general anesthesia.

Results: In all 32 patients we finished the procedure successfully. For 9 pts we should change the size of occluder with the average time of the procedure of 46 ± 26 min. The PLAATO system was used in 25 pts and Watchman in 7. Using ICE we proved the optimal position of the ultrasound catheter in coronary sinus or right ventricle outflow tract to get long axis of LAA with appropriate measurements of long axis and short axis diameter. These measurements didn't differ from TEE and angiography measurements. Using both methods we didn't detect thrombus formation in LAA space. During follow up we performed TEE in 1 and 6 months after procedure and we didn't validated and significant communication in between LAA and left atrial cavity.

Conclusion: This was the first study validated ICE as a method for monitoring catheter occlusion of LAA in patients with Afib and high risk of stroke.

RISK ASSESSMENT IN PRIMARY AND SECONDARY INTERVENTION

P1507 Achievement of guideline-defined treatment goals in primary care in Germany: results of the Coronary Risk Management (CoRiMa) study



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Background: Optimal treatment of known risk factors is essential for reduction of morbidity and mortality in patients with coronary artery disease (CAD), hypertension, and diabetes mellitus (DM). This study investigates the efficacy of coronary risk factor treatment in patients with cardiovascular disease and/or DM in primary care in Germany.

Methods: In selected (general practitioner and internal medicine) physician offices in Germany, all patients seen between January 1998 and June 2005 were identified. The data were exported anonymously and transferred into the project database. Age, sex, blood pressure (BP), serum lipids, HbA_{1c} levels, and information regarding risk factors were analyzed. The last office visit of each patient was used for the analysis of treatment goals based on reference values stated in current guidelines.

Results: A total of 392.000 patients treated in the selected offices were analyzed. Hypertension was present in 64%, DM in 41%, CAD in 31%, and hyperlipidemia in 54%. 39.6% of all patients had cardiovascular disease and/or diabetes. These 155.187 patients are the basis of this analysis. During the last office visit, treatment goals were achieved in: total cholesterol (C): 20%; LDL-C: 30%; blood pressure: 32%; HbA_{1c} in patients with DM: 39%. For hypertension, the majority of

patients not achieving treatment goals were close to the treatment goals (51%) whereas there was substantial deviation from the treatment goals for lipid values (CAD and/or DM: LDL-C: 77% $\geq$ 100 mg/dl), and $>$ 40% of patients with DM had HbA1c-values $>$ 7% and 20% $>$ 8%.

Conclusions: (1) $>$ 60% of patients do not achieve treatment goals stated in current guidelines. (2) Although a subgroup of patients (51%) comes close to the treatment goals (blood pressure), others show significant deviation from the treatment goals (LDL-C in DM/CAD patients: 77% $\geq$ 100 mg/dl).

P1508 Visceral and total abdominal fat distributions in relation to cardiovascular events



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Objective: To examine the abdominal fat distribution using computed tomography (CT) scan in relation to cardiovascular (CV) events in a hospital population. To evaluate the correlation between waist circumference and abdominal fat distribution.

Methods: We used our administrative and medical computerized databases to design a case-control (100 cases/100 controls) study including patients hospitalized in a university hospital, who had 1) an abdominal CT scan and 2) for 'cases': an actual CV event (stroke, abdominal aortic aneurysm or ischaemic heart disease); for 'controls': no CV events matched for age and sex. Patients having a disease possibly explaining a major decrease in total fat (cancer, AIDS, hospitalization in an intensive care unit) were not included. Visceral (VAT), subcutaneous and total abdominal fat (TAT), as well as waist circumference, were measured using a single CT scan at the L4-L5 level. Cases and matched controls were compared using Wilcoxon signed rank tests. Odds ratios were estimated using conditional logistic regression. Correlations were assessed using Spearman coefficients.

Results: Patients with CV events had significantly more visceral ($p=0.035$) and total abdominal ($p=0.027$) fat than the control patients. Within the whole group of patients, a 25 cm² increase of the visceral fat area was associated with a 10% increased risk of CV events ($p=0.04$). Among patients above the median age (62.5 years), this increase was associated with a 33% increased risk of CV events ($p=0.003$), while a 40 cm² increase of total abdominal fat area was associated with a 23% increased risk of CV events ($p=0.007$); a significant association between CV events and VAT/TAT was also found ($p=0.024$). Waist circumference was strongly correlated with both visceral and total abdominal fat among both cases and controls (VAT: $r=0.76$ and 0.75 , respectively; TAT: $r=0.88$ and 0.85 respectively; all p values <0.001).

Conclusions: Both VAT and TAT excess were associated with CV events, particularly in older patients. Both measures were strongly correlated with waist circumference, a parameter that is easy to measure in clinical practice. Future prospective studies would need to be considered to confirm those results.

P1509 International comparisons of the prevalence of obesity in patients with overt cardiovascular disease



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Background: The prevalence of obesity is increasing around the world but accurate international rates have been difficult to estimate in patients with cardiovascular disease (CVD).

Methods: CardioMonitor[®] is an annual survey of outpatients with CVD developed from records provided by primary care physicians and cardiologists around the world. In the 2004 survey, details of 17,935 CVD patients including their height and weight measurements were collected in the five countries discussed below. Baseline demographic and medical history information was recorded, as well as laboratory and physical findings. Extrapolation to country populations was performed using weighting methodology based on each physician as representative of the physician population and each patient based on proportion of workload and frequency of consultation. To qualify for the survey, patients must have been diagnosed with at least one cardiovascular condition.

Results: In 2004, the majority of CVD patients in these countries (67.7% overall)

Table 1. BMI measurement in the cardiovascular population (data for Spain from mid-2004 only)

BMI (kg/m ²)	US (n=4584)	UK (n=3645)	France (n=3801)	Germany (n=3993)	Spain (n=1912)
Less than 25	25.9	31.5	45.7	29.8	28
25 - 26.9	16.4	20.3	19	23.1	26
27 - 29.9	20.5	20.8	19.3	25.3	26.2
30 and over	37.3	27.4	16.1	21.8	19.8

were overweight (BMI $>$ 25). Over half (57.8%) of the patients with CVD in the US were either significantly overweight (BMI $>$ 27) or obese (BMI $>$ 30), with nearly half meeting these criteria in the UK (48.2%), Germany (47.1%), and Spain (46.0%) but less than half (36.4%) in France. A significant portion of patients with CVD met criteria for obesity, ranging from 16.1% in France to 37.3% in the US (see Table 1).

Conclusion: With such a high percentage of patients with CVD being overweight or obese, physicians should systematically target obesity in addition to the other major risk factors, especially in the US.

P1510 Coronary artery calcifications are correlated with breast arterial calcifications, but their aetiology is predominantly different



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Objective: Vascular calcification is considered a marker of cardiovascular risk and imaging of calcium is increasingly used for cardiovascular (CV) screening purposes. It is not known whether calcifications in the breast arteries are related to coronary artery calcifications.

Methods: We studied 499 women, aged 49-70 years, participating in a breast cancer screening program and investigated whether arterial calcifications in the breast (BAC) are associated with coronary arterial calcifications (CAC) after a mean follow-up of 9 years. Baseline mammograms of all women were reviewed on the presence of BAC by two independent reviewers. CAC was assessed by multislice computed tomography (MSCT), with 3.0 mm slices, using the Agatston score. Logistic regression analysis was performed to investigate the independent effect of BAC and various risk factors and reproductive factors on the occurrence of CAC.

Results: BAC was present in 58 of 499 women (12%) at baseline and CAC score $>$ 0 was present in 262 of 499 women (53%) after follow-up. Age was the most important determinant for both BAC and CAC. In all age groups CAC was more prevalent than BAC. The presence of BAC was strongly associated with the occurrence of CAC (OR 3.2, 95% CI 1.71-6.04) and this remained significant after adjustment for age and the duration of follow-up (OR 2.1, 95% CI 1.10-4.23). Most of the coronary heart disease risk factors were associated with CAC but not with BAC. The only common risk factor was parity, which was significantly associated with both increased CAC (OR 2.1, 95% CI 1.26-3.50) and increased BAC (OR 5.4, 95% CI 1.28-22.52). Breastfeeding after pregnancy was associated with BAC (OR 3.7, 95% CI 1.55-8.83) but not with CAC (OR 1.4, 95% CI 0.95-2.08).

Conclusion: We found that breast arterial calcifications are predictive of calcifications in the coronary arteries. However, the fact that there are no common coronary risk factors for BAC and CAC suggests a predominantly different aetiology between both types of vascular calcification.

P1511 Creatinine clearance is an independent predictor of long-term mortality in middle-aged women surviving an acute coronary event



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Objectives: We have investigated the association of cardiovascular mortality and renal function among middle-aged women recovering from an acute coronary event.

Material and methods: The Stockholm Female Coronary Risk Study included females aged $\leq$ 66 years, resident in the greater Stockholm area, that were recently hospitalized for an acute coronary event between February 1991 and February 1994. A total of 292 patients were included. Extensive clinical screening was performed 3-6 month after the coronary event and the patients were followed up for a median of 9 years. The renal function was defined by measuring of serum creatinine concentration at hospital admission and we have calculated the creatinine clearance data from them according to the Cockcroft and Gault formula.

Results: Creatinine clearance data were divided in tertile categories. In our analysis the lowest creatinine clearance was the reference category, the tertile 1st. Multivariate Cox proportional hazard model was used to assess the relationship between renal function and clinical outcome. In the unadjusted model there were statistically significant differences between patients in the 3rd tertile and those with the worst renal function in the 1st tertile regarding to all-cause mortality: HR= 0.32 (0.13-0.75), cardiovascular mortality: HR= 0.27 (0.09-0.83) and combined outcome of cardiovascular mortality and recurrent events: HR= 0.43 (0.21-0.89) for the benefit of the patients with the best creatinine clearance in the 3rd tertile. After controlling for the potential confounders such as age, BMI, diabetes mellitus, index event, left ventricular dysfunction remained the difference between patients with the highest creatinine clearance and those with the lowest creatinine clearance statistically significant regarding all-cause mortality: HR:0.23 (0.06-0.93).

Conclusion: Creatinine clearance is a strong independent predictor of all-cause mortality in middle-aged women surviving an acute coronary event.

P1512 Plasma osteoprotegerin level as a biochemical marker of atherosclerosis in patients with coronary artery disease



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Background: Osteoprotegerin(OPG) is a glycoprotein that acts by competing with receptor activator of nuclear factor- κ B(RANK) for binding RANK ligand(RANKL) and plays a critical role in bone remodeling. Recently, OPG has been reported to be associated with cardiovascular disease. The aim of this study is to investigate the relation between plasma OPG level and conventional cardiovascular risk factors in patients with definite coronary artery disease(CAD).

Methods: In 583 consecutive patients(mean age: 62 ± 10 yrs, M:F=398:185) underwent percutaneous coronary intervention(PCI) in St Mary's hospital from April 2003 to February 2005, plasma OPG levels were determined at the time of coronary angiogram. Baseline clinical and laboratory data including HbA1c and hsCRP were obtained at the day of admission. Intima media thickness(IMT) of common carotid artery were also assessed among 252 patients.

Results: 1. Plasma OPG level was correlated with IMT($r=0.184$, $p=0.003$) and median plasma OPG level was elevated in accordance with the severity of CAD(2704 in 1VD vs 2914 in 2VD vs 3046pg/ml in 3VD, $p=0.024$). 2. Median plasma OPG levels were significantly higher in female(3024 vs 2828 pg/ml, $p=0.003$) and DM patients(3098 vs 2711 pg/ml, $p<0.001$) but not in hypertensive patients. 3. Plasma OPG level was positively correlated with age($r=0.340$, $p<0.001$), fasting glucose($p=0.002$, $r=0.129$) and HbA1C level($r=0.102$, $p=0.035$) but showed inverse correlation with BMI($r=-0.199$, $p<0.001$). 4. Plasma OPG level was not correlated with lipid profile and hsCRP. 5. By multivariate logistic regression analysis, increasing age(odds ratio 1.053 [95% confidence interval, 1.034-1.073]), DM(odds ratio 1.664 [95% confidence interval, 1.149-2.410]), lower BMI less than 25kg/mm² (odds ratio, 1.625 [95% confidence interval, 1.142-2.314]) was associated with supramedian OPG level(2831pg/ml) but association of female gender disappeared.

Conclusion: Plasma OPG level has close relation with the severity of CAD, carotid atherosclerosis, and also with well known cardiovascular risk factors especially DM and age. It might suggest the role of OPG as a biochemical marker of atherosclerosis.

P1513 Heavy alcohol intake and cardiovascular deaths in Russia: findings from three population studies using different designs



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Objectives: To investigate the relationship between heavy alcohol intake and cardiovascular diseases in three different population studies (cohort study, case-control study, and autopsy series) in Novosibirsk, Russia.

Methods: First, a cohort study of 6502 men aged 25-64 years at baseline examined in the WHO MONICA surveys in 1985/86, 1988/89 and 1994/95 and in a pilot in 1984 (average follow-up 10.3 years). Second, a case control study of myocardial infarction (MI); 390 cases aged 25-64 years registered in one Novosibirsk district were compared with population-based controls. Third, autopsy was conducted on representative sample of sudden cardiac deaths (SCD); 415 cases aged 25-64 in the same Novosibirsk district.

Results: In the cohort study, the adjusted relative risk of death from MI, coronary heart disease or cardiovascular diseases (CVD) was not related to typical alcohol dose or drinking frequency, but CVD mortality was elevated in a small group of frequent binge drinkers (≥ 120 g of ethanol at least 3 times a week; RR=2.1; 95% CI 1.1-3.9). In the case-control study, alcohol intake during the year preceding the MI or the interview did not differ between cases and controls, except of a lower proportion of non-drinkers among cases. However, binge drinking sessions during the week prior MI was more common in fatal cases than in non-fatal events (38.5% vs 10.8%, $p<0.001$; OR=5.2; 95% CI 2.2-12.2). In the autopsy study, 16% of SCD cases had blood alcohol concentrations indicating mild intoxication (0.3-1.5‰), 7% had moderate/severe intoxication (1.5-3.0‰) and 9% had potentially lethal alcohol level (>3.0 ‰). High concentrations of alcohol were more common in SCD cases with multiple coronary plaques than in cases with no plaques and/or with coronary stenosis.

Conclusion: These three studies support the hypothesis that heavy or binge drinking is associated with increased risk of CVD death. The case-control study and the autopsy series suggest that at least some of this association is due to acute effects of alcohol intoxication.

P1514 Impact of an interleukin-10 promoter polymorphism on life-span: the ohasama study



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Background: Pro- or anti-inflammatory cytokines are reported to affect individual life-span expectancy by influencing the type and intensity of the immune-inflammatory responses against environmental stressors. Genetic polymorphisms responsible for a lower inflammatory response may better control inflammatory responses involved in atherogenesis and reduced the risk of atherogenesis complication. IL-10 is an appropriate candidate because it exerts powerful inhibitory effects on pro-inflammatory function. IL-10 production is controlled by several polymorphisms in promoter region of the IL-10 gene. Therefore, these polymorphisms might result in an increased chance of long life-span.

Methods and Results: We recruited 1,659 subjects in a rural Japanese community (the Ohasama Study). We analyzed single-nucleotide polymorphisms (-592C/A) in the IL-10 gene by the TaqMan chemical method. There was a significant difference in age among the genotype. Therefore, we divided this population into two groups by a median-age (59 years). There was a significant difference in the distribution of the genotypes between the two groups ($p<0.03$). The frequency of the -592A allele was significantly higher in the older group than in the younger group ($p<0.01$).

Conclusions: The possession of the -592A allele in the IL-10 gene is significantly increased in the older population of the Ohasama study. This polymorphism may be associated with longevity.

P1515 Asymmetric dimethylarginine/dimethylamine ratio in patients with coronary artery disease



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An elevated plasma level of asymmetric dimethylarginine (ADMA) is a major risk factor for coronary artery disease (CAD) and predicts coronary events. Mechanistically, ADMA induces endothelial dysfunction by inhibition of the endothelial nitric oxide synthase and impairs number and function of endothelial progenitor cells. ADMA is metabolised by dimethylarginine dimethylaminohydrolases (DDAH) to yield citrulline and dimethylamine (DMA). DDAH activity may be estimated by the ratio of DMA to ADMA. Little is known about the ratio of urinary ADMA and DMA in patients with coronary artery disease. Seventy-seven consecutive patients admitted to hospital because of stable angina aged 39 to 83 years (mean age 65.9 ± 1.1 years) were enrolled. All patients underwent cardiac catheterization and were divided in patients with no CAD or 1-3-vessel disease. The urinary DMA/ADMA ratio was significantly increased in patients with 3-vessel disease (22.0 ± 4.7 vs. 13.7 ± 1.1 ; $p=0.014$ vs. patients without CAD). In a stepwise multivariate regression analysis the DMA/ADMA ratio correlated with ejection fraction (standardized coefficient -0.39; $p=0.003$) and C-reactive protein (standardized coefficient 0.30; $p=0.001$), but was independent of age, gender, plasma or urinary creatinine, total cholesterol, LDL, HDL, presence of diabetes or high blood pressure. Urinary DMA/ADMA ratio is increased in patients with severe coronary artery disease and correlates with ejection fraction. Its potential clinical value in the diagnosis of coronary artery disease or cardiac dysfunction is intriguing, but warrants further studies.

P1516 Poor exercise capacity increases the likelihood of left ventricular hypertrophy in pre-hypertensive men and women



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Background: Left ventricular hypertrophy (LVH) is an independent cardiovascular risk factor and it is more closely related to exercise BP and 24-hr BP than casual BP. Since fitness is associated with lower exercise and 24-hr BP, we sought to determine if fit, pre-hypertensives have lower exercise and 24-hr BP and lower risk for LVH than unfit pre-hypertensives. Thus, we assessed cardiac and exercise parameters and 24-hr BP.

Methods: Pre-hypertensive men and women ($n=790$; age= 52 ± 10 yrs), non-smokers, free of overt heart disease were consented to undergo echocardiographic assessments, exercise stress test and 24-hour BP. LVH was considered as left ventricular mass (LVM) index >104 g/m² for women and >116 g/m² for men. Low, Moderate and High-Fit categories were established based on exercise time adjusted for age.

Results: Significant correlations were noted between exercise BP, 24-hr BP and LVM index. Over 22% of pre-hypertensives had LVH. The risk was 2.6 times higher in Low versus Moderate and High-Fit individuals. There was a 40% reduction in the risk for LVH for every 1-MET increase in the workload (OR: 0.60; CI: 0.52-0.69). After adjusting for age, BMI and resting BP, Moderate and High-

fit groups had significantly lower LVM index, 24-hr BP and exercise BP. The strongest predictors of LVH were daytime systolic BP (OR: 1.18; CI: 1.14-1.22) and systolic BP at the exercise intensity of 5 METs (OR: 1.17; CI: 1.13-1.21). Exercise systolic BP threshold for LVH was ≥ 150 mm Hg. There was a 4.7-fold increase in the likelihood of having LVH for every 10 mm Hg increase above this threshold.

Fitness levels, LV mass and BP

	LVM Index	Rest SBP	Daytime SBP	5-MET SBP
LOW-FIT	102 $\pm$ 24*	131 $\pm$ 7	147 $\pm$ 12*	156 $\pm$ 15*
MOD-FIT	92 $\pm$ 20	132 $\pm$ 6	140 $\pm$ 9	147 $\pm$ 10
HIGH-FIT	89 $\pm$ 19	130 $\pm$ 6	139 $\pm$ 9	144 $\pm$ 10

Conclusions: 1) Low-fit, pre-hypertensive individuals have a higher likelihood of LVH than moderate and high-fit. There is a 40% reduction in the risk for LVH for every 1-MET increase in the workload. 2) The strongest predictors of LVH were exercise systolic BP at 5 METs and daytime systolic BP. 3) The threshold for LVH is ≥ 150 mm Hg and the likelihood of having LVH increases by 4.7-fold for every 10 mm Hg increase above this threshold.

P1517 Dynamics of serum C-reactive Protein (CRP)

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CRP is one of the central "players" in the search of the place of inflammation in cardiovascular pathology-one of "acute phase reactants". Many cardiovascular events by their timing and outcome show significant links with such cosmophysical parameters: Solar, Geomagnetic (GMA), Cosmic Ray (CRA) activity, space Proton flux. The aim of this study was to check the relationship between level of CRP with the level of Solar, GMA and CRA.

Methods: 25399 CRP test - data from an University hospital performed in years 2002-2004 was compared monthly and daily with concomitant Solar, GMA and CRA (Neutron) activity. The cosmophysical data come from NOAA, USA, Russian Academy of Science.

Results: By monthly (n=36) comparison CRP failed to correlate with GMA (r=0.258, p=0.13), but inverse links with Neutron activity (r=-0.35, p=0.03) were significant; daily (n=1057) it was a correlation with GMA (r=0.97, p=0.02) and, inverse, with Neutron activity (r=-0.97, p=0.025) by comparison of CRP levels (mg/dl) with 422-I, 433-II, 172-III and 32-IV degrees of daily GMA. The CRP on I GMA days - 3.8mg/dl $\pm$ 3.16- was lower compared with higher degrees (II-IV) of GMA (P=0.0002 - 0.00003), in 9084, 11079, 4351, 865 tests. Daily Neutron activity higher on days of 0-1.0 mg/dl (n=289) and 0-1.5 mg/dl (n=1213), compared with higher (>1.5) CRP values (n=23897), (p<0.0001).

Conclusion: the level of serum CRP, in addition to links with inflammation, is linked with daily level of GMA and, inverse, with Neutron activity.

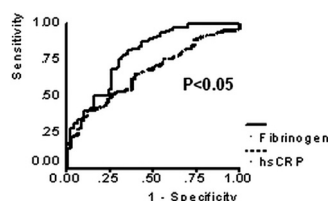
P1518 Prothrombotic markers predict the presence of erectile dysfunction

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Purpose: Recent studies have shown that erectile dysfunction (ED) is associated with atherosclerosis. Aim of the present study was to evaluate the prothrombotic (fibrinogen and von Willebrand Factor [vWF]) and inflammatory (high-sensitivity C-reactive protein [hsCRP]) state in men with ED and to investigate whether such markers are predictive of the presence of impaired sexual performance.

Methods: Erectile function was evaluated in 121 consecutive men (mean age 58.6 years). ED was diagnosed with medical and sexual history, and a score of the 5-item Sexual Health Inventory for Men <21. Levels of the above mentioned markers were measured in venous blood.

Results: All markers were significantly increased in patients with ED (n=71) compared to subjects without ED (n=50), after adjusting for age, systolic BP and risk factors (fibrinogen: 317 vs 242 mg/dL; vWF: 91.7 vs 70.1%; hsCRP: 1.51 vs 1.05 mg/L; all P<0.01). ROC curve analysis for the prediction of the presence of ED showed that areas under the curve (AUCs) for fibrinogen, vWF and hsCRP level were 79% (95% CI: 71 to 87%), 75% (66 to 84%) and 67% (57 to 76%) respectively. AUC for fibrinogen was significantly greater than AUC for hsCRP (difference between AUCs 12.2%, 95% CI: 2.2 to 22.2%, P<0.05, Figure). A fibrinogen value



> 255 mg/dL combined with vWF >77% was the best predictor of ED (63% sensitivity, 82% specificity, and 83% positive predictive value).

Conclusions: Erectile dysfunction is associated with increased levels of prothrombotic and inflammatory markers, but the former are better predictors of impaired sexual performance. These findings underscore the pathophysiological involvement of endothelial prothrombotic activation in ED and have implications for increased cardiovascular risk in these patients.

P1519 Comparison of the cardiovascular risk of workers in Spain and Cuba

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Purpose: to compare the cardiovascular risk prevalence in population samples of workers from Spain and Cuba, with a coronary heart disease (CHD) mortality of 54/100,000 and 111/100,000 inhabitants, respectively.

Methods: We included the 179 Cuban workers from a single chemical company (year 2005), and 1,483 Spanish workers from a variety of labour environments taken from a random population representative sample recruited from 1995 to 2000, all aged 30-59 years and with no history of CHD. All measurements used comparable standard methods.

Results: See Table. Cuban workers had more education and showed less smoking, diabetes and obesity than the Spanish sample. Total, high- and low-density lipoprotein (HDL and LDL) cholesterol, glycaemia and body mass index were significantly lower. The average 10-year cardiovascular risk of the Spanish population was twice that of Cuban workers.

Table

	Cuba	Spain	p-Value
Age (years)	40.5 (7.9)	44.2 (8.2)	<0.001
Women (%)	58.1%	45.1%	0.001
Some college (%)	24.6%	16.0%	0.004
Smoker or ex-smoker < 1 year	22.3%	33.4%	0.003
Hypertension (TA > 139/89, treated or history)	35.8%	29.5%	0.083
Systolic blood pressure (mmHg)	121 (18)	126 (18)	0.001
Diastolic Blood pressure (mmHg)	80 (12)	80 (10)	0.531
Dyslipaemia: treatment or LDL > 159mg/dl	27.9%	35.1%	0.576
Total cholesterol (mg/dl)	206 (46)	218 (42)	<0.001
HDL cholesterol (mg/dl)	42 (10)	52 (15)	<0.001
LDL cholesterol (mg/dl)	136 (45)	145 (38)	<0.001
Impaired fasting glycaemia	2.2%	13.3%	<0.001
Diabetes	1.1%	6.3%	<0.001
Body mass index	25.3 (4.3)	26.9 (4.6)	<0.001
10-year CV risk (REGICOR: Framingham adapted)	3% (2)	4% (3)	<0.001

Demographic and risk factor characteristics in working populations aged 30 to 59 years in Cuba and Spain

Conclusions: The lower HDL-cholesterol levels and higher hypertension prevalence could explain the paradoxically higher cardiovascular mortality rates with an overall lower cardiovascular risk profile in Cuba than in Spain.

P1520 Coronary atherosclerosis in HIV infection: a marker of advance disease?

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Background: With the protective effects of antiretroviral therapy and improved treatment of opportunistic infections, patients with HIV infection are living longer and presenting with different clinical characteristics. Coronary artery disease (CAD), which is a common cause of morbidity and mortality in the overall population, is overrepresented in patients with HIV infection. Aim of this study is to describe the clinical, immunologic, and angiographic characteristics of patients with HIV infection and suspected CAD, in order to investigate the presence of a potential cause-effect link between HIV infection and CAD.

Methods: Forty-seven consecutive patients with HIV infection who underwent coronary angiography at our Institution between 1996 and 2002 were enrolled. A group of 100 patients without HIV infection were selected matching the date of procedure, and considered a control group. A Chi-square test (or Fisher's exact test, when necessary) was used for qualitative variables, while T test for unpaired data was used for quantitative variables.

Results: When compared to the control group, HIV-infected patients were significantly younger (46 $\pm$ 8 yrs vs 56 $\pm$ 12, P<0.001), more often males (85% vs 53%, P<0.001), and were more often smokers (66% vs 32%, P<0.001), while no differences were noted in the other risk factors (hypertension, diabetes, hyperlipidemia, family history). At coronary angiogram, HIV patients were more often found to have significant (>50% diameter stenosis in one or more major coronary artery) CAD (68% vs 58%, P=0.040), and more often had triple vessel disease or left main disease (30% vs 21%, P=0.010). When comparing HIV+ patients with CAD to those without CAD, no differences were found in prevalence of risk factors, duration of HIV diagnosis, or viral load, whereas the CD4 count was signifi-

cantly lower in patients with CAD (249 ± 89 vs 496 ± 147 , $P=0.02$). No difference was found in the use of antiretroviral therapies. Co-infection with HBV was associated with significantly higher risk of having significant CAD (OR 13.0 [1.18-334.0], $P=0.017$).

Conclusions: HIV infected patients referred for coronary angiogram are more often male and smokers, and are more likely have significant coronary artery disease, with a greater prevalence of triple-vessel and left main disease. Although this difference may simply due to referral biases, the finding of lower CD4 counts in HIV+ patients with CAD compared to HIV+ patients without CAD may suggest that advanced HIV (and AIDS) may promote coronary atherosclerosis progression.

P1521 Cardiac troponin I elevation in healthy female individuals: a population based 10-year survival study



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Hypothesis: the 99th percentile troponin concentration in apparently healthy individuals is commonly used as the upper reference limit of normal. Recent data show higher reference values for troponin immunoassays in subgroups such as males and older individuals. Little is known with regard to the incidence and impact of elevated troponin in apparently healthy women.

Methods: a population based cohort of 6311 women, participating in the Eindhoven Perimenopausal Osteoporosis Study, was followed for 10 years. In 1994 the established risk factors were scored and serum was stored. For 127 fatal cases and 254 matched controls (age; body mass index; hypertension) cardiac troponin I (cTnI) was assessed three times in a row from one serum sample. cTnI was considered positive if measurable in at least 2 of 3 measurements.

Results: Groups were well matched. In 17 females cTnI was positive. A history of cancer was the strongest prognostic indicator. Multivariate analysis was performed excluding females with such a history (table 1).

Table 1	Univariate analysis		
	Fatal Cases (n=127)	Living controls (n=254)	p-value
Baseline:			
History of malignancy (%)	15	8	0.04
Mean clearance (ml/min)	63	67	ns
Mean creatinine concentration ($\mu\text{mol/L}$)	99	95	ns
Mean body mass index (kg/L^2)	26.0	25.8	ns
Mean cTnI(+) concentration ($\mu\text{g/L}$)	0.007	0.006	ns
	cTnI ²	cTnI ²	Multivariate-p
Creatinine < 75 th percentile	0.011	0.004	0.06
Clearance > 25 th percentile	0.011	0.004	0.08

1) cTnI(+): at least 2 out of 3 measurements with a measurable reading; 2) Mean cTnI concentration excluding females with a history of malignancy

Conclusion: Marginal troponin values occurred infrequently in apparently healthy females. Yet, in view of our results cTnI could be of prognostic impact in healthy females who are without a history of cancer and have good renal function. More studies are warranted to further fuel the search for highly sensitive troponin assays with improved precision at even lower detection levels to allow risk stratification in healthy individuals.

P1522 Mild to moderate renal impairment is associated with increased Left Ventricular Mass



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Objective To examine the relationship between mild to moderate renal dysfunction and left ventricular mass (LVM). Design Retrospective cross-sectional study. Background Mild to moderate renal impairment has recently been found to be associated with excess cardiovascular mortality but the reason for this relationship is unclear. Left ventricular hypertrophy (LVH) has a well-established association with severe renal dysfunction and increased cardiovascular mortality. However it is not known whether LVH also occurs in patients with milder renal dysfunction. Setting Zhongshan Hospital, Shanghai Medical University, China Patients 336 consecutive patients with chest pain who underwent concurrent coronary angiography, serum creatinine (Cr) and LVM assessment were recruited into the study. Main Outcome Measures LVM as determined by M-mode echocardiography and normalised for body surface area (NLVM); renal function determined by Cr, creatinine clearance (CrCl) (Cockcroft-Gault equation) and glomerular filtration rate (GFR) (Modification of Diet in Renal Disease equation).

Results Mean $\pm$ SD age was 56.8 ± 9.5 years, 282(84%) were male, mean NLVM $107.1\pm 36.8\text{ gm/m}^2$, Cr $0.94\pm 0.22\text{ mg/dL}$, CrCl $82.7\pm 21.7\text{ ml/min/1.73m}^2$ and GFR $89.4\pm 24.6\text{ ml/min/1.73m}^2$. NLVM was related to Cr ($r=-0.30$), CrCl ($r=0.19$) and GFR ($r=0.24$) (all $p<0.001$). Multivariate adjusted odds ratio (OR) of ele-

vated NLVM was significantly greater in the highest quartile of renal function when compared with the lowest quartile: Cr 1.06-2.00 mg/dL: OR 2.82 (95% CI 1.34-5.96); CrCl 34.8-67.5 4 ml/min/1.73m²: OR 2.29 (1.13-4.66); GFR 36.2-73.4 ml/min/1.73m²: OR 2.76 (1.33- 5.75), respectively.

Conclusion In a setting of patients being investigated for chest pain, mild to moderate renal insufficiency is significantly and independently associated with increased LVM.

P1523 ACS versus non thrombotic troponin elevation in hospitalized patients: clinical predictors and survival analysis

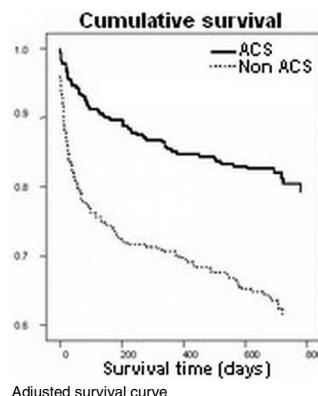


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Aims: To characterize the differences between patients with ACS and non-thrombotic troponin elevation in hospitalized patients.

Methods: Between 1.1.2003 to 1.10.2003, all patients with elevated troponin levels (cutoff value 0.1 ng/ml) at our hospital were analyzed. Demographic and clinical data were collected and death date was recorded. The study population was divided according to the principal diagnosis to two subgroups: ACS and non-thrombotic troponin elevation (NTTE). Predictors for the diagnosis of ACS were characterized by multivariate regression analysis. Short and long term adjusted mortality analysis were performed.

Results: 615 patients comprised the study group. The mean age was 68 ± 15 ; 398 patients were males (64.7%). Only 326 patients (53%) were diagnosed as ACS while 254 patients (41%) had a wide spectrum of conditions such as sepsis, respiratory failure, CVA, renal failure and surgical emergencies. In the other 35 patients (5.7%), the diagnosis could not be determined. The positive predictors for the diagnosis of ACS were age between 40-70, a history of HTN or IHD, normal renal function and troponin level above 1ng/ml. Hospitalization in a surgical department was a strong negative predictor for ACS. In hospital as well as long term adjusted mortality rates were significantly lower in the ACS group ($P<0.001$).



Adjusted survival curve

Conclusions: In hospitalized patients, non-thrombotic troponin elevation is common. These patients are older, suffer from multiple medical conditions and have a poorer prognosis compared to ACS patients.

P1524 Cardiorespiratory fitness and European systematic coronary risk evaluation in the prediction of acute myocardial infarction and ischemic stroke



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Background: Our previous studies have shown the associations of poor cardiorespiratory fitness with an increased risk of stroke and coronary heart disease. The role of cardiorespiratory fitness among subjects with high and low European risk scores with respect to atherosclerotic cardiovascular events is not well known, although it is suggested that the global risk score may be used for risk stratifying in asymptomatic individuals.

Methods: In this follow-up study, cardiorespiratory fitness (maximal oxygen uptake) was measured on an electrically braked cycle ergometer with respiratory gas analyses at baseline. The study is based on a random population sample of 1639 men (42-60 years) without previous history of type II diabetes, coronary heart disease, stroke or claudication. Those who had European risk score over 5% and low maximal oxygen uptake $\leq 31.8\text{ ml/kg/min}$ were included in the high risk group. During an average follow-up of 13.4 years, a total of 155 acute coronary events and 61 ischemic strokes occurred.

Results: The risk of acute coronary events was 4.48 (95% CI 2.71- 7.42,

$p < 0.001$) fold among men with high European risk score and low maximal oxygen uptake and 2.46 (95% CI 0.88 - 6.88, $p = 0.087$) fold among those who had high European risk score but good maximal oxygen uptake, as compared to those with low European risk score and good maximal oxygen uptake, after adjustment for risk factors (C-reactive protein, alcohol consumption, atrial fibrillation, exercise-induced ST changes, the use of medication for hypertension or dyslipidemia and the use of aspirin, waist-to-hip ratio, serum HDL-cholesterol and physical activity). Furthermore, the respective risk for ischemic stroke was 3.44 (95% CI 1.40 - 8.50, $p = 0.009$). In a multivariate model, 1% increase in European risk score was associated with the risk of acute coronary events (RR 1.16, 95% CI 1.09-1.24, $p < 0.001$) and ischemic stroke (RR 1.16, 95% CI 1.05-1.28, $p = 0.005$), whereas VO_{2max} (for 1 MET increment) was inversely related to the risk of acute coronary events (RR 0.87, 95% CI 0.79-0.95, $p = 0.002$) and ischemic stroke (RR 0.86, 95% CI 0.74-0.99, $p = 0.045$).

Conclusion: This prospective study shows that European risk score with the assessment of cardiorespiratory fitness provides additional information from those who are at high risk for cardiovascular events such as acute coronary events and ischemic stroke. Cardiorespiratory fitness together with European risk score risk maybe used as a screening tool in asymptomatic individuals.

P1525 Heart failure in different occupational classes in Sweden



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Background: A diagnosis of heart failure is associated with a serious prognosis. Therefore it is important to demonstrate risk factors for this disease. We investigated the longitudinal relationship between socioeconomic status and risk of hospital discharge or death certificate diagnosis of heart failure.

Methods: 6,999 men who were 47 to 55 years old in 1970 to 1973, without prior stroke or myocardial infarction, derived from a population sample of 9,998 men were prospectively followed up until 1998.

Results: One thousand and four (14.3%) men had a hospital discharge diagnosis or a death certificate diagnosis of heart failure. There was an inverse relationship between occupational class and risk of heart failure. Compared to men in the highest occupational class, intermediate non-manual men had a multiple-adjusted hazard ratio (HR) of 1.28, 95% confidence interval (CI) 0.98-1.67, lower officials, foremen had a HR of 1.57 (1.22-2.03), semiskilled and skilled workers 1.48 (1.15-1.89) and unskilled workers 1.72 (1.34-2.20). Results were similar if only men with a principal diagnosis of heart failure ($n = 516$) were considered, and irrespective of whether a diagnosis of acute myocardial infarction (AMI) or coronary by-pass operation had been recorded at any time.

Conclusions: We found a strong, inverse and independent association between occupational class, such that men in the lowest occupational class had a more than 70% increased risk to die or to be hospitalised with a diagnosis of heart failure.

P1526 Natural history of congestive heart failure and associated cardiovascular diseases in outpatient HIV-infected subjects: rationale and design of the HIV-HEART study



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Background: Not only does the infection with the human immunodeficiency virus affect the immune system, but also disorders of other organs, in particular cardiac diseases, have been discovered and became a most notable health subject. In the course of time, rising cardiovascular morbidity and mortality rates are expected in the HIV-infected population and efforts are required to analyze frequency and clinical course of HIV-associated heart diseases in order to improve prevention and therapeutic options.

Methods: The HIV-HEART (HIV-infection and HEART disease) study is a prospective, long-term cohort study. It is designed and powered to define incidence and prevalence of congestive heart failure, particularly HIV-associated dilated cardiomyopathy, in 800 HIV-infected males and females with and without antiretroviral therapy in an urban population using non-invasive techniques, i.e. laboratory parameter, electrocardiogram, echocardiography and endurance testing by a six-minute walk test. Additionally, the study examines heart failure depending diseases, predictive values of conventional cardiovascular risk factors for development of coronary atherosclerosis, new candidate and socioeconomic risk factors, certain genetic polymorphisms, and signs of subclinical disease. The analysis of health economy is an inherent part of the study.

Conclusions: The HIV-HEART study will define the significance of congestive heart failure due to dilated cardiomyopathy in a HIV-infected urban population and classify appropriate methods of identifying high-risk patients, the basis for

risk stratification and therapy. The HIV-HEART study is part of the German Heart Failure Network and is supported by the sponsorship of the Federal Ministry of Education and Research Germany.

P1527 Long-term prognosis in vascular surgery patients using perioperative troponin T release: Is there a threshold?



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Background: Cardiac troponin T (TnT) is a sensitive marker for myocardial injury. Perioperative release of TnT > 0.1 predicts mortality in patients undergoing major vascular surgery. Recently developed immunoassay techniques allow detection of TnT levels between 0.03 and 0.1 ng/ml. This study investigates whether a cut-off value of 0.03 ng/ml identifies additional patients at increased risk.

Methods: Between October 2000 and December 2005, 558 survivors of abdominal aortic aneurysm repair ($n = 283$) or lower extremity bypass surgery ($n = 275$) were enrolled. Patients were screened for cardiac risk factors and serial TnT levels were measured on day 1, 3, and 7 after surgery with the Elecsys 2010 analyzer (lower detection limit: 0.03 ng/ml). The highest of the patient's serial TnT was used for analysis. All-cause mortality was noted during follow-up (mean: 3.5 ± 2.6 years).

Results: TnT levels < 0.03 ng/ml, between 0.03-0.1 ng/ml and > 0.1 ng/ml were observed in 490, 27, and 54 patients, respectively. In these groups, long-term mortality occurred in 79 (16.1%), 13 (48.1%), and 37 (68.5%) patients, respectively. Multivariate analysis revealed that patients with TnT between 0.03-0.1 ng/ml (HR: 3.4, 95% CI: 1.8-6.1, $p < 0.001$) and > 0.1 ng/ml (HR: 4.7, 95% CI: 3.1-7.2, $p < 0.001$) were at increased risk for long-term mortality compared to patients with TnT < 0.03 ng/ml (Figure). Comparable results were obtained after excluding patients with renal dysfunction ($n = 30$).

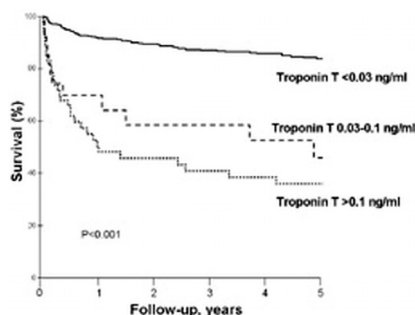


Fig. 1. Survival curves for 5-year follow-up.

Conclusion: This study demonstrates that patients with perioperative troponin T release between 0.03 and 0.1 ng/ml are at increased risk for long-term mortality. Detection of high-risk patients may be improved by using a cut-off value of 0.03 ng/ml instead of 0.1 ng/ml.

P1528 High C-reactive protein - a predictor of long term mortality and adverse cardiac events in patients treated with sirolimus-eluting stents?



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Objectives To assess the predictive value of elevated levels of C-reactive protein (CRP; > 3 mg/L) on early and late adverse cardiac events (death, myocardial infarction and target vessel revascularization) in an unselected patient population treated with sirolimus-eluting stents (SES) at three years of follow-up.

Background Elevated levels of inflammatory markers, particularly C-reactive protein (CRP), have been associated with higher rates of cardiovascular disease. SES have been shown to reduce clinical as well as angiographic restenosis. Currently, no data is available on the influence of elevated CRP levels in patients undergoing PCI with SES.

Methods From April 29 2002 to October 16 2002, CRP levels were measured in 384 patients undergoing PCI solely with sirolimus-eluting stents. Patients were followed at 1, 2 and 3 years for the occurrence of death, myocardial infarction and repeat revascularization.

Results At three years, the cumulative incidence of all-cause mortality was significantly higher in patients with elevated CRP levels (11.8% versus 3.8%; $p = 0.004$). The combined endpoint of all-cause death or MI was 16.6% in the elevated CRP group versus 7.2% in the normal CRP-group ($p = 0.006$). There was no significant difference between the elevated versus normal CRP-group in target vessel revascularization: 17.7% versus 13.6% respectively ($p = 0.31$). The cumulative in-

cidence of MACE was higher in the elevated CRP-group: 29.1% versus 17.7% ($p=0.01$). In Cox multivariate proportional hazard analysis, CRP was independently associated with long-term mortality (HR 2.56, 95% CI 1.05 - 6.23). Pre-selected variables were: age, gender, hypertension, diabetes, renal impairment, previous intervention, old MI, smoking, statin therapy, treatment of the left main coronary artery, saphenous vein bypass graft treatment and CRP-level.

Conclusions: At three years of follow-up, CRP showed to be an independent predictor of mortality in patients treated with sirolimus-eluting stents. Although highly significant in univariate analysis, the incidence of death or MI was similar between both groups. Elevated levels of CRP were not associated with higher rates of target vessel revascularization and major adverse cardiac events at three years.

P1529 Troponin elevation is a powerful marker of poor prognosis after percutaneous coronary intervention



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Introduction: Troponin I (Tn-I) elevation is a poor prognosis marker in coronary disease. However, the prognostic value of Tn-I elevation after percutaneous coronary intervention (PCI) is debated. We sought to determine poor prognosis factors after PCI, and particularly to identify prognostic role of the Tn-I. **Methods:** Data result from 781 consecutive patients undergoing no emergency PCI in our institution from May 2000 to October 2001. Blood samples were collected immediately before and at 24 h after procedure. This study included 433 patients with out Tn-I elevation before PCI. The primary endpoint was the occurrence of major adverse cardiac events (MACE) after PCI: death, myocardial infarction (MI) or repeat revascularisation.

Results: Mean age was 62 ± 11 years and 77% of the patients were males. Stents were implanted in 394 patients (91%). Post procedural Tn-I increased in 150 patients (34.6%). During a median follow-up of 12.4 months, MACE occurred in 87 patients (20.1%). Among clinical, biological, angiographic and procedural studied characteristics, independent predictive factors of MACE were Tn-I elevation (HR=1.62 [1.03-2.57]; $p=0.036$) and the coronary restenosis (HR=2.81 [1.56-5.07]; $p=0.001$). Among patients with Tn-I elevation, independent predictive factors of MACE were the Tn-I value (HR=1.05 [1.02-1.07]; $p < 0.001$) and the restenosis (HR=5.03 [2.40-10.56]; $p < 0.001$).

Conclusion: Tn-I elevation was a factor of poor prognosis after PCI. In case of elevation, Tn-I value after PCI is a continuous marker of cardiovascular morbidity at long-term.

P1530 Predictive factors and in-hospital outcome of multiple complex coronary lesions on coronary angiography in the setting of acute myocardial infarction. Data from RICO survey



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Purpose: Only sparse data are available on the predictive factors and in-hospital outcome of patients with multiple complex coronary lesions (MCL) on coronary angiography in the setting of an acute myocardial infarction (MI).

Methods: 1592 non-selected patients from the RICO survey, which includes all the patients hospitalised for an acute MI in one region of eastern France, who underwent coronary angiography during their hospital stay, were analysed. Coronary angiographies were systematically reviewed by 2 experienced physicians in order to identify complex coronary lesions, which was defined by the presence of thrombus, ulceration, irregular plaque and flow impairment. Patients were divided into 2 groups: single complex coronary lesions (SCL), and multiple complex coronary lesions (MCL). Multiple logistic regression analysis including clinical and biological parameters available on admission were performed to determine their association with presence of MCL. Outcome was analysed as the onset of ma-

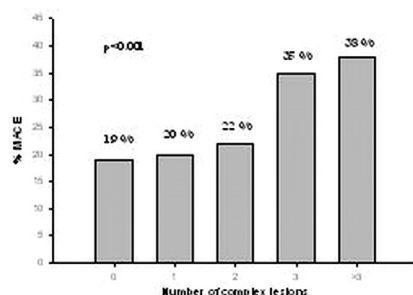


Fig. 1. MACE and complex lesions

for cardiac events (MACE) (death, recurrent MI or cardiogenic shock) during the hospital stay.

Results: Among the 1542 patients, MCL were identified in 421 (27%), with similar rates between STEMI and NSTEMI. After adjustment for age, prior MI (OR 1.8, 95%CI 1.2-2.6, $p=0.3$ mg/dl are independently correlated ($p<0.05$).

Conclusions: Our population-based study showed that presence of MCL in patients with acute MI is associated with worse in-hospital outcome and that risk factors such as CRP are able to identify patients at high risk for MCL. Evaluation of an early specific management strategy needs to be evaluated.

P1531 Defective recovery of QT dispersion predicts late mortality after percutaneous coronary intervention



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Background and aim: The range of QT interval durations on the standard surface ECG (QT dispersion: $QTd=QT_{max}-QT_{min}$) is thought to reflect spatial differences in myocardial recovery time. We tested the hypothesis that a defective recovery of QTd predicts an adverse outcome after percutaneous coronary interventions (PCI).

Methods: Rate-corrected QT dispersion (QTcd) was analysed in 535 consecutive patients (pts) before PCI, 6h and 18h after PCI. According to median QTcd variation ($\Delta QTcd = \text{Baseline QTcd} - 18h \text{ after PCI}$) pts were grouped into:

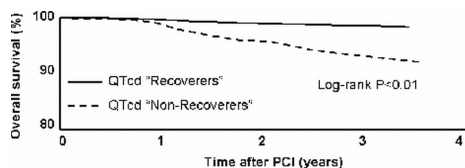
"QTcd-Recoverers" = $\Delta QTcd > 2$ ms, $n = 267$;

"QTcd-non-Recoverers" = $\Delta QTcd < 2$ ms, $n = 268$.

During follow-up major adverse coronary events (MACE: death, myocardial infarction and target vessel revascularization) were recorded.

Results: A post-PCI CK-MB > 19 IU/L (normal value) was detected in 20% of pts. QTcd decreased from 55 ± 26 ms at baseline to 50 ± 28 ms 6h after PCI ($P < 0.01$) and 50 ± 29 ms 18h after PCI ($P < 0.01$ vs baseline, $P=NS$ vs 6h after PCI). CK-MB release was significantly lower in "QTcd-Recoverers" (14 ± 21 IU/L) compared with "QTcd-Non-Recoverers" (24 ± 31 IU/L, $P < 0.01$).

After 38 ± 9 months, 21 deaths (4.6%) were recorded in 453 pts (85%). "QTcd-Recoverers" showed a higher overall survival (98.3%), and a similar MACE-free survival (86%), when compared with "QTcd-Non-Recoverers" (92.4%, $P < 0.01$ and 84%, $P=NS$, respectively). By multivariate Cox regression analysis, age ($P < 0.001$) and a reduced $\Delta QTcd$ ($P=0.016$), but not CK-MB ($P=NS$), were independent predictors of mortality.



Conclusions: QTcd decreases after successful PCI. A defective recovery of QTcd suggests the persistence of myocardial areas with repolarization inhomogeneities and is related to long-term mortality, likely due to a relationship with sudden death.

P1532 Prevalence of atherosclerosis in middle-age: results from the ASKLEPIOS study in 2524 subjects free from overt cardiovascular disease



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Purpose: Early detection and recognition of atherosclerosis (e.g. ultrasound) has received increased attention and atherosclerosis phenotypes are currently advocated as intermediate phenotypes in cardiovascular risk prediction, as surrogate end-points in clinical trials and as phenotypes in biomarker discovery. Nevertheless population data on the prevalence of various atherosclerotic phenotypes such as intima-media thickening (IMT) or plaque at different sites (carotid, femoral) within a single population databases are limited.

Methods: The ASKLEPIOS Study is a cross-sectional and longitudinal study focusing on the interplay between aging, cardiovascular haemodynamics and inflammation in (preclinical) cardiovascular disease. The participants (1300 F; 1224 M) are a representative cohort of apparently healthy Belgian 35-55 year-old subjects (median age 45.9 years) free from overt cardiovascular disease at study entry. Extensive physical and laboratory evaluations were performed. All measurements including echography (GE/Vingmed Vivid 7) were single observer, single device, at a single site during a consecutive 2-year period. Phenotypes under study include: IMT (cut-off for thickening 0.9 mm) and plaque (Mannheim criteria) at both carotid and femoral arteries.

Results: Using conservative definitions 40% of subjects had identifiable atherosclerosis (femoral 30%; carotid 22%). However these crude prevalence figures are highly age and gender dependent, showing a fourfold prevalence

increase over the age-range under study. Males have a prevalence increase of 20%/5 years; females of 10%/5 years. Prevalence data are highly dependent on the definition used, using less conservative definitions would dramatically increase prevalence figures for atherosclerosis to >80% of subjects.

Prevalence of atherosclerosis

	35-40 years	41-45 years	46-50 years	51-56 years
Males	23%	46%	61%	78%
Females	11%	22%	32%	46%

Prevalence of carotid and/or femoral atherosclerosis (intima-media thickening or plaque).

Conclusions: Ultrasound evidence for atherosclerosis, either defined by IMT or plaque is very common in apparently healthy 35-55 year old subjects with pronounced age and gender gradients. Certain current definitions of atherosclerosis may overestimate "true" atherosclerosis prevalence in young, low risk populations.

MISCELLANEOUS

P1533 The practice environment of Physician Assistants in cardiology



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Introduction: Physician Assistants (PAs) practice medicine under supervision of physicians. Approximately 60,000 PAs practice in the United States in primary care practice settings, internal medicine specialties, and surgical specialties. Over 3% of PAs identify cardiology as their primary practice discipline. To better understand the clinical role and practice demographics of PAs in a cardiology practice discipline, the Association of Physician Assistants in Cardiology (APAC) conducted a survey.

Methods: In 2004, 280 PAs listing cardiology as their primary practice discipline completed a comprehensive questionnaire of their practice environment. Descriptive statistics and step wise regression tests were applied to analyze the data. A p-value <0.05 was considered significant

Results: There were 56.1% female respondents versus 43.9% male respondents. The age range was 30-49 years. The typical length of time identified in the cardiology practice setting was 1-5 years (54.5%). The highest degrees in Physician Assistant studies for this group were the Bachelor's or Master's degree (70%). The primary practice setting most commonly identified was the combined noninvasive and invasive practice (69.7%). The typical annual gross salary was \$60,000 - \$99,000. The highest salaries were most likely to be provided to those PAs with more years of clinical experience (p<0.05) and of male gender (p<0.05). In the clinical setting PAs were involved in both outpatient and inpatient care. Common clinical duties included admission history and physicals, discharge summaries, outpatient and post-operative management, cardiology consults, exercise stress testing, and critical care management. Approximately 11% of Cardiology PAs were assisting in invasive procedures including central line placement, intra-aortic balloon pump placement, temporary pacemakers, and right heart catheterizations. PAs also assisted in left heart catheterizations (5.1%) and permanent pacemaker placements (3.0%). More than half of respondents were involved in clinical education (58.6%) and research (23.2%).

Conclusion: The utilization of PAs is gaining greater physician acceptance in all settings. Cardiology PAs provide a vast resource of medical services for the clinical cardiologist. Considering an anticipated shortage of cardiologists in the United States over the next couple of years, PAs offer an option to assist cardiologists in providing continued and efficient clinical care. A study of the attitude of cardiologists on PA utilization in cardiology practices would be of interest.

P1534 Impact of socioeconomic profile on heart failure-related deaths in the city of Rio de Janeiro, Brazil



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Background: Socioeconomic status appears to have an impact on heart failure-related mortality. Such impact has not been well studied to date.

Objectives: To evaluate the impact of extreme poverty (monthly income < US\$1.00 per person-days) on heart failure-related mortality between 2000 and 2003 in the city of Rio de Janeiro, Brazil.

Materials e Methods: We undertook a detailed analysis of all death certificates issued between January 1, 2000 and December 31, 2003, and identified all deaths attributed to heart failure in persons aged 30 or greater. According to data from the 2000 Brazilian National Census (IBGE), we identified 2 groups of districts within the city of Rio de Janeiro, encompassing the following communities: Botafogo, Copacabana, Lagoa, Centro e Tijuca (Group 1 - G1; extreme poverty rates of 4.3 ± 1.1%) and Complexo do Alemão, Jacarezinho, Santa Cruz, Guaratiba e Cidade de Deus (Group 2 - G2; extreme poverty rates of 27.5 ± 1.2%). Data on heart-rate mortality were then compared between those 2 groups.

Results: In the beginning of 2000, population in G1 and G2 totaled 488,763 and 238,702 individuals, respectively. By the end of 2003, there had been 256 e 276 deaths by heart failure in G1 and G2, respectively (0.052 vs 0.116%, p<0.01, OR=2.2, 95%CI= 1.8-2.6). Average age of death by heart failure was 80.9±11.3 and 72.1±10.3 years, respectively, for G1 and G2 (p<0.001). The proportion of deaths by heart failure in individuals younger than 50 was 0.8 and 5.4%, respectively (p<0.01; OR=6.9, 95%CI=2.0-24.4). Multivariate logistic regression analysis identified age (OR=1.004, 95%CI= 1.003-1.006), male gender (OR=0.83, 95%CI=0.70-0.97), lower schooling (OR=1.77, 95%CI=1.44-2.09) and belonging to G2 (OR=1.88, 95%CI=1.57-2.26), as independent predictors of heart failure-related death.

Conclusion: Extreme poverty is a risk factor for heart failure-related mortality in the city of Rio de Janeiro. Specific public health policies geared towards the prevention and management of heart failure among the poor are of vital importance in order to attenuate the impact of poverty in deaths caused by heart failure.

P1535 Escalating cardiovascular risk factors in urban Indian men are related to obesity



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Background: Trends in cardiovascular risk factors have not been adequately studied in developing countries. To evaluate changes in cardiovascular risk factors in an urban Indian location and correlate it with measures of obesity we performed serial epidemiological studies.

Methods: Successive epidemiological Jaipur Heart Watch (JHW) studies were performed in Western India in rural (JHW-R, years 1992-93, n=3148) and urban locations (JHW-1, 1993-94, n=2212; JHW-2, 1999-2000, n=1123; and JHW-3, 2002-03, n=458). The studies included adults >20 years evaluated using standardized methodology. For the present analysis we included males in age-group 20-59 years (1700, 1294, 469 and 179 in various groups, n=3642). Prevalence of various coronary risk factors: tobacco use, sedentary habits, overweight/obesity (body mass index, BMI >25 kg/m²), central obesity (waist:hip >0.9), hypertension, diabetes, dyslipidemias and metabolic syndrome were determined and trends analyzed.

Results: Prevalence (%) of overweight/obesity and central obesity was significantly greater in the urban cohorts (p<0.05). Prevalence of overweight in various cohorts (JHW-R, JHW-1, JHW-2, and JHW-3) was at age 20-29 years 3.9, 12.7, 20.2 and 33.3, at 30-39 years 9.5, 22.2, 35.3 and 53.3, at age 40-49 years 15.8, 26.2, 47.0 and 65.5, and 50-59 years was 11.6, 29.4, 52.0, 82.3 (p for trend <0.05). Central obesity at age 20-29 years 37.6, 55.7, 34.3 and 57.1, at 30-39 years 36.9, 61.2, 45.7 and 75.5, at age 40-49 years 35.9, 42.1, 66.7 and 84.5, and 50-59 years was 27.8, 56.0, 76.0, 85.3 (p for trend <0.05). Obesity and central obesity significantly correlated with mean levels of systolic blood pressure, fasting glucose, cholesterol, LDL cholesterol, and triglycerides and inversely with HDL cholesterol (Spearman correlation p<0.01 for various parameters) as well as with prevalence of hypertension, diabetes and hypercholesterolemia (least squares regression for trend <0.05). Smoking and tobacco use was significantly greater in rural cohorts (33-63%) as compared to the urban groups (19-46%).

Conclusions: The present study shows significant increase in obesity and central obesity in Indian urban subjects. This correlates significantly with escalating major cardiovascular risk factors, hypertension, high cholesterol, diabetes and low HDL. Obesity targeted cardiovascular preventive approach is recommended in developing countries such as India.

P1536 Prevalence and prevention status of cardiovascular disease and risk factors in clalit health services



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Background: High-risk patients in need for primary and secondary prevention of cardiovascular disease (CVD), are under-evaluated and under-treated.

Aim: To evaluate CVD prevention status among high-risk patients for CVD events, or have CVD.

Methods: All patients, aged 30-74y from primary care clinics of Clalit Health Services in Israel, were included. Computerized primary care records, laboratory data and drug prescriptions were used to identify patients at high-risk for CVD using an automatic risk-profile processor based on the presence of diabetes, the European "Score" (>5% CVD death/10y) and the "Framingham" (>20% CVD event/10y) risk scales. Current guidelines adopted by Clalit Health Services were used to evaluate patient care status.

Results: Out of 1649366 patients, 4.9% have established CVD and additional 229162 (13.9%) patients were found to be at high risk for a cardiovascular event. Risk factors prevalence and management status is presented in the table. As much as 75% of the patients do not have data regarding smoking and obesity.

Conclusions: This baseline survey, demonstrates a significant gap in monitoring and treatment of modifiable CVD risk factors in the primary care setting. These

Risk factors prevalence and management status

Risk Factors	%	Data	On Target
Prevalence of Diabetes	9.8%		HbA1C < 7 mg%
Diabetics without medication	30.5%	35.8%	64.3%
Diabetics with medication	69.5%	54.8%	32.8%
Prevalence of Hypertensive	8.5%		BP < 140/90 mmHg
Hypertensive without medication	14.2%	55.4%	27.7%
Hypertensive with medication	85.8%	70.0%	28.0%
Prevalence of Dyslipidemia	10.2%		LDL < 100mg/dL
On medication without a diagnosis	24.1%	63.9%	35.5%
Dyslipidemic without medication	21.4%	48.9%	8.6%
Dyslipidemic with medication	54.5%	71.3%	31.6%

Data +: With 1 Lab test/BP < 6 months

findings serves as a basis for an HMO- nation wide intervention program using the commercial Clicks® patient medical record system

P1537 Angiotensin II Type 1 receptor blocker prevents coronary stenosis in patients with coronary aneurysm after Kawasaki disease



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Objectives: Angiotensin II Type 1 receptor blocker (AT-1RB) has been thought to prevent an intimal hyperplasia of vascular wall. Coronary stenotic lesions are often observed at proximal and/or distal portion of aneurysm because of intimal hypertrophy in Kawasaki disease (KD). Then we tested whether AT-1RB had potential to prevent significant stenosis of coronary artery which was caused by intimal hyperplasia in KD.

Subjects: 88 KD children aged 9 months to 8 years old who have coronary aneurysm (less than 4 times diameter of adjacent normal-looking vessel) in acute stage of KD were subjected and grouped; AT-1RB group; 42 patients (onset years 2000-2005) and, non-AT-1RB group; 46 patients (onset years 1994-1999). Administered dose of gamma-globulin were 3.2 ± 0.7 g/kg in AT-1RB group and 3.0 ± 0.8 g/kg in non-AT-1RB group.

Methods: 0.2-0.4 mg/kg of AT-1RB (Candesartan) was administered in AT-1RB group patients just after diagnosed existence of coronary aneurysm by 2-D echo for 6 to 12 months. Harada's score (score for clinical severity by the Kawasaki Disease Research Committee of the Japanese Ministry of Health and Welfare), gene polymorphism of AT-1 A/C gene polymorphism and angiotensin converting enzyme (ACE) I/D polymorphism which have been thought to be candidate gene polymorphism for intimal hypertrophy were tested. Coronary aneurysms were checked by longitudinal 2-D echo. Existence and severity of coronary stenosis (CS) were diagnosed by CAG and IVUS at least 3 months after taking of AT-1RB or KD onset.

Results:

Table 1. Clinical results

	Harada's score	AT-1 C or ACE D	AT-1 C and ACE D	>75% CS
AT-1RB	5.3±1.2	77.2%	45.5%	4.5%*
Non-AT-1RB	5.7±1.4	73.3%	43.3%	23.3%

AT-1RB: Angiotensin II type 1 receptor blocker; AT-1 C: Angiotensin II type 1 receptor gene allele; CACE D: Angiotensin II converting enzyme gene allele D. *p<0.05.

3 patients had POBA and 2 patients had CABG in non-AT-1RB group. No patients who had AT-1RB had any side effects.

Conclusions: Thus, AT-1RB therapy could be effective to prevent coronary stenosis in patients with coronary aneurysm after acute stage of KD.

P1538 Heart rate recovery after exercise testing associated with renal function in IgA nephropathy



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Background: Heart rate recovery (HRR) appears to be related to the balance of the sympathetic and parasympathetic tone. Attenuated HRR is an independent predictor of mortality in patients with a history of coronary artery disease. There is no data available about the correlation of HRR and renal function in chronic renal diseases.

Purpose: To estimate the HRR and determine the relationship to the actual renal function in chronic glomerulonephritis.

Methods: One hundred and seven patients suffering from renal biopsy-proved chronic IgA nephropathy were examined (71 males, 36 females, mean age 45 ± 11 years). HRR was measured as the heart rate difference between the peak value and the heart rate 1 min after exercise. The renal patients were divided into three groups on the basis of glomerular filtration rate (GFR) estimated by Cockcroft-Gault formula: group 1: $GFR \geq 90$ ml/min (n=46), group 2: $60 \leq GFR < 90$ ml/min (n=38), group 3: $GFR < 60$ ml/min (n=23). We compared their data with 22 diabetic patients' values with normal renal function (mean age 54 ± 9 years). In the

control group there were 21 people free from any renal disease (mean age 43 ± 13 years).

Results: HRR values in group 3 with impaired renal function were significantly lower compared to the the patients in group 2 (16.3 vs. 24.5 bpm, p=0.015), in group 1 (16.3 vs. 27.6 bpm, p<0.001) and to the control group (16.3 vs. 29.3 beat/min, p<0.001), respectively, but appeared to be similar to the data of the diabetic group (16.3 vs. 16.8 beat/min, p=ns). HRR reduction showed significant correlation with the decrease of renal function ($r=0.422$ p<0.001). Univariate linear regression analysis found that factors associated with HRR were age, hypertension in history, GFR, systolic 24 hour BP on ABPM, pulse pressure, dyslipidaemia and body mass index. Only GFR was independently associated with decreased HRR by multiple regression analysis.

Conclusions: HRR is highly associated with actual renal function in chronic IgA nephropathy. The attenuation of HRR in patients with impaired renal function is similar to the decrease observed in diabetic patients with normal renal function.

P1539 Atorvastatin but not vitamin C improves endothelial function by reducing asymmetrical dimethylarginine levels and inflammatory process, in normocholesterolemic patients with diabetes mellitus type 2



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Endothelial dysfunction in diabetes mellitus (DM) is associated with increased oxidative stress, enhanced proinflammatory cytokines expression and increased levels of endogenous nitric oxide synthase inhibitor asymmetric dimethylarginine (ADMA).

Aim: We evaluated the effect of atorvastatin and vitamin C, on endothelial function, inflammatory process and ADMA levels, in normocholesterolemic patients with DM.

Methods: Forty-one patients with DM and low cholesterol level were randomized to receive atorvastatin 10mg/day (ATR, n=15), vitamin C 2g/day (n=13) or no treatment (controls, n=13) for 4 weeks. Forearm blood flow (FBF) was evaluated by gauge strain plethysmography, and endothelium dependent dilation (EDD) was expressed as the %change of FBF during post-ischemic hyperemia. Levels of ADMA, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and soluble vascular cells adhesion molecules (sVCAM-1) were determined with ELISA.

Results: Maximum hyperaemic FBF and EDD were increased in ATR (5.8 ± 0.7 and 42.9 ± 4.9 to 6.82 ± 0.8 ml/100ml tissue/min p<0.01 and $58.5 \pm 4.8\%$ p<0.05 respectively), but not in vitamin C (7.6 ± 0.8 and 51.3 ± 6.0 to 8.3 ± 0.7 ml/100ml tissue/min and $59.0 \pm 7.9\%$ respectively p=NS for both) or control group (6.6 ± 0.5 and 43.9 ± 5.1 to 6.9 ± 0.6 ml/100ml tissue/min and $46.1 \pm 6.1\%$ respectively, p=NS for both). ADMA, TNF-α, IL-6, sVCAM-1 and CRP were decreased in ATR (1.21 ± 0.18 , 2.51 ± 0.54 , 2.27 ± 0.55 , 484 ± 31 and 3.84 ± 1.16 to $0.72 \pm 0.08 \mu\text{M}$, 1.62 ± 2.71 pg/ml, 1.36 ± 0.19 pg/ml, 363 ± 13 ng/ml and 2.34 ± 0.71 mg/ml respectively, p<0.05 for all) but not in vitamin C (1.02 ± 0.09 , 2.71 ± 0.87 , 2.65 ± 0.42 , 381 ± 61 and 2.4 ± 0.3 to $0.98 \pm 0.07 \mu\text{M}$, 2.59 ± 0.49 pg/ml, 494 ± 32 ng/ml and 2.32 ± 0.28 mg/ml respectively, p=NS for all) or in controls (0.95 ± 0.07 , 1.96 ± 0.22 , 2.28 ± 0.59 , 450 ± 37 and 2.4 ± 0.7 to $0.93 \pm 0.08 \mu\text{M}$, 2.05 ± 0.19 pg/ml, 2.41 ± 0.51 pg/ml, 2.21 ± 0.73 mg/ml respectively, p=NS).

Conclusions: Atorvastatin improves endothelial function and decreases ADMA levels and the expression of proinflammatory cytokines and adhesion molecules in patients with DM, while antioxidant treatment is ineffective. These findings suggest that atorvastatin improves endothelial function, partly by reducing ADMA and inflammatory process in diabetic patients.

P1540 Atherosclerotic plaque characteristics on multi-slice computed tomography in diabetic and non-diabetic population



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Purpose: Multi-slice computed tomography coronary angiography (MSCT CA) allows detection of coronary plaques and different plaque components. The purpose of the study was to evaluate the differences in total plaque burden and morphology of coronary plaques on MSCT with regard to the presence of diabetes.

Methods: 184 patients (132 men, 64 with diabetes, mean age 59 ± 12 years) with known or suspected coronary artery disease were examined with MSCT CA (4- (n=22), 16- (n=53) and 64-slices (n=109)). Plaque burden was evaluated by determining the extent (number of diseased coronary segments) and types of coronary plaques (non-calcified, mixed and calcified). The plaque characteristics were compared in patients with and without diabetes.

Results: There were no significant differences between patients with diabetes and non-diabetic patients with regard to gender, age, mean Agatston score, presence of obesity, hypercholesterolemia, smoking and use of medications. Hypertension was more prevalent in the diabetic population (48% vs 69%, p=0.007). Coronary plaques were found in coronary angiograms of 148 patients. The number of segments with plaques in patients with diabetes and in non-diabetic patients was the same and was 5 ± 3 per patient, with 1 ± 2 plaques being obstructive (>50% stenosis). Detailed analysis of plaque morphology in non-diabetic and

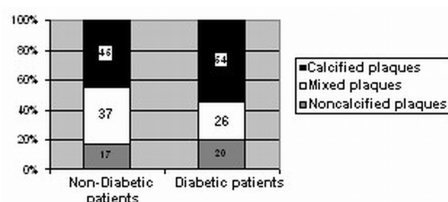


Fig. 1. Coronary plaques vs presence of diabetes.

diabetic patients showed 17% (76/452) and 20% (50/253) non-calcified plaques, 38% (172/452) and 26% (66/253) mixed plaques and 45% (204/452) and 54% (137/253) calcified plaques ($p=0.006$).

Conclusions: The extent of coronary plaques did not differ with regard to presence of diabetes. Diabetic patients showed relatively more calcifications, whereas more mixed plaques were observed in the non-diabetic population.

P1541 Oxidative stress and increased thrombogenicity in diabetes mellitus: is there a role for antioxidant treatment?



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Type 2 diabetes mellitus (DM) and coronary artery disease (CAD), are both associated with increased oxidative stress, endothelial dysfunction and increased thrombogenicity.

Aim: We examined the short-term effect of high-dose vitamin C on endothelial function and plasma levels of antithrombin III (ATIII), proteins C and S, factors V and VII, vonWillebrand factor (vWF), tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) in patients with combined DM and CAD.

Methods: Thirty-nine patients with combined CAD and DM were randomly divided into two groups and received vitamin C 2g/day (vitC group, $n=19$) or no antioxidant (control group, $n=20$) for 4 weeks. Forearm blood flow was measured using venous occlusion strain-gauge plethysmography. Endothelium dependent dilation (EDD) and endothelium independent dilation (EID) were expressed as the % change of flow from baseline to the maximum flow during reactive hyperemia or after sublingual nitroglycerin administration, respectively. Thrombotic markers were determined with ELISA.

Results: EDD was significantly increased in VitC group (from 51.84 ± 4.72 to $72.5 \pm 6.5\%$, $p<0.05$), while remained unchanged in control group (from 43.8 ± 4.7 to $41.8 \pm 4.5\%$, $p=NS$). Plasma levels of vWF, tPA, PAI-1 and fV were decreased in VitC group (from 134 ± 15 , 12.2 ± 0.98 , 3.1 ± 0.36 and 144 ± 5.7 to $109 \pm 11\%$, 8.3 ± 0.60 ng/ml, 2.5 ± 0.42 IU/L and $122 \pm 6\%$ respectively, $p<0.05$ for all), but not in controls (from 141 ± 26 , 12.2 ± 1.3 , 2.18 ± 0.40 and 127 ± 10 to $129 \pm 21\%$, 13.5 ± 2.6 ng/ml, 2.62 ± 0.46 IU/L and $120 \pm 8\%$ respectively). ATIII, prtC, prtS and fVII remained unchanged in both VitC (from 82 ± 3 , 104 ± 5 , 88 ± 8 and 100 ± 9 to $79 \pm 3\%$, $96 \pm 5\%$, $83 \pm 6\%$ and $91 \pm 6\%$, respectively, $p=NS$ for all) and control group (from 85 ± 3 , 88 ± 9 , 90 ± 6 and 72 ± 9 to $83 \pm 5\%$, $81 \pm 11\%$, $96 \pm 5\%$ and $69 \pm 8\%$ respectively, $p=NS$ for all).

Conclusion: Short-term administration of high-dose vitamin C improved endothelial function and decreased plasma levels of factor V, tPA, PAI-1 and vWF in patients with diabetes mellitus of type 2 and CAD. These findings indicate the important role of oxidative stress and the possible beneficial effect of high-dose antioxidant treatment in diabetic patients with coronary artery disease.

P1542 Is Impaired fasting glucose associated with increased risk of coronary atherosclerosis?



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Background: Impaired fasting glucose identifies individuals at high risk of progression to diabetes but the role of IFG as a coronary artery disease risk factor, independent of its progression to diabetes and its association with other coronary artery disease risk factors, is unclear.

Methods: A cross-sectional study was conducted to evaluate the hypothesis that impaired fasting glucose increased the likelihood of atherosclerotic plaque formation. Blood chemistry data as well as traditional coronary artery disease risk factors from 812 patients referred for coronary angiography to heart centers in Shahid-Chamran and Sina hospital, Isfahan, Iran from May 2004 to April 2005 were recorded. The population were stratified into three groups according to American Diabetes Association criteria: normal fasting glucose ($n=608$), impaired fasting glucose ($n=92$) and diabetes mellitus ($n=112$). We use extent, Vessel and stenosis scores to indicate the coronary artery involvement.

Results: Kruskal-Wallis test showed that the means of extent, Vessel and stenosis scores are not significantly different between three groups ($P>0.05$). Multivariate linear regression analysis, using extent score of coronary artery disease as dependent variable and traditional risk factors and impaired fasting glucose as independent variables did not show any significant difference either.

Conclusion: Our data suggested that impaired fasting glucose is not associated with increased risk of coronary atherosclerosis. Key words: Atherosclerosis, Coronary artery disease, Impaired fasting glucose, Angiography.

P1543 Rapid healing of a therapy refractory diabetic foot after combined transplantation of autologous bone marrow stem cells



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Background: The diabetic foot mainly depends on painless pressure lesions, which are based on diabetic polyneuropathy and microangiopathy. In these cases the regenerative potential of adult autologous mononuclear stem cells could serve as causal therapy.

Methods: A 63 year old patient with long lasting type II diabetes suffers from a reduced walking distance of 200 meters and a therapy refractory ulcer at the right ball of the great toe. Therefore we decided to perform a combined intraarterial and intramuscular transplantation of stem cells into the right limb for the first time on this disease. Bone marrow was harvested from iliac crest and afterwards the mononuclear cell fraction was separated. The cell suspension was transplanted intramuscular (5 ml into the thigh and 5 ml into the lower leg) and intraarterial (10 ml into the femoral artery) on the affected limb.

Findings: Already 8 weeks later the ulcer healed completely. Furthermore, 6 months after transplantation the walking distance increased from 226 meters to 500 meters, on venous occlusion plethysmography the arterial blood circulation at rest increased from 2.03 up to 2.50 ml/100 ml tissue/min and the reactive hyperaemia increased from 4.6 to 7.2 ml/100 ml tissue/min. Capillary-venous oxygen saturation in 12mm depth stayed alike on a high level (thigh: from 72% to 74%, lower leg: from 72% to 75%).

Conclusion: The combined intraarterial and intramuscular transplantation of autologous bone marrow stem cells could constitute a novel, clinical feasible and safe therapy for patients with diabetic foot syndrome. The success of this approach may be ascribed to microangiogenesis and to an antiinflammatory effect of the transplanted stem cells.

P1544 Acetylcysteine versus bicarbonate or combination to prevent contrast-induced nephropathy in patients with diabetes and chronic renal insufficiency: ABC contrast study



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Contrast-induced nephropathy (CIN) is one of the most causes of new acute renal failure among hospitalized patients.

Objective: To compare the prophylactic effectiveness of N-acetylcysteine (NAC) with saline hydration versus sodium bicarbonate versus NAC with bicarbonate in patients with chronic renal failure (CRF) and/or diabetes undergoing angiography.

Methods: Prospective, single centre, randomized trial included 210 pts (mean age 61.9 ± 8.6 years) with DM and/or CRF ($\text{Scr} \geq 150 \mu\text{mol/l}$). Pts were randomly assigned to receive 12 h before and 12 h after administration of the contrast agent, one of the three following prophylactic regimens: (1) NAC group: NAC orally (1200 mg twice daily) + saline hydration (1000 ml; 0.9%); (2) Bicar group: received 500 ml of sodium bicarbonate 14%; (3) (NAC-Bicar group): NAC orally + 500 ml of sodium bicarbonate 14%. All the procedures were performed with ionic, high-osmolality contrast agents (diatrizoate). The primary endpoints were the occurrence of CIN (increase in $\text{Scr} \geq 25\%$ within 48 hours) and the change in Scr within 48 h post-angiography.

Results: CIN occurred in 18.6% of the pts in the NAC group, 14.3% in the Bicar group and 20% in NAC-Bicar group ($p=ns$). In the NAC and in the NAC-bicar group, Scr increased significantly from 102.5 ± 41 to $114.7 \pm 65 \mu\text{mol/l}$ ($p=0.03$) and from 98.2 ± 36 to $110.7 \pm 48 \mu\text{mol/l}$ ($p=0.007$), respectively. No significant difference was observed in the Bicar group (95.8 ± 34 vs $101.4 \pm 43 \mu\text{mol/l}$; $p=ns$) (figure).

Conclusions: No significant differences were observed between the three pro-

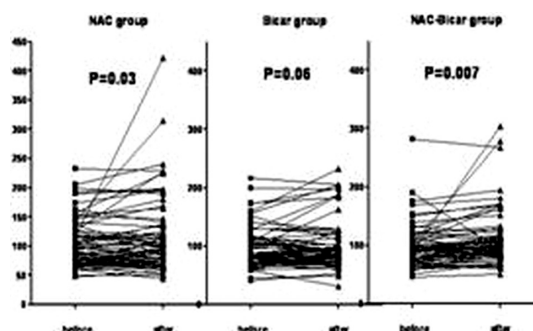


Fig. 1. Scr change in all groups.

phylactic strategies with regard to occurrence of CIN, whereas we showed no significant change in serum creatinine after angiography with sodium bicarbonate compared to NAC alone or NAC with bicarbonate.

P1545 Long term prognostic influence of glucose metabolism changes in acute coronary syndrome patients



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Background: Despite diabetes (DM) and coronary disease pandemics, little is known about the prognostic impact of diagnosis and treatment of abnormal glucose metabolism in acute coronary syndromes (ACS) patients.

Aim: To clarify the relationship between abnormal glucose metabolism and ACS. **Methods:** Prospective analysis of 199 consecutive patients admitted for ACS in a single centre between October/03 and May/04. Patients were divided in 3 groups based on fasting glucose and oral glucose tolerance test (OGTT): A-DM (n=90); B-impaired fasting glucose/impaired glucose tolerance (IFG/IGT) (n=50); C-normal (n=59).

Results: Patients with DM were older, had more risk factors, family history of DM and dyspnoea at presentation. Previous coronary disease and cardiovascular therapy were more prevalent in DM. C reactive protein levels were higher in DM, despite having more unstable angina and less ST-elevation infarction; however, in-hospital morbidity rate was higher in these patients. DM patients received less angiotensin converter enzyme inhibitors but more beta blockers; they were more submitted to coronariography and angioplasty. Mean follow-up time was 17 months (6-25), similar in 3 groups and revealed a higher mortality rate in DM (figure 1A). The composite endpoint (death, rehospitalization for cardiovascular disease, ACS, angioplasty and coronary artery bypass graft) was also more prevalent in DM; however IFG/IGT had an events profile similar to DM and clearly worst than normal patients (figure 1B).

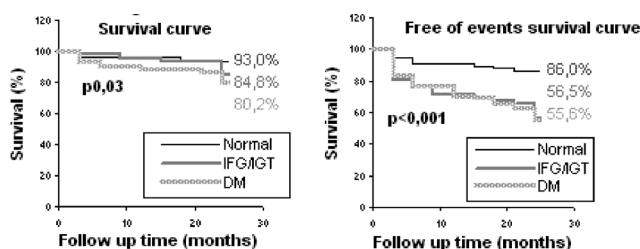


Fig. 1. A. Survival curve. B. Free of events survival curve.

Conclusions: These results emphasize the importance of OGTT in ACS patients, to assess their glucose metabolism, as even minor abnormalities carry a poor prognosis. It is also clear that all patients with glucose abnormalities should receive comprehensive anti-ischemic and glucose modulating therapy.

P1546 Prognosis impact of glomerular filtration rate in elderly patients admitted to hospital with the diagnosis of heart failure

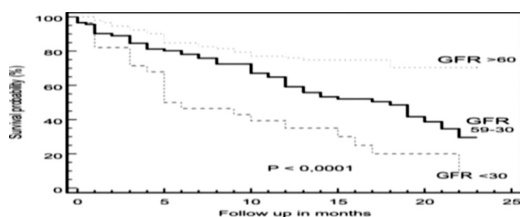


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Aim: The presence of renal dysfunction is a well known prognosis factor in Heart Failure (HF), its incidence and impact in the old and high comorbidity populations admitted to hospital with the diagnosis of HF is not well studied.

Methods: Prospective study of consecutive patients admitted for hospitalization in the period of the year 2004 in an Internal Medicine department with the diagnosis of HF. Demographics, comorbidity, drug therapy, lab test and examination findings were abstracted from the case notes. We estimated the Glomerular Filtration Rate (GFR) with the Levey equation.

Results: We studied 228 patients, mean age 76.5 ± 10.8 years, 115 (50.4%) women, 64 (28.1%) with diabetes mellitus, 119 (52.2%) hypertension, 55 (24.1%) ischaemic cardiomyopathy. The mortality at the end of the year 2005 was 43% with a median of follow-up of 14 months. The distribution of the study subjects in



Survival adjusted by GFR

Distribution of Glomerular Filtration Rate in the study population

Glomerular Filtration Rate (mL/min/1.73m ²)	Number of patients (% of patients)
Normal or mild renal dysfunction (>60)	102 (44.7%)
Moderate renal dysfunction (50-59)	98 (43.0%)
Severe renal dysfunction (<30)	28 (12.3%)

groups of GFR was the next that is shown in the GFR table. The 55.3% of the population studied shown a moderate or severe renal dysfunction. In the picture we can see the strong impact in mortality of GFR value at the admission.

Conclusions: Renal dysfunction at the admission is very frequent in elderly patients with HF and has a strong impact in the prognosis.

P1547 Oxidized LDL autoantibodies in acute myocardial infarction without classical risk factors. A case-control study



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Introduction: In recent years several emerging cardiovascular risk factors have been suggested to be predictive of acute myocardial infarction (AMI): among them, oxidized LDL autoantibodies (OLAB) are inversely related with oxidized-LDL levels. Our aim was to establish the role of several non-classical risk factors for myocardial infarction.

Methods: A multicentre case-control study including 537 patients. Cases: 128 patients with a first AMI without classical risk factors (hyperlipidemia, hypertension, smoking habits, and diabetes). Controls: 409 population-based healthy controls randomly recruited from the census. At the admission we measured: Glucose, lipid profile, Body Mass Index (BMI), triglycerides, lipoprotein(a), homocysteine. Physical activity in the previous year was measured by the Minnesota Leisure Time Physical Activity questionnaire. OLAB were measured 6 months after the acute phase inpatients under medication some of them with antioxidant properties (i.e. statins).

Results: Cases were older (64 vs. 44.1 years, $p < 0.001$) and with lower previous physical activity (205 vs. 423, $p < 0.001$) than controls. There were no differences in BMI, total and LDL cholesterol, triglycerides, Lp(a), and homocysteine. Cases had higher glucose (116 vs 95 mg/dL, $p < 0.001$) and lower HDL-cholesterol (47 vs. 57 mg/dL, $p < 0.001$) than controls. OLAB levels were lower in cases (205 vs. 377, $p < 0.001$) than controls. In the multivariate logistic regression analysis only OLAB levels remained independent risk factor (OR 2.39, 1.15-4.99 (IC95%)) after adjusting for age, sex, glucose and lipid profile.

Conclusions: Patients with first AMI without classical risk factors presented low levels of OLABs indicating a higher degree of LDL oxidation, despite the use of antioxidant medications. This feature suggested that oxidative status measured by OLAB could be a risk factor for development of AMI.

P1548 Association between dietary intake of n-3 polyunsaturated fatty acid and systemic low-grade inflammation: a community-based cross sectional analysis



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Background: Intake of n-3 polyunsaturated fatty acid (PUFA) has been reported to reduce cardiovascular events. Activation of systemic inflammation such as elevated serum CRP levels is positively associated with progression of atherosclerotic cardiovascular disease. However, the association between dietary intake of n-3 PUFA and CRP levels has not been fully examined in the general population and optimal dietary intake of n-3 PUFA for suppressing inflammatory reaction has not been determined.

Methods: A nutrition survey was conducted and serum high-sensitivity CRP (hsCRP) levels (mg/L) were measured in 4,351 men and 9,844 women aged 40 years to 69 years who visited a community health examination. Serum hsCRP levels and multivariate adjusted logarithm-transformed hsCRP levels were compared between quartile groups according to dietary intake of n-3 PUFA (expressed as % of total energy intake) after adjusting for age, body mass index, systolic blood pressure, total cholesterol level, HDL cholesterol level, HbA1c level, smoking status, exercise habit and regularity of drinking.

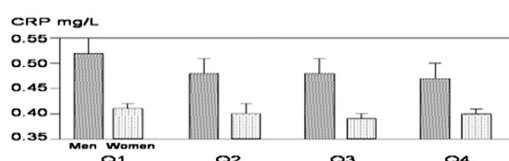


Fig. 1. Adjusted geometric means of CRP (95%CI)

Results: Adjusted mean of CRP levels were significantly higher in the lowest quartile category (dietary intake of n-3PUFA < 1% of total energy intake: n-3PUFA < 2.8 g/day) than in the other three groups among men (see figure). However, this relationship was not observed in women.

Conclusion: Dietary intake of n-3PUFA more than one percent of total energy intake (>2.8 g/day) is significantly associated with low levels of CRP in men, but not in women. This suggests that beneficial effects of n-3PUFA intake on systemic inflammation may be favorable in men, but obscure in women.

P1549 NORTH-TO-SOUTH GRADIENT IN LIPID PEROXIDATION IN MEN IN EUROPE



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Purpose: The low myocardial infarction incidence in southern Europe could be related to higher consumption of antioxidants, resulting in lower lipoperoxidation. A north-to-south gradient across Europe is posited, based on the degree of low density lipoprotein cholesterol oxidation (oxLDL) in the population. The aim of this study was to compare lipid peroxidation across Europe in coronary heart disease (CHD) patients.

Methods: A cross-sectional multicenter study included 692 stable CHD male subjects aged 25 to 74 years (mean 60.2 ± 8.9) from five European countries in three regions: Northern Europe (Finland and Sweden), Central Europe (Germany), and Southern Europe (Greece and Spain). Lipid peroxidation was determined by the level of circulating oxLDL.

Results: Adherence to a Mediterranean diet, antioxidant intake, alcohol intake, and lipid profile were significantly associated with oxLDL. The logarithm of triglyceride-adjusted oxLDL levels in the adjusted models were higher in Northern (60.9 U/L) than in Central (54.4 U/L) and Southern populations (53.8 U/L), $p=0.01$, and paralleled the increasing CHD mortality and incidence rates observed in other studies. The probability of Northern Europe scoring the highest oxLDL levels was 95.5% and 98.9%, in the logarithm of triglyceride-adjusted and fully adjusted models, respectively. The probability for this order to hold after adjustment by country was 78.4%.

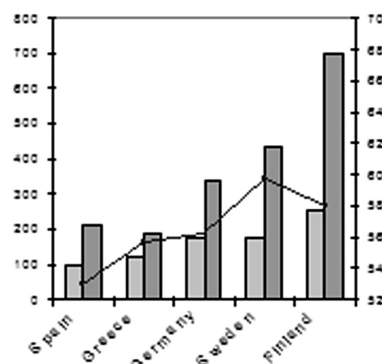


Fig. 1. Male coronary heart disease age-standardized mortality (lighter column); myocardial infarction incidence (dark column) rates per 100,000 observed in other studies on the left axis, and oxidized low-density lipoprotein levels (U/L) adjusted for triglyceride levels (line) on the right axis, ordered by increasing mortality rates of the participant countries.

Conclusions: A gradient in lipoperoxidation from northern to central and southern Europe is very likely to exist, and parallels that observed in the CHD mortality and incidence rates. Northern populations may have lower LDL resistance against oxidation compared to central and southern populations in Europe.

P1550 Endothelial function is impaired in polycystic ovary syndrome: the role of Dehydroepiandrosterone-sulfate (DHEA-S)



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Purpose: Women with polycystic ovary syndrome (PCOS) constitute a metabolically intriguing group of young women suitable for investigating the combined effects of insulin resistance and sex steroids abnormalities on the cardiovascular system. Endothelial dysfunction has been suggested to play a fundamental role in the pathogenesis of cardiovascular disease (CVD). Dehydroepiandrosterone-sulfate (DHEA-S) is the most abundant androgen produced by the adrenals and there is evidence that has a protective effect against age-related disorders, including CVD. The aim of this study was to assess endothelial function of young women with PCOS and Idiopathic Hirsutism (IH) a condition possibly related to

PCOS. The possible relationship between endothelial function and androgen levels was also examined.

Methods: Fifty six women, 27 with PCOS, 16 with IH and 13 healthy age matched women were studied. Endothelial function was assessed by measuring forearm blood flow response during reactive hyperemia utilizing venous occlusion strain-gauge plethysmography. Metabolic and hormonal parameters such as insulin, testosterone, DHEA-S, glucose were estimated in this study population. Insulin sensitivity was evaluated with Homeostasis Model Assessment (HOMA) method using the formula: (fasting plasma glucose x fasting serum insulin) divided by 22.5.

Results: The duration of reactive hyperemia (durRH), an index of endothelial function, was shorter in PCOS group (63.75 ± 13.33 sec) when compared with controls (113.18 ± 20.92 sec, $p=0.036$) and with IH (105 ± 17.20 sec, $p=0.05$). The durRH did not differ between IH and controls (ns). Interestingly, a significant positive linear correlation was found between the durRH and DHEA-S, ($r=+0.48$, $p=0.04$) in the PCOS group. The HOMA index differed significantly between PCOS, controls (2.45 ± 0.77 vs. 0.36 ± 0.14 , $p<0.0001$) and IH groups (0.50 ± 0.17 , $p=0.002$). There was no significant correlation between durRH and HOMA index or testosterone levels in the PCOS group.

Conclusions: Endothelial dysfunction may be an early sign of cardiovascular system abnormalities in young PCOS women. It is possible that increased DHEA-S levels may offer a cardioprotective advantage that attenuates the effects of cardiovascular risk factors that accompany PCOS.

P1551 Increased abdominal circumference as a cardiovascular risk factor in Germany:



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Background: The role of overweight as a risk factor for cardiovascular complications has recently decreased due to body mass index (BMI) being used to reflect total overweight instead of abdominal (visceral) fat being used as a marker for increased cardiovascular risk. The prevalence of abdominal adiposity in Germany, however, is not known.

Methods: Various professional societies define an "increased risk" for metabolic complications when the abdominal circumference in males is ≥ 94 , in females ≥ 80 cm. A "significantly increased" risk has been defined when the abdominal circumference in male is ≥ 102 and in females ≥ 88 cm. Therefore, in a snapshot registry we prospectively investigated the abdominal circumference of 55,518 persons. The results were related to age and gender and to the presence of coronary artery disease in relation to traditional cardiovascular risk factors.

Results: The mean abdominal circumference ($\pm$ standard deviation) are listed in the following table. A significant difference ($p<0.05$) could be shown for all subgroups comparing patients with or without the traditional risk factors:

Table 1

	Male	Female
All patients	99.9 cm $\pm$ 13.8 cm	89.7 cm $\pm$ 15.4 cm
CAD known	103.7 cm $\pm$ 12.3 cm*	103.7 cm $\pm$ 12.3 cm*
CAD unknown	99.1 cm $\pm$ 13.9 cm	89.1 cm $\pm$ 15.4 cm
arterial hypertension	105.3 cm $\pm$ 13.0 cm*	97.1 cm $\pm$ 14.3 cm*
no arterial hypertension	96.3 cm $\pm$ 13.1 cm	85.7 cm $\pm$ 14.4 cm
hyperlipidemia	104.1 cm $\pm$ 12.9 cm*	95.0 cm $\pm$ 14.3 cm*
no hyperlipidemia	97.8 cm $\pm$ 13.7 cm	87.7 cm $\pm$ 15.3 cm
diabetes	106.9 cm $\pm$ 12.6 cm*	100.0 cm $\pm$ 14.7 cm*
no diabetes	98.4 cm $\pm$ 13.3 cm	88.2 cm $\pm$ 14.9 cm
smokers	98.6 cm $\pm$ 14.7 cm*	85.5 cm $\pm$ 14.4 cm*
non-smokers	101.3 cm $\pm$ 13.1 cm	91.3 cm $\pm$ 15.1 cm

Conclusion: The present study documents for the first time the role of an increased abdominal circumference in a large patient cohort in Germany. The limits as defined by various professional societies also make sense in every day practice.

P1552 Erectile dysfunction is associated with increased aortic stiffness in patients with and without coronary artery disease



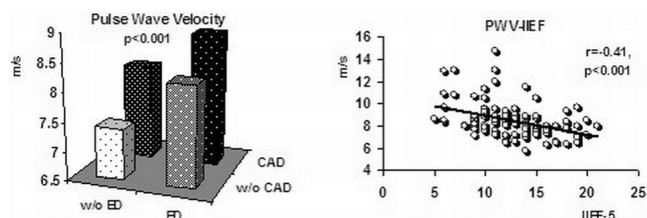
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Background: Accumulating evidence suggests that erectile dysfunction (ED) may be an early manifestation of generalized vascular disease. Aortic stiffness is an independent marker and prognosticator of cardiovascular risk. The association of ED with aortic stiffness has not been defined.

Methods: A total of 167 men were studied: 64 men (aged 58 ± 10 yrs) had ED without clinical and exercise stress test evidence for CAD, 42 men (60 ± 9 yrs) had ED and angiographically documented CAD, 28 men (58 ± 11 yrs) had angiographically documented CAD and normal erectile function and 33 men (57 ± 6 yrs) were controls with normal erectile function and no CAD. Diagnosis of ED was based on the 5-item brief form of the International Index of Erectile Function

(IIEF-5). Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness using an automated non-invasive device (Complior®).

Results: In patients without CAD, subjects with ED had significantly increased PWV compared to subjects without ED ($p < 0.01$, left figure). Furthermore, in patients with CAD, subjects with ED had significantly increased PWV compared to subjects without ED ($p < 0.05$). There were no significant differences between the four subgroups regarding systolic and diastolic pressures. In men with ED, a negative correlation between PWV and IIEF-5 score was observed (right figure). Moreover, in separate backward elimination multiple regression model, PWV was significantly associated with IIEF-5 score, after controlling for age, BMI, mean pressure, cholesterol, triglycerides, hsCRP, hypertension, diabetes and history of smoking, ($p = 0.01$, $R^2 = 0.44$).



Conclusions: ED is associated with impaired aortic elastic properties. This finding provides further evidence for the potential link between ED and cardiovascular risk.

P1553 Under-use of guidelines-recommended treatment in women admitted for acute myocardial infarction: sexism or actual contra-indications?



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Background: In acute myocardial infarction (MI), registry studies have shown that women frequently receive less guidelines-recommended therapy than men, resulting in higher mortality. The reasons for this disparity remain unclear.

Methods: Prospective multicenter registry including all cardiology centers ($n = 10$) of the Franche-Comte region (1.2 million inhabitants) in France. Demographic and clinical characteristics were recorded at admission, as well as all indications, prescription and contra-indications for guidelines-recommended treatment. "Compliance" was defined as a treatment actually given when indicated and in the absence of contra indication.

Results: After 6 months recruitment, 535 patients (263 STEMI and 273 NSTEMI) were included: 351 males and 184 females, mean age 67 ± 14 years. Age and GRACE risk score at admission were significantly higher in women. Compliance with recommendations regarding reperfusion strategy, aspirin and beta-blockers was comparable, but a significant and unexplained under-use of GP2b/3a inhibitors, statins and ACE inhibitors was observed in women.

	NSTEMI		STEMI	
	Women (n=99)	Men (n=174)	Women (n=85)	Men (n=177)
Age	73±14	62±15	76±12	65±13
GRACE risk score	170±46	151±44	156±41	134±42
Aspirin	91/93 (98)	169/174 (97)	82/83 (99)	175/177 (99)
GP2b/3a inhibitors	49/81 (60)	124/165 (73)		
Reperfusion therapy (STEMI)			47/59 (77)	128/158 (81)
ACE inhibitors	77/96 (80)	143/168 (85)	54/80 (67)	134/164 (82)
Beta-blockers	59/87 (68)	122/151 (73)	48/74 (65)	108/148 (73)
Statins	82/95 (86)	166/173 (96)	67/83 (81)	168/176 (95)

Age, GRACE score=mean±SD, all other values actual/eligible (%).

Conclusions: Women admitted for acute MI were, on average, 10 years older than men, and had a higher risk score at admission. Despite the absence of contra-indications, they less frequently received guidelines-recommended treatment, namely GP2b/3a inhibitors, ACE inhibitors and statins.

P1554 Gender differences in quality of life of cardiac rehabilitation patients



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Introduction: Evaluation of quality of life at the baseline of cardiac rehabilitation (CR) is nowadays recommended, since the psychosocial status of the patient is an important success factor in CR. In the Netherlands about 60-70% of CR centers now use the Quality of Life after Myocardial Infarction (QLMI) questionnaire as a needs assessment instrument at CR baseline.

Objective: To examine differences in quality of life between males and females measured at CR baseline.

Methods: Demographic, QLMI, and clinical data were prospectively collected for

all patients admitted to 8 Dutch CR centers during a period of six months in 2005. All data were collected using an electronic patient record, and randomly validated with independent sources afterwards.

Results: Data from 1530 patients were collected; 1388 patients (91%; 1051 males and 337 females) filled in the QLMI questionnaire. The mean total score of the QLMI was $121.6 (\pm 23.6)$ out of 168. The mean scores for the physical, social and emotional domain of the QLMI were $47.8 (\pm 11.2, \text{max } 70)$, $37.5 (\pm 7.5, \text{max } 49)$ and $55.5 (\pm 12.6, \text{max } 77)$. Female patients scored significantly lower than male patients ($p < 0.001$, Mann-Whitney U test) on all domains of the QLMI (total score 114.9 vs. 123.7; physical 44.9 vs. 48.8; social 35.9 vs. 38.0; emotional 51.9 vs. 56.7). These results were corrected for differences in age, smoking status, body mass index, and diagnosis/intervention.

Conclusion: Female patients' quality of life at CR baseline is worse than that of male patients, in particular on the emotional domain. We conclude that in women cardiac health problems have a greater impact on quality of life than in men. The difference could be partially explained by a referral bias.

P1555 The impact of age and gender on the prognostic importance of N-terminal pro brain natriuretic peptide, high sensitivity C-reactive protein and urine albumin/creatinine ratio in apparently individuals



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Background: We have previously shown that N-terminal pro brain natriuretic peptide (Nt-proBNP), high sensitivity C-reactive protein (hsCRP) and urine albumin/creatinine ratio (UACR) predicted cardiovascular (CV) events in a general population aged 41, 51, 61 or 71 years. In this study we wanted to investigate the impact of age and gender on the prognostic importance of Nt-proBNP, hsCRP and UACR in a subgroup of 1994 apparently healthy individuals without diabetes, prior stroke or myocardial infarction, who did not receive any CV, anti-diabetic or lipid-lowering treatment.

Methods: In 1993 we measured CV risk factors, serum Nt-proBNP, UACR and serum hsCRP. The composite CV endpoint (CEP) of CV death and non-fatal stroke or myocardial infarction was assessed after 9.5 years. The two youngest and two eldest age groups were merged.

Results: In Cox regression analyses, log(Nt-proBNP) and logUACR predicted CEP in men as well as in women, whereas log(hsCRP) only predicted CEP in men ($P < 0.05$ for interaction). Log(Nt-proBNP) and logUACR predicted CEP primarily in older subjects (both $P < 0.05$ for interaction), whereas log(hsCRP) predicted CEP in younger as well as in older subjects. Actually, log(hsCRP) did not predict CEP significantly in 71 years old subjects ($HR = 1.22$, NS).

Cox hazard ratios for prediction of CEP

	Men	Women	41 or 51 years	61 or 71 years
Log(Nt-proBNP)	1.77***	1.79**	0.91	1.46**
LogUACR	2.15***	2.35***	1.42	2.68***
Log(hsCRP)	1.72***	1.10	1.34*	1.33**

* $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$

Conclusion: Nt-proBNP and UACR were strong predictors of CEP independently of gender, but primarily in older subjects aged 61 or 71 years, whereas hsCRP was a strong predictor of CEP in middle-aged men. This supports the hypothesis that hsCRP, as a marker of inflammation, is elevated early in the development of atherosclerosis whereas Nt-proBNP and UACR may be markers of later subclinical CV damage.

P1556 Does the change of Left Ventricular torsion after dynamic exercise assessed by novel two-dimensional speckle tracking imaging contribute to increase diastolic suction?



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Purpose: Left ventricular (LV) torsion was believed to store potential energy and to play an important role in generating diastolic suction. And a newly developed two-dimensional speckle tracking imaging (STI) provide a more objective estimation of LV torsion. However there was no report about comparison of LV torsion assessed by this novel method with LV diastolic functional parameters after exercise.

Methods: The study group included 112 participants (56 men and 56 women, mean age 40.5 ± 1.1 years, range 15 to 66 years) with normal resting LV function and no detectable structural heart disease confirmed by echocardiography and exercise treadmill test. Two-dimensional echocardiographic examinations were

performed at rest and immediately after exercise treadmill test. Postexercise image acquisition was completed within 3 minutes. 3 cardiac cycles from each baseline and postexercise recording were digitized and analyzed. LV torsion was measured by STI at papillary muscle level of LV.

Results: Participants showed normal LV systolic functions ($EF=65.4\pm0.4\%$) and normal left atrial volume index ($21.9\pm0.6\text{cc/m}^2$). Participants exercised for an average of $10\text{ min } 47\text{ sec}\pm7\text{ sec}$ and achieved $94.6\pm0.8\%$ of maximally predicted for age with a mean peak heart rate $170\pm2\text{ bpm}$. After exercise, LV torsion increased 23%, from 4.3 ± 0.1 to 5.2 ± 0.2 degrees ($p=0.000$). Also the duration difference between pulmonary venous atrial flow reversal and transmitral A wave, LV end diastolic volume, transmitral E/A ratio and deceleration time of transmitral E wave decreased ($p=0.000$, $p=0.000$, $p=0.000$ and $p=0.001$, respectively). And as we expected, the change of LV torsion showed significant correlations with the change of transmitral E/A ratio ($r=-0.356$ and $p=0.000$). For assessing LV torsion at resting and after exercise, the correlation coefficient was $r=0.92$.

Conclusions: Increased LV torsion after exercise contributes to improve diastolic function. And two-dimensional STI may be a promising new method in assessing LV torsion after exercise as well as at resting.

P1557 Low-to-moderate intensity exercise training reduces myocardial infarct size in rats



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Background: Exercise training(ET) programs are known to be effective in reducing coronary heart disease risk factors in humans and rats. However, there is a paucity of data on whether ET reduces infarcted size after experimental infarct in rats.

Objective: We tested whether ET would have a protective effect on the heart by reducing infarcted size after experimental infarct in rats.

Methods: Twelve male Wistar rats were submitted to an incremental exercise testing on a motor treadmill until exhaustion, and peak oxygen(peakVO₂) was further determined. Rats were randomly assigned into sedentary(S) and trained(T). ET was performed on a treadmill for 60 min, 5 times/week for 12 weeks at 60% of peakVO₂. Forty eight hours after the last ET session, a catheter was inserted in left ventricle(LV) for measurements of left ventricular end-diastolic pressure(LVEDP) and myocardial infarction(MI) was induced by coronary ligation technique. Seven days after MI induction, rats were killed and hearts were harvested. Sections were stained with hematoxylin and eosin, and Masson for examination with a light microscope. Infarct size was expressed by evaluation of necrotic area, expressed as a % of the risk region(total LV area). Data were expressed as mean $\pm$ SD.

Results: In relation to S, ET significantly increased exercise capacity by improving peak VO₂ in T rats($p=0.02$) without changing body weight(499 ± 38 vs 461 ± 38 g; $p=0.1$). However, LVEDP measured pre-MI($p=0.1$) and 5 min post-MI induction($p=0.8$) were not different between S and T rats. Of interest, ET significantly reduced infarcted size(24 ± 12 vs $7\pm4\%$; $p=0.007$).

Data from sedentary and trained groups

	Sedentary	Trained	p
Exercise tolerance(Distance)-m	328 $\pm$ 79	774 $\pm$ 292	0.0001
Delta VO ₂ (VO ₂ peak-VO ₂ rest)-ml/min/kg	20 $\pm$ 6	25 $\pm$ 4	0.02
LVEDP pre MI-mmHg	3.2 $\pm$ 0.9	4.5 $\pm$ 1.7	0.1
LVEDP post MI-mm Hg	16.3 $\pm$ 1.5	16.1 $\pm$ 2.5	0.8
LVArea-micrometre	50094773 $\pm$ 6910409	60562255 $\pm$ 15008279	0.13
MI Area/LV Area(%)	24 $\pm$ 12	7 $\pm$ 4	0.007

Conclusions: Collectively these data provide direct evidence for the beneficial effects of ET protecting the heart from ischemic injury reducing infarcted area in rats.

P1558 The impact of mild renal insufficiency on long-term outcome in patients with known or suspected coronary artery disease



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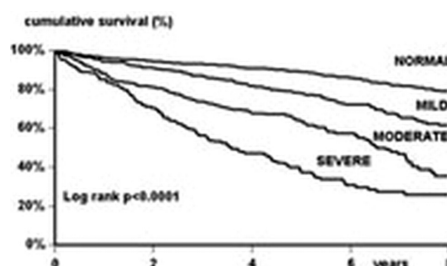
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Objective To determine the association between renal dysfunction, in particular, mild dysfunction, and long-term mortality and hard cardiac events in patients with known or suspected CAD. **BACKGROUND** Renal impairment is an important predictor of adverse cardiac outcome in patients with CAD. The effect of milder degrees of renal insufficiency as a risk factor on the long-term outcome is less clear.

Methods We investigated whether the level of renal function, estimated by glomerular filtration rate (GFR), was associated with the risk of mortality, cardiac death and hard cardiac events (cardiac death or nonfatal MI) among 1788 patients with known or suspected CAD. None of the patients were on hemodialysis. The mean follow-up was 6 years (range, 6 months to 12 years).

Results Renal function was normal (GFR >80 ml/min) in 44% of the patients. Impairment of renal function was mild (61-80 ml/min) in 26%, moderate (41-60

ml/min) in 19% and severe (<40 ml/min) in 11%. Cumulative survival rates in these groups were 90%, 88%, 73% and 52% at 5 years, respectively, and 82%, 72%, 57% and 32% at 8 years ($p<0.0001$). Compared with patients with normal renal function, the multivariable hazard ratios for all cause mortality was 1.7 (95%CI 1.3-2.1) in patients with mild impairment, 2.4 (95% CI, 1.9-3.2) with moderate impairment, and 5.1 (95% CI, 3.8-6.7) with severe renal impairment. Similar relations with cardiac death and hard cardiac events were found.



Conclusions: The present study shows that renal function is a graded and independent predictor of long-term mortality. In particular, mild renal insufficiency in patients without symptoms or signs of renal disease, is an important predictor of hard cardiac adverse events. Intense treatment and close surveillance of these patients should be implemented.

P1559 ST elevation in lead aVR during exercise testing should not be ignored



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Purpose: The diagnostic significance of ST elevation (STE) in lead aVR during exercise is controversial. It is electrically opposed to leads V5 and V6 and so changes are felt to represent ST depression (STD) in these leads. Lead aVR is directed towards the left ventricular (LV) cavity and so changes may also indicate LV dysfunction on exercise. We aimed to assess the diagnostic value of STE in aVR during exercise prior to Tc99-sestamibi scanning and its predictive value in identifying ischemic territory and angiographic findings.

Methods: Consecutive patients attending for Tc99-sestamibi perfusion imaging between April 2004 and Aug 2004 were enrolled. Patients completed a treadmill protocol. Peak exercise ECGs of these patients were coded by 2 blinded investigators. STE $>0.5\text{mm}$ in lead aVR was considered significant. Perfusion imaging results including gated images assessing LV function were recorded. A proportion of the images were double reported by a blinded investigator. Findings at coronary angiography were assessed.

Results: Of the 557 patients studied, STE in lead aVR occurred in 25% (138) of the patients. More patients with STE in aVR had a reversible defect on imaging compared with those that had no STE in aVR (41% 56/138 vs 27% 114/419, $p=0.003$). Defects indicating a left anterior descending artery (LAD) culprit lesion were more common in the STE aVR group (20% 27/138 vs 9% 39/419, $p=0.001$). The presence of STE in aVR did not indicate more severe ischemia as measured by the stress hypoperfusion index - 7.1 (2.8-12.9) vs 6.1 (2.6-11.5) $p=0.125$. Rest and stress ejection fractions were not significantly different between the STE aVR group and those who did not develop STE in aVR on stress ($p=0.281$).

There was a trend towards coronary artery stenosis ($>70\%$) in a double vessel distribution involving the LAD in those patients who had STE in aVR compared to those who did not (22% 8/37 vs 5% 4/76, $p=0.06$).

Logistic regression analysis demonstrates that STE in aVR (OR 1.36 $p=0.233$) is not an independent predictor of inducible abnormality when adjusted for STD $>0.1\text{mV}$ (OR 1.7 $p=0.003$), however using anterior wall defect as an endpoint STE in aVR (OR 2.77 $p=0.008$) remained a predictor after adjustment for STD (OR 1.4 $p=0.281$).

Conclusions: STE in aVR during exercise occurs frequently. It does not diagnose significantly more inducible abnormalities than STD alone. However, unlike STD which is not predictive of a territory of ischemia, STE in aVR is associated with an anterior wall reversible defect.

P1560 Metabolic syndrome in an Iranian adult population



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Background: The clustering of several cardiovascular disease(CVD) risk factors such as abdominal obesity, hypertension, dyslipidemia and disturbances in glucose metabolism has been termed Metabolic Syndrome "MS". The MS has been shown to predict CVD and diabetes. Some epidemiological studies showed that CVD is the main cause of worldwide mortality; also they showed that diabetic patients have excessive risk to CVD mortality.

Methods: According to the Adult Treatment Panel (ATP III) reports, participants having >3 of the following criteria were defined as having the MS: Abdominal obesity: waist circumference > 102 cm in men and >88 cm in women, Hypertriglyceridemia: ≥ 150 mg/dl, Low high-density lipoprotein (HDL) cholesterol: <40 mg/dl in men and <50 mg/dl in women, High fasting blood sugar ≥ 110 mg/dl, High blood pressure $\geq 130/85$ mmHg.

Results: Overall, the age-adjusted prevalence of the MS in Iranian population was 21.9%. Its overall prevalence is 21.9 selected population and are 25.4% and 21.7% in urban and rural areas of Isfahan respectively. It was highest among rural Isfahani 50-59 year women (68.9%) and lowest among rural Arakian men (5.6%). Men had the highest prevalence of hypertriglyceridemia 54.8% and women had the highest prevalence of abdominal obesity 86.1% and 65.6% low HDL cholesterol concentration. In both genders, the metabolic syndrome score increased by the BMI class.

Conclusion: We found that approximately one fifth of Iranian adults living in central part of Iran have the MS, with an increasing prevalence of the MS components with higher classes of the body mass index. Our study showed an increasing risk of features of the MS among middle-aged women in urban area. The results indicate that primary prevention should not only consider biological risk factors, but must also take socio-demographic characteristics to identify those at high risk of diabetes and CVD.

P1561 Is there a need to increase number of cardiology specialist to improve hypertension treatment and control efforts?



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Background: WHO Global Programme on Evidence for Health Policy reported that over 61% of cardiovascular disease is due to hypertension (HTN). Disparities in HTN treatment and control by age, sex, and race/ethnicity continue to exist. In the U.S. there is a decreased quality of life among more than 70% of HTN adults. This study examines patterns in HTN treatment and control, HTN-related hospitalization and mortality, and numbers of cardiologist in U.S. and those coming from medical schools.

Methods: This report presents on mortality from the nation's National Vital Statistics System for 1990-2002; on HTN treatment and control from the National Health and Nutritional Examination Survey (NHANES 1999-2002); hospitalizations from the National Hospital Discharge Survey for 1990-2002; Medicare hospital claims information for 1990-2002; and information from AMA and medical schools for 1990-2005. Five data systems were used to complete this report.

Results: Since 1990, the numbers of deaths and hospitalizations, death rates, and hospital rates have increased for HTN, particularly among blacks, women and older adults. Death rates were higher for blacks than whites, men than women throughout the past two decades. From 1990 to 2002, total hospitalization due to hypertension increased 50% from 124 to 185 per 100,000 populations. The increase was among women (53%) than men (48%). Death rates and Medicare hospital rates have been higher for blacks than whites during the past 10-12 years. Two distinct geographic clusters were observed for the highest hospital rates in the Medicare population and the highest death rates for HTN - one in the south-eastern US and a second in the northeastern region. About 23.2% of adults had HTN, 50.0% of HTN adults were treated, and 63.3% of those treated were adequately controlled. HTN prevalence was higher among insured (23.8±standard error of 1.2%) compared to uninsured adults (19.9±1.3%). These differences were more marked among adults with lower income, aged >45 years, lower attained education, and who were NHB.

Conclusion: Increases in mortality and hospitalization for HTN; regional differences in HTN-hospitalization; poor HTN treatment and control reflects increased need for health care providers that have special training and knowledge for HTN management. Public Health Impact & Challenges: At present, public health initiatives should support professional education efforts to further increase physician awareness that early detection is needed to initiate prompt, effective disease management and increase number of specialist available.

P1562 Factors associated with compliance with dyslipidemia screening and monitoring



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Background: Many of patients with coronary artery disease (CAD) are under screened and under monitored (S&M) for dyslipidemia. The 4C data base gives an opportunity to reveal factors associated non-adequate S&M.

Objectives: To characterize independent factors associated with non-adequate S&M.

Methods: Patients with CAD, aged 20-80, from 56 intervention clinics and 56 demographically matched clinics providing routine practice were enrolled in the study. By incorporating computerized databases we created a comprehensive registry including demographics, diagnosis, and laboratory results. Reminders were sent to GP's of patients requiring S&M in the intervention arm. Follow-up

period was divided into 6 months intervals. Patients with at least 75% of screened intervals were considered to have adequate monitoring of LDL levels.

Results: Follow-up was available for 7448 patients with CAD. 51.7% of patients were defined as adequately S&M. Independent Factors associated with adequate S&M are presented in the table.

Table 1. Independent Factors associated with adequate Screening & Monitoring

p-value	95%CI	OR	
0.001	1.44-2.72	1.98	Latin America origin
0.001	1.44-2.47	1.89	Treated in a Kibbutz
0.001	1.36-1.79	1.56	Post CABG
0.001	1.45-1.79	1.61	Diabetes
0.001	1.38-1.68	1.53	Re-Hospitalization
0.001	1.18-1.63	1.39	East Europe origin
0.001	1.29-1.59	1.43	Dyslipidemia
0.001	1.13-1.43	1.28	Post PCI
0.001	1.15-1.39	1.27	Intervention Arm
0.030	1.02-1.35	1.17	Age >55 years
0.004	0.71-0.94	0.82	After CVA
0.001	0.72-0.80	0.80	Active smoking
0.001	0.52-0.77	0.63	Minority

Conclusions: Under S&M is a major obstacle to implement effective secondary prevention of cardiovascular disease. Demographic and clinical backgrounds of patients are associated with the rate S&M. Improving secondary prevention measures is feasible using automatic computerized reminders system.

P1563 Results of 22-year prospective study in children with normal and elevated blood pressure



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The timely identification of children and adolescents at risk of hypertension when they reach adulthood can be of use in the reduction of its prevalence. 22-year prospective study of blood pressure (BP) dynamics in children since they were 13 years old took place in Moscow.

Materials and the results of the study: Representative sample of male and female patients with different levels of blood pressure 13 years old (N=311) was repeatedly examined till patients were 35 years old. The increase with age of systolic (SBP) and diastolic blood pressure (DBP) was found in boys and girls both, but the end of puberty was marked by more pronounced rise of BP (especially SBP) in boys. BP at adult age correlated with BP and its covariates during childhood though the latter determined only 15% and 32% of dispersion of future SBP level and 22% and 27% of dispersion of future DBP level in males and females correspondingly.

Conclusion: Further studies are necessary for identification of additional factors determining BP levels and age-specific dynamics. Revealed characteristics of BP age-specific dynamics warrant preventive measures during childhood (at puberty or early prepubertal period).

P1564 Prevalence of peripheral arterial disease in patients with acute coronary syndrome



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Lower extremity peripheral arterial disease (PAD) refers to a chronic obstructive atherosclerotic disease that affects approximately 20% of adults older than 55 years. PAD is associated with ongoing atherogenesis in other vascular beds and increased mortality, but is often underdiagnosed.

We designed a multicentric, prospective study to assess the prevalence of PAD in patients suffering an acute coronary syndrome (ACS). Patients older than 40 years, admitted with an ACS were included during a 3 month period and screened for PAD with a resting ankle brachial index (ABI) test. PAD was defined as an ABI of less than 0.90 or previously diagnosed PAD (ie. previous angiography or invasive procedure such as angioplasty or arterial bypass surgery).

Table

Age (years)	65.7 (12.2)
Male gender:	979 (71.4%)
Hypertension:	1107 (79.5%)
Diabetes mellitus	583 (41.9%)
Current smoker	425 (31.8%)
Hypercholesterolemia	1178 (84.6%)
Previous coronary artery disease	579 (41.6%)
Previous cerebrovascular disease:	122 (8.8%)
Previous PAD	232 (16.7%)
ABI	0.90 (0.2)
Diagnosed PAD	610 (43.8%)

Clinical characteristics of patients admitted with ACS (n= 1392)

A total of 1392 patients were included (mean age 65.7 ± 12.2 years; 71.4% male). Clinical characteristics of the study patients are shown in table. The majority of patients were admitted for Non ST elevation ACS (747; 56.1%) and 41.6% had previous coronary artery disease. PAD was known in 232 patients (16.7%), but after a vascular examination with ABI, prevalence of PAD increased to 43.8% (378 patients newly diagnosed of PAD).

In this study, using a simple, noninvasive and reliable test, we detected a high prevalence of PAD among patients with ACS. Furthermore, the use of ABI established this diagnosis in an additional 27.1% of patients that otherwise would have been misdiagnosed. The use of this simple test would improve our diagnostic and prognostic accuracy in patients with ACS and should be used as part of the vascular risk assessment.

P1565 Cardiovascular disease risk prediction in the elderly in Spain: The EPICARDIAN Risk Score

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Purpose: To develop a simple and specific CVD risk assessment tool for the elderly in Spain. To improve the existing European Score taking the diabetic status into account.

Study population and methods: The score was based on the data of a long-term follow-up of the EPICARDIAN cohort. A population based-sample of people older 65 years from Madrid ($n=1,297$). Baseline examination in 1994. The follow-up was complete for 76.4% (median 7.7 years). CVD events were classified using the International Classification of Diseases (codes 401-448 for the ninth revisions). Subjects with previous MI at baseline were excluded. The diagnosis of diabetes, was based on the WHO-1999 definitions and hypertension on JNC-VII definition. The risk functions were calculated using Cox proportional hazard model. The risk scores were derived from the beta-coefficients in the linear part of the Cox proportional hazards model. Only those factors, significant in the multivariate models, were included. The model was stratified on sex, separate hazard functions were calculated for men and women.

Results: Independent risk factors, adjusted for confounding and interactions, were: age (RR 4.38, 95%CI: 1.84, 10.46); male gender (RR 1.94, 95%CI: 1.32, 2.86); diabetes (RR 2.31, 95%CI: 1.33, 4.02); and hypertension (RR 2.78, 95%CI: 1.30, 5.96). A negative interaction was found between age and hypertension. Smoking and total-cholesterol were not significant variables in any of the different models tested. The absolute risk increased exponentially with age, both in men and women. Males consistently showed a two-fold risk than women for each risk category at all age-groups. The presence of diabetes, hypertension or both on the same individual, significantly increased the CHD 8-year risk. However, the contribution of hypertension and diabetes at oldest ages (85 years) to the CHD incremental risk was marginal, both in males and females. For instance, the 8-years CHD absolute risk in males without diabetes and hypertension increased from 2% at 65 years to 27% at 85 years, whereas only increased from 12% to 27% respectively when both diabetes and hypertension were present. Similar trends were observed for females.

Conclusions: Age was the strongest predictor of 8-year CHD, both in males and females. Males had two-fold risk than women for all risk categories and age-groups. Smoking and total-cholesterol were not significant risk factors for CHD in this elderly cohort. The EPICARDIAN Risk Score is the first specific tool for the assessment of CVD risk for the Spanish elderly population.

P1566 Family relationships of cardiovascular risk factors in adolescents

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Objectives: To assess prevalence and relationships of CVD risk factors in adolescents aged 14-17 and their parents.

Design and methods: Four cross-sectional surveys of representative samples of school children aged 14-17 in 1989 (656), in 1994 (620), in 1999 (626) and in 2003 (667) were carried out. Total sample was 2569 (1214 males and 1355 females). Body mass index (BMI, kg/m^2), systolic (SBP) and diastolic blood pressure (DBP), serum total cholesterol (TC), high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol (LDL-C) were measured. Postal questionnaire for parents with self-reported information was used. Blood lipids of hypercholesterolemic adolescents' parents were evaluated (98 mothers and 38 fathers). Elevated blood pressure was revealed using JNC-7 criteria. Adolescent's overweight registered if body mass index (BMI, kg/m^2) was ≥ 85 percentile, parent's overweight - if BMI was $\geq 25 \text{ kg/m}^2$. Smoking was determined as regular for adolescents - cigarette/week, for adults - cigarette/day. Lipid disorders were defined in adolescents with NCEP-peds criteria (1992), in adults - with NCEP ATP III criteria (2001).

Results: Prevalence of classic CVD risk factors in adolescents and their parents is presented in Table 1. Relationships of parents' and children's blood pressure and BMI levels were revealed. Among adolescents whose mothers had elevated

blood pressure, this risk factor was registered twice more often compared with normotensive mothers' children. In adolescents with overweight and obesity both mothers and fathers had BMI higher than in adolescents with normal BMI. Adolescents' smoking was revealed two times more often in smoking families than in non-smoking families. In adolescents with hypercholesterolemia fathers' total cholesterol levels were higher than in population.

Table 1

CVD risk factors	Boys	Girls	Fathers	Mothers
Pre-hypertension	53,7%	35,2%	32,7%	23,5%
Arterial hypertension	6,5%	2,7%	24,0%	18,0%
Overweight	10,7%	12,9%	53,0%	52,0%
Smoking	40,2%	23,6%	53,4%	5,6%
Physical inactivity	52,0%	72,0%	41,6%	53,7%

Conclusion: Family aggregation of CVD risk factors indicates necessity of preventive actions at a family level.

P1567 Role of gender in the development of coronary artery disease in Greek cohort of Familial Combined Hyperlipidemia

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Purpose: Familial Combined Hyperlipidemia (FCH) is one of the most commonly inherited dyslipidemias in humans. FCH is characterized by a varied expression of hypertriglyceridemia and hypercholesterolemia, and an increased risk of premature coronary artery disease (CAD). Aim of the present study was to estimate the incidence of CAD in males and females of a large Greek population with FCH and to evaluate in each gender the role of lipid and non-lipid risk factors for the development of CAD.

Methods: The study population consisted of 880 untreated patients with FCH (565 males and 315 females), who were referred to our Lipid Clinic. Demographic characteristics and cardiovascular risk factors were recorded and lipid and lipoprotein variables were measured in all participants. CAD was defined as a documented history of previous myocardial infarction, coronary revascularization, angina pectoris with positive stress test or abnormal coronary angiogram (stenosis of $>50\%$ in a major vessel).

Results: The incidence of CAD was 22.2% in men and 4.6% in women ($P<0.001$). Males were younger (45 ± 11 vs. 54 ± 9 years, $P<0.001$) and they had an increased incidence of smoking (44.6 vs. 30.8%, $P<0.001$) compared with females. Both genders had similarly ($P=NS$) increased body-mass index (28.1 ± 3.3 vs. $27.5 \pm 4.0 \text{ kg/m}^2$) and incidence of hypertension (41.7 vs. 39.7%), metabolic syndrome (52.6 vs. 46.8%) and diabetes (14.1 vs. 12.8%). Women had increased level of total cholesterol (300 ± 48 vs. $280 \pm 56 \text{ mg/dl}$, $P<0.001$), low-density lipoprotein cholesterol (207 ± 50 vs. $183 \pm 52 \text{ mg/dl}$, $P<0.001$), apolipoprotein-B (175 ± 38 vs. $162 \pm 39 \text{ mg/dl}$, $P<0.001$), fibrinogen (327 ± 68 vs. $303 \pm 67 \text{ mg/dl}$, $P<0.001$) and lipoprotein-a (34 ± 36 vs. $27 \pm 28 \text{ mg/dl}$, $P=0.005$) compared with men. Moreover, women had a higher concentration of high-density lipoprotein cholesterol (46 ± 10 vs. $38 \pm 9 \text{ mg/dl}$, $P<0.001$) and apolipoprotein A1 (153 ± 25 vs. $133 \pm 20 \text{ mg/dl}$, $P<0.001$). On the other hand, men have higher levels of uric acid (6.0 ± 2.2 vs. $4.5 \pm 1.4 \text{ mg/dl}$, $P<0.001$) and triglycerides (316 ± 159 vs. $266 \pm 151 \text{ mg/dl}$, $P<0.001$). In multivariate analysis, risk of CAD was found increased in males than in females independent of the above mentioned differences between the two genders.

Conclusions: The overall incidence of CAD in males with FCH is almost 5-fold increased compared with females with FCH. Male gender is associated with a significant risk of CAD, independent of lipidemic profile and other risk factors.

P1568 Analysis of clinical presentation and outcome of atrial fibrillation in the elderly: are they so different? (The GEFAUR-2 study)

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Background: Older patients could be sometimes undertreated, in the believing that their clinical profile is greatly different. Limited information concerning this topic is available in atrial fibrillation (AF), a major cause of heart failure and stroke widely present in this etary group.

Objectives: To analyse the influence of patients' age on clinical presentation, symptom relieving and outcome of AF. To determine if different management strategies for older patients are justified.

Methods: Prospective multicenter observational study carried out in 12 emergency departments, July-2001&Feb-2002. Elderly patients (>75 years) were compared with the general series and with those <75 years. Clinical data, management in the acute setting and outcome were collected. No management recommendations were made.

Results: 1481 patients were included, age 74 ± 12 ($57\%>75y$), 58% female. Higher prevalence in >75 of females (61vs59% OR1.7), disability (34vs 7% OR6.2), hypertensive cardiomyopathy (62vs37% OR 1.5), permanent AF

(78vs56% OR 2.5), hypertension (63vs53% OR 1.5) and stroke (22vs9% OR 2.7). Higher prevalence of AF duration<48h (30vs15% OR 2.1) and valvulopathy (43vs20% OR 2.1) in <75. Clinical presentation as palpitations (33vs12% OR 3.4), chest pain (18vs12% OR 1.5) or casual finding (4vs1% OR 3) was more frequent in younger patients as were dyspnea (31vs25% OR 1.2), syncope (5vs2% OR 2.1) or symptoms non-related with AF (46vs30% OR 2) in younger patients. Rapid HR was more frequent in younger (49vs36% OR 1.4) and heart failure (HF) in elder ones (27vs20% OR 1.5). Secondary (non-cardiac origin) AF was uncommon (4.3%), mainly related with fever in elder patients (80vs30% OR 1.6). More frequent symptom relieving in younger patients (48 vs32% OR 1.6), as was admission [36vs21% OR 1.3, mainly if patients attended for dyspnea, syncope or palpitations ($p<0.001$)] without differences in ED length of stay.

Conclusions: The majority of patients with AF in daily clinical practice are elderly ones. Their main AF related factor is hypertension and the impact of non-cardiac factors (mainly fever) is greater. They attend with AF of longer duration, with a lower heart rate(HR) and clinical presentation is related with HF, HR and non-cardiac diseases. Presenting symptoms are frequently non-related with AF, so a high index of suspicion is needed to avoid pitfalls in diagnosis and management. Relieving of symptomatology is achieved in most of them so accurate strategies of rate control and trombotrophylaxis must be warranted to improve prognosis and quality of life of this major of patients with AF.

P1569 The transmitral flow in elderly patients with aortic stenosis and congestive heart failure with preserved systolic function



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Background: Aortic stenosis (AS) is the most frequent heart valve disease in the elderly in many countries. Like the AS, the prevalence of congestive heart failure (CHF) with preserved systolic function increases with age. The objective of this study was to determine the influence of AS on the transmitral flow (TMF) in elderly patients with CHF with preserved systolic function.

Methods: 151 patients (male 142, female 9, age 79.4 ± 1.2) with NYHA II-III functional class CHF due to ischemic heart disease or arterial hypertension and 26 age-matched controls were enrolled. Patients with CHF were divided in two groups: 1-st - 56 patients (all males, age 77.3 ± 1.3) with AS; 2-nd - 95 patients (male 84, female 9, age 78.9 ± 1.2). Isolated AS was defined by a maximum aortic velocity as assessed by Doppler echocardiography >2.5 m/s without significant associated valve diseases. All patients have had left ventricular ejection fraction $>45\%$.

Results: The patients with CHF have had more prolonged deceleration time (DT) (275 ms vs 204 ms , $P<0.05$) and left atrium enlargement (4.2 cm vs 3.4 cm , $P<0.02$). The pts with AS compared with pts without valvular diseases have demonstrated decreased E/A ratio (0.72 vs 0.98 , $P<0.05$) and decreased DT (240 ms vs 280 ms , $P<0.05$). In elderly patients the AS more often was associated with pseudo-normalization of TMF (61.5% vs 40.2%). In additions, in 18,8% patients with AS was determinate elevations in left atrial pressure, a so-called restrictive pattern. Data suggest that this pattern carries a poor prognosis for patients with CHF.

Conclusions: The elderly patients with AS and CHF with preserved systolic function have decreased E/A ratio and DT compared with patients without valvular diseases. Besides, AS in elderly more often was associated with restrictive pattern of TMF, which has poor prognosis for patients with CHF.

P1570 Age, gender and mortality for acute coronary syndromes: is male gender a true risk factor?



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Introduction: It was already demonstrated that men and women have different prevalences and mortalities regarding acute coronary syndromes (ACS). However, there is no consensus on if the age has or not a different impact of the mortality rates in men and women with ACS.

Aim: To evaluate, in a population of ACS patients, if there are or not differences between male and female in the correlation between age and in-hospital mortality due to ACS.

Population and Methods: Retrospective analysis of a nationwide database containing 15894 patients admitted since 2002 in intensive care units and cardiology wards with an ACS. This population was divided in two groups: male (Group A, $n=11028$) and female (Group B, $n=4866$) and each group was then divided in decades, according to the age on admission due to ACS. For each age group, a comparison of the mortality rate by gender was performed.

Results: Figure 1 shows that, for both genders, in-hospital mortality increased with age (from 0% in male and female patients below 30 years until 19.5% in males and 32.8% in females above 89 years of age - $p<0.001$ for each gender). In all the age groups, ACS mortality was higher in females, reaching statistical significance between 50 and 79 years of age. However, in patients aged 90 or higher the trend shifted and male patients had higher in-hospital mortality than females.

Conclusion: In ACS patients, female gender is associated with a lower prevalence but with higher in-hospital mortality, especially in post-menopause ages, a



Fig. 1. Results

trend that has a sudden shift in very old patients. These data must be taken into account when planning for strategies to fight coronary artery disease.

P1571 Gender gap in DNA damage due to diagnostic radiation: evidence from children with congenital heart disease



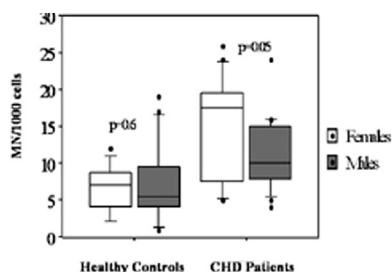
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Background: According to recent estimates provided by the BEIR (Biological Effects of Ionizing Radiation) VII Committee, the same radiation in the first year of life produces 3 to 4 times the cancer risk as exposure between the ages of 20 and 50. Female infants have almost double the risk as male infants. Direct evaluation of surrogate biological endpoint in exposed children could support these estimations.

Aim: to assess the gender-dependent chromosomal damage in patients with congenital heart disease (CHD) and a positive history of diagnostic procedures employing ionising radiation.

Methods: We enrolled 34 patients who had undergone ionising testing (with at least one cardiac catheterisation) at <1 year: 17 females (mean age: 17.4 ± 9.7 years) and 17 males (mean age: 14.7 ± 9.7 years). A control group of 32 healthy subjects consisting of 17 males (age: 16.1 ± 12.3 years) and 15 females (12.1 ± 10.5 years) was also included. Micronucleus assay (MN) in peripheral blood lymphocytes was used as a sensitive biomarker of chromosomal damage and intermediate endpoint in carcinogenesis.

Results: MN levels were higher in patients when compared to healthy controls. Female patients had higher levels of MN than male patients, whereas no gender difference was found in age-matched controls (figure). Female and male patients were comparable for age ($p=0.45$), type of CHD ($p=0.8$) and cumulative effective dose (females= 16.7 mSv vs males= 19.5 mSv , $p=0.41$).



Conclusion: For a given levels of radiation exposure in early infancy, female children develop increased chromosomal damage. The use of surrogate endpoints corroborates the current radioprotection assumption that female children are at higher risk than males.

P1572 Gender differences in the relation of ultrasound identified atherosclerosis to Framingham Risk Scores



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Atherosclerosis as manifest in coronary artery disease, cerebrovascular disease and peripheral vascular disease is the leading cause of death in the United States. Mortality of first events, particularly with myocardial infarction, is very high and it is urgent that we have a method of identifying people at risk before that initial event. The use of Common carotid intimal medial thickness (CIMT) is well established as a surrogate for cardiovascular disease events. The use of screening vascular ultrasound of the carotid and femoral arteries as a surrogate of coronary atherosclerosis has been validated by the CAFES-CAVE study. Framingham Risk Score (FRS) has been the traditional method of identifying cardiovascular risk. In the present study, 120 untreated and unselected patients drawn from a university based group medical practice were evaluated by ultrasound for the presence and type of carotid and femoral arterial bifurcation plaque and the measurement of common carotid intimal medial thickness (CIMT). The age range was 34 to 74 years and there were 50 women and 70 men evaluated. Distribution of FRS was among men: 0-6, 31%; 7-12, 39%; 13-25, 30% while among women:

0-6, 72% and 7-18, 28%. The correlation of FRS with Average CIMT was $r=0.40$ ($p<0.001$) for all patients and the correlation of FRS with Maximum CIMT was $r=0.40$ ($p<0.001$). When CIMT measurements were divided by gender, correlation of FRS with Average mean CIMT ($r=0.49$) and Maximum CIMT ($r=0.47$) was highly significant ($p<0.001$) among men while there was no correlation for Average CIMT ($r=0.04$, $p=0.7$) or for Maximum CIMT ($r=0.07$, $p=0.6$) among women. This gender based divergence of the correlation of CIMT with FRS was repeated in the assessment of arterial plaque. Among men, the incidence of any plaque for each FRS group was: 0-6, 27%; 7-12, 59%; 13-25, 67% while among women: 0-6, 50% and 7-18, 43%. Screening vascular ultrasound analysis produces a different pattern of risk assessment than does traditional Framingham risk analysis particularly in women. The use of Screening vascular ultrasound as a complement to traditional risk analysis will uncover additional patients at risk and allow earlier intervention to prevent disease progression.

P1573 Race and gender differences in thrombogenic potential and risk of ischemic events following coronary stenting



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Background: Mortality risk following coronary revascularization is higher among African Americans (AA) compared with Caucasians (C), and women compared with men. We postulated that race and gender differences in outcomes might be due to differences in thrombogenic potential impacting risk of ischemic events in the post-treatment period. We previously demonstrated that measures of clotting strength and kinetics can be used to stratify patients by risk of ischemic events.

Methods: Ex-vivo clot parameters (platelet-fibrin clot strength (MA), time to platelet-fibrin clot formation (R) and clot index (CI)) were measured using the Thrombelastography (TEG) in 252 consecutive patients undergoing stenting. The incidence of adverse ischemic events was assessed over a six-month follow-up period.

Results: Forty (15.9%) ischemic events were reported with higher rates in AA ($p=0.111$) and in women ($p=0.002$). Incidence was highest for AA women (37.5%) and lowest for AA Men (6.5%). All TEG clot parameters were significantly different between ischemic and non-ischemic patients at six months post PCI ($p<0.001$). AA women in the ischemic group had values for clot parameters reflecting a higher thrombogenic potential than the other race-gender groups (Table). Multivariate logistic regression identified MA and gender as significant independent predictors of ischemic events six months post PCI.

	Ischemic Patients (n=40)		p	Non-Ischemic Patients (n=212)	
	AA (n=14)	C (n=26)		AA (n=49)	C (n=163)
MA (mm)	77±4	70±4	<0.001	68±6	66±7
R (min)	4±1	4.4±2.2	ns	4.4±1.4	5.1±2
CI	4.4±1.2	2.8±2.1	0.012	2.6±1.9	1.9±2.5

	Women (n=23)		p	Men (n=17)	
	Women (n=67)	Men (n=145)		Women (n=67)	Men (n=145)
MA (mm)	74±6	70±4	0.02	68±6	66±7
R (min)	4.5±2.3	4±1.2	ns	4.8±2.1	5±2
CI	3.5±2.4	3.2±1.2	ns	2.3±2.4	1.8±2.4

Conclusion: Thrombogenic potential varies by race and gender, is highest for AA women, and predicts frequency of ischemic events following PCI. Use of these measures may lead to more intensified antithrombotic therapy and reduced mortality in selected patients.

P1574 Impact of cardiac rehabilitation on the clinical course of coronary heart disease in post-CABG women



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Cardiac rehabilitation (CR) has been shown to be an effective means of secondary prevention in patients with CAD, with potential to reduce the morbidity and mortality associated with the disease. It is currently an under-utilized program in the USA, especially in women. There is no data available on the impact of exercise training on women who undergo CR following CABG surgery. We evaluated the effects of a 12-week physician-directed CR exercise program in women, initiated 10-14 days after CABG. From 1/00 to 12/05, 122 post-CABG women (mean age 69) were enrolled in a supervised CR exercise program. The exercise prescription used a preset protocol consisting of ECG-monitored, symptom-limited bicycle ergometry and treadmill walking up to 60 minutes per session, 3 days a week for 12 weeks. Multiple indices of exercise tolerance, LV function and metabolic parameters were recorded at entry and completion of (Phase II) CR.

Results: See Table 1.

Conclusions: (1) In women with CAD who undergo CABG surgery, a 12-week supervised CR program significantly improves multiple indices of functional capacity and major metabolic parameters. (2) This is paralleled by significant improvement in global LV systolic and diastolic performance, indices that are known

Table 1. Results

Variable	Pre-Rehab	Post-Rehab	P Value
NYHA Class	2.8	1.4	0.003**
Resting HR (bpm)	84.6	72.5	0.000*
Treadmill Time (min)	12.2 ± 3.6	21.0 ± 3.8	0.001*
Cycle Ergometry Time (min)	9.78 ± 4.0	20.85 ± 3.88	0.001*
GXT Workload (METs)	4.32 ± 1.43	7.29 ± 2.88	0.000*
LVEF (%)	32.48 ± 7.54	39.38 ± 10.63	0.002**
Diastolic dysfx.	39.1%	12.4%	0.001*
Total Cholesterol (mg/dL)	177.0	144.3	0.026**
FBS (mg/dL)	122.48	101.60	0.001*

*P value significant at <0.0001; **P value significant at <0.05; FBS: fasting blood sugar

to impact long-term cardiac morbidity and mortality. (3) Our data demonstrates that CR may have an important modifying effect on the course and progression of CAD in women. These promising results should stimulate a wider referral to and more aggressive use of CR in female patients following CABG surgery.

P1575 Effect of aerobic versus combined aerobic-resistance training on health-related quality of life in female cardiac patients



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Background: The benefits of cardiac rehabilitation (CR) are well established for men and women with cardiovascular disease (CVD). Resistance training (RT) during CR has been shown to improve the performance of strength-related activities of daily living (ADL) in men. Few studies have examined RT in women with CVD. Health-related quality of life (HRQL) and the functional ability to perform ADL may be the most important rehabilitation outcomes for female cardiac patients. For women, ADL may require strength more than endurance; thus women may stand to benefit the most from RT during CR.

Purpose: To compare the effect and sustainability of a supervised, 6-month, twice weekly, combined aerobic-resistance training (ART) program versus aerobic training (AT) alone in women following coronary artery bypass graft surgery (CABG) or myocardial infarction (MI).

Methods: This was a prospective, randomized controlled trial using a two-group repeated measures design (n=92). The primary outcome was HRQL; measured by the physical (PCS) and mental (MCS) component summary scores of the Medical Outcomes Study SF-36. Secondary outcomes included exercise capacity (peak VO₂, KPM, METs) and strength (one repetition maximum -1RM) for leg press, bench press, leg flexion and arm flexion. RT was initially prescribed at 30-50% of 1RM, progressing to 70% by 4 weeks of RT. Total exercise time was equal for both groups. Outcomes were assessed upon CR entry, at 2 and 6 months and one-year following completion of the program.

Results: Groups were comparable with respect to demographic characteristics, HRQL, exercise capacity and strength at study entry. After 6 months of exercise training both groups showed significant improvements in the PCS ($p=0.0002$). At this time there were no between group differences in HRQL, though there was a trend in favor of the ART group. At the one-year follow-up there was a significant treatment effect on the PCS for the ART group ($p=0.05$). Although improvements in strength occurred in both groups, there were significantly greater improvements in leg press ($p=0.018$), bench press ($p=0.003$) and leg flexion ($p<0.0001$) in the ART group after 6-months of exercise training. Exercise capacity increased 22-34% in both groups ($p<0.0001$).

Conclusions: Both AT and ART are associated with short-term improvements in physical HRQL in women after CABG or MI. Combined ART may be associated with long term sustainability of HRQL benefits compared to AT alone and should therefore be considered as an important adjunct to women's CR programs.

P1576 Estrogen replacement therapy and withdrawal during and after percutaneous coronary intervention: in-hospital and one-year outcomes



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Purpose: Women on estrogen replacement therapy (ERT) are at higher risk for cardiovascular events. The effect of ERT on adverse events following percutaneous coronary intervention (PCI) in the modern era, and whether ERT can be safely discontinued at discharge, remain unknown.

Methods: The incidences of death and myocardial infarction (MI) were collected prospectively on 4159 consecutive patients who underwent PCI in 16 centers between October 2001 and March 2002 and February and May 2004 as part of the NHLBI Dynamic Registry. Among post-menopausal women (n=1017), 147 (14%) were on ERT at the time of PCI. Procedural, in-hospital and one-year outcomes were compared to those without ERT (n=870). Of 146 ERT patients alive at discharge, one-year outcomes were then compared between those who did (n=63) and did not (n=83) continue ERT.

Results: ERT patients were younger (65.4 vs. 70.7 years, $p < 0.001$), and less likely to have diabetes, renal disease and multi-vessel disease. Known coronary disease, heart failure, hypertension, hyperlipidemia and tobacco use did not differ between groups. Stenting rates were similar (ERT 87.1% vs. no ERT 91.0%, $p = \text{NS}$). Angiographic (92.5% vs. 95.7%, $p = \text{NS}$) and procedural success (96.6% vs. 96.6%, $p = \text{NS}$) did not differ between groups, nor did procedural complications of embolization, abrupt closure or no-reflow. In-hospital death (0.7% vs. 1.3%, $p = \text{NS}$) and MI (1.4% vs. 2.0%, $p = \text{NS}$) were similar in those with and without ERT, and remained so after adjustment at one-year (death RR 0.50, 95%CI 0.17-1.45 and MI RR 0.41 95%CI 0.15-1.14). Those who discontinued ERT had similar one-year death (2.60% vs. 1.75%), MI (2.47% vs. 3.17%) and death/MI (5.07% vs. 4.94%, $p = \text{NS}$ for all) to those who continued ERT.

Conclusions: ERT is not associated with higher procedural, in-hospital or one-year adverse events after PCI in the modern era, and may be safely withdrawn at hospital discharge.

P1577 Effect of fosinopril on progression of the asymptomatic carotid atherosclerosis at hypertensive patients with left ventricular hypertrophy



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Aim of the study was to determine influence of the ACE inhibitor Fosinopril on the common carotids intima-media thickness (CC-IMT) and on the left ventricle mass (LVM) after 9 months of treatment at high risk hypertensive patients. The study included 40 patients with arterial hypertension and left ventricle hypertrophy (LVH) proved echocardiographically (Index LVM $\geq 134 \text{ g/m}^2$ for men and $\geq 110 \text{ g/m}^2$ for women). patients were randomized on A) ACE-inhibitor - Fosinopril and B) without ACE inhibitor - atenolol, and they have been tracked for 9 months. Groups did not differ by age, sex, and metabolic status. ColorDuplex ultrasonography of the carotid arteries was performed on Acuson Sequia C236 with high-frequency linear probe on 8 MHz). On the same device, from the M-mode and 2D was determined the left ventricle mass and other parameters of the left ventricle. After 9 months, BP was at both groups decreased by similar range. The CC-IMT at patients using Fosinopril was decreased by $-0.0278 \pm 0.03 \text{ mm}$ ($p = 0.013$), while in the group of patients that did not use the ACE-inhibitor it was increased by $0.078 \pm 0.13 \text{ mm}$ ($p = 0.035$). The LVM at patients using Fosinopril was decreased by 5 grams ($312 \pm 72 \text{ g}$ vs. $307 \pm 77 \text{ g}$), while at patients from the group B it was increased by 5 grams ($323 \pm 79 \text{ g}$ vs. $328 \pm 58 \text{ g}$). Diastolic function expressed thru relation E/A was improved minimally in the A-group, while it worsened by 0.1 in the B-group. After 9 months at two patients from the group A serious cardiovascular events were registered (one infarction of myocardium and one hospitalization due to the unstable angina pectoris), while four patients from the group B had serious CV events (1 cerebrovascular stroke and 3 hospitalizations due to unstable angina pectoris).

Results of our study showed that application of the Fosinopril at patients with arterial hypertension and of the LVH can efficiently block further progression of the complex of the CC-IMT, decrease of the LVM, and improve diastolic function of the left ventricle with lower frequency of serious cardiovascular events.

P1578 Ventricular remodeling and autonomic modulation after long-term beta-blockade differ in hypertensive, ischemic and idiopathic dilative cardiomyopathy



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In patients (pts) with heart failure treated with beta-blockers, the improvement in survival is accompanied by autonomic modulation and reverse ventricular remodeling: whether these effects are influenced by heart failure aetiology is poorly known. In this retrospective analysis, 23 pts with heart failure (HF) without comorbidities (18 males, 61 ± 4 years, NYHA 3.2 ± 0.07 , already treated with ACE-inhibitors and diuretics) were divided in 3 groups according to HF aetiology: (1) hypertensive HF ($n = 7$, normal coronary arteries, untreated or poorly treated hypertension); (2) ischemic HF ($n = 6$, previous MI and/or revascularisation); (3) idiopathic HF ($n = 10$). Before and after 6 months of full-dose carvedilol (previously titrated up to $53 \pm 5 \text{ mg/die}$), pts underwent cardiopulmonary test, echocardiogram and autonomic evaluation. For the latter we performed spectral analysis of RR intervals variability during 10 min of rest and 10 min of standing (adrenergic orthostatic stimulus): the ratio LF/HF between low and high frequency components of individual spectra was taken as the index of sympatho-vagal balance. After long-term beta-blockade, all pts improved NYHA class (to 2.0 ± 0.03 , $p < 0.05$) and exercise performance (by 15%, $p < 0.05$). Group 1 normalized ejection fraction (EF) and left ventricular end-diastolic volume (LVEDV); pts increased their systolic blood pressure (SBP, 144 ± 6 from $109 \pm 9 \text{ mmHg}$, $p < 0.01$), and end-diastolic interventricular septum thickness (IVST, from 9.1 ± 0.2 to $11.3 \pm 0.3 \text{ mm}$, $p < 0.01$). No remodeling was present in Group 2 (EF, LVEDV and IVST were unchanged). In Group 3, IVST was unchanged, while EF and LVEDV improved (38 ± 9 from $27 \pm 4\%$ and 140 ± 30 from $187 \pm 28 \text{ ml}$ respectively, $p < 0.01$). Autonomic modulation was also different. At baseline, all pts showed adrenergic activation at rest (LF/HF $8.2 \pm 1.6 \text{ n.u.}$) without changes of LF/HF with standing. Af-

ter beta-blockade, Groups 2 and 3 showed reduced adrenergic activation at rest (LF/HF 5.1 ± 0.9 and $3.2 \pm 1.1 \text{ n.u.}$ respectively) and a normal response to orthostatic challenge. However, no change in LF/HF was seen in Group 1 neither at rest or during active standing. In conclusion, hypertensive heart failure displays significant ventricular remodeling and some degree of hypertrophy with long-term beta-blockade: adequate treatment could thus revert the ominous transition between compensatory hypertrophy and failure in hypertensive cardiomyopathy. Moreover, this subset of pts displayed a persistent high adrenergic tone, most likely of central origin, whose role may be to sustain ventricular function despite the increase in systolic blood pressure.

P1579 An atrial natriuretic peptide (ANP) promoter gene variant and the risk of hypertension



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Background: Experimental and clinical studies suggest that ANP is a major cardiovascular (CV) risk factor. Moreover, genetic variants of ANP have been previously associated with an increased risk of cerebrovascular accidents and with increased left ventricular mass.

Aim: In the present study we characterized the role of an ANP gene promoter variant in the predisposition to develop hypertension (HPT) and CV diseases in a sample of relatively young male population ($n = 395$, age 35.2 ± 2 years) followed up for 28 years. This ANP gene variant (that exists mainly in the heterozygous state) has been previously associated to a significantly lower circulating peptide levels.

Results: Compared to wild type individuals ($n = 378$), subjects carrying the allelic variant ($n = 17$) had significantly higher systolic BP at entry (131.8 ± 23.5 vs $123.6 \pm 14 \text{ mmHg}$, $p = 0.02$) and a trend for higher diastolic BP (86 ± 15.7 vs $81.5 \pm 9.9 \text{ mmHg}$, $p = 0.07$). At this time the prevalence of HPT was higher among the heterozygous subjects (47% vs 24.5%, $p < 0.05$). A significantly higher prevalence of HPT in this group was still observed at the 12-year follow up examination, and a trend in the same direction was detectable up to the 28-year visit. Moreover, we observed that antihypertensive treatment (as prescribed by the participants' family physicians) was more common among heterozygotes than in wild type individuals at 12 years (28.6% vs 7.4% , $p < 0.01$) with a similar trend thereafter. Finally, the heterozygotes showed a higher occurrence of transitory cerebral ischemic events (5.9% vs 0.5%) and reported a greater number of strokes among first degree relatives (0.53 ± 0.72 vs 0.29 ± 0.50 , $p = 0.05$).

Conclusions: An ANP promoter gene variant, that is associated with lower plasma peptide levels, was associated with higher BP levels at an early age and with an increased predisposition to develop hypertension and CV diseases over a 28-year period.

P1580 Blood pressure progression and angiotensinogen gene variants in young patients with type 1 diabetes



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Background: Angiotensinogen (AGT) polymorphisms have been shown to increase the risk for elevated blood pressure and hypertension in the general population and in patients with diabetes. A genetic background has been reported also for the progression of blood pressure (BP) from childhood into adulthood. The objective of this study was to examine the impact of AGT gene polymorphisms on the trend of ambulatory BP measurements in the course of type 1 diabetes.

Methods: Baseline and recent BP measurements were compared in 215 german adolescent patients. The impact of the AGT variants C-532T, -6A, M235T and T174M on the progression of various ambulatory systolic (SBP) and diastolic (DBP) blood pressure recordings was studied.

Results: Over an observation period of 5.4 years, there was a significant decrease of age-adjusted (sds) daytime SBP ($p < 0.001$) and DBP values ($p < 0.001$) in the entire population. In patients with the 235T variant the daytime DBP (sds) increased ($p = 0.018$). The percentage of elevated daytime SBP (eSBP, $p = 0.0013$) and DBP (eDBP, $p = 0.027$) measurements increased with the T174 and the -6A variant (eSBP, $p = 0.017$). In contrast, it decreased with the C-532/T174 (eDBP, $p = 0.007$ and eSBP, $p = 0.007$) and the C-532/M235 genotype (eDBP, $p = 0.041$).

Conclusion: The progression of BP values in the patients was modulated by AGT polymorphisms. Combinations of the AGT promoter variant C-532 with the M235 and T174 polymorphisms reduced the risk for progression of BP values. Identifying genetic factors for the progression of BP might lead to earlier diagnosis and more accurate therapy of patients at risk for hypertension.

P1581 Beyond RAAS: does parathyroid hormone play a role in hypertensive heart disease?



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Background: The heart responds to chronic pressure overload by an activation of the sympathetic nervous system and the renin-angiotensin-aldosterone-system (RAAS). Meanwhile it is clear that even under conditions of ACE inhibition, aldosterone is still increased, reducing plasma calcium and inducing the release of parathyroid hormone (PTH). In addition, the introduction of PTH and PTHrP peptides into clinical studies directed against osteoporosis further underlines the requirement for data about the long-term effects of these peptides on the function of cardiomyocytes, that have already been identified as potential target cells.

Methods: Isolated ventricular rat cardiomyocytes from adult hearts were treated for 24 h with PTH(1-34), PTHrP(1-36), PTHrP(107-111) (=osteostatin) at increasing concentrations. Cell shortening was investigated at 0.5 - 2.0 Hz.

Results: PTH increased basal cell shortening at all frequencies at 20-200 pmol/l (2 Hz: +39.4±3.4%, n=48). This effect was accompanied by an accelerated contraction and relaxation velocity of 164±7 vs. 123±3 μm/s and 151±5 vs. 119±3 μm/s, respectively. Neither PTHrP nor osteostatin (20 pmol/l to 20 nmol/l each) did not evoke such an effect. The effect of PTH was inhibited in the co-presence of the PKC inhibitor BIM. Stimulation of beta-adrenoceptors further increased the cell shortening of PTH-treated myocytes. Acute stimulation of beta-adrenoceptors further increased the cell shortening of PTH-treated myocytes. In control cultures, isoprenaline increased cell shortening by 42.3%. In cells cultured for 24 h at 200 pmol/l PTH, isoprenaline increased cell shortening by 42.2%. Thus, no desensitizing effect caused by PTH was observed.

Conclusion: Chronic exposure of cardiomyocytes to plasma relevant PTH concentrations increases the cellular function, while the structurally related peptides PTHrP and osteostatin did not. This opens the possibility that aldosterone-dependent hyperparathyroidisms supports remodeling and this may, at least in part, explain the favorable effects of aldosterone-antagonists in addition to ACE inhibition.

P1582 Soluble CD40 Ligand and C-Reactive Protein concentrations in essential hypertension: effects of hyperglycemia and hyperinsulinemia



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Background: Subclinical inflammation and platelets activation are involved in the pathophysiology of cardiovascular disease (CVD). Recently both sCD40L (a molecule released by activated platelets) and hs-CRP (an inflammatory marker) have been reported higher among hypertensive patients, but factors accounting for the large variability of both parameters in hypertensive subjects are poorly understood. Objective. To measure hs-CRP and sCD40L in 89 CVD event-free men with essential hypertension.

Patients and Methods: We studied 89 patients (mean age 49±11 yrs, range of BMI: 18.4-34.5 kg/m², serum creatinine below 1.2 mg/dl and cystatin-C concentration ranging from 0.53 to 1.18 mg/l). All subjects underwent a 24 hr ABPM and an OGTT. Lipid and lipoprotein concentrations were measured in a fasting blood sample. Specific immunoassay were used for sCD40L and hs-CRP. Among these subjects, 18% had IFG, 8% IGT, 5% both conditions. Metabolic syndrome (MS, NCEP/ATPIII criteria) was present in 30 out of 89 subjects (34%). Data were analyzed by a SPSS package and were expressed as mean±sd or range.

Results: Mean levels of hs-CRP were 2.4±2.3 (range 0.4 to 8.5) ng/ml; mean levels of sCD40L 8.8±5.0 (range 0.8 to 18.5) ng/ml. No correlation was observed between hs-CRP and sCD40L (p=0.97) and no differences in both parameters emerged in subjects with and without MS. Neither hs-CRP and sCD40L did correlate with age, BMI, systolic and diastolic 24h ABPM parameters, renal function indexes or urinary albumin excretion. Within lipid parameters, a weak positive regression was observed between total cholesterol and sCD40L (p=0.047). hs-CRP strongly correlated with fibrinogen levels (p<0.0001). sCD40L positively correlated with fasting glucose (r=0.23, p=0.029), basal insulin levels (r=0.34, p=0.002), and HOMA-IR (r=0.37, p=0.001), while hs-CRP weakly correlated with the insulinogenic index (r=0.25, p=0.05) and the area under the OGTT curve for insulin (r=0.32, p=0.027). In a multiple regression model, HOMA-IR emerged as the main determinant of the variability of sCD40L levels, while AUC insulin was the main determinant of the variability of hs-CRP concentrations.

Conclusion: Minor changes in glucose and insulin metabolism might account at least in part for the inflammatory disorders related to essential hypertension.

P1583 Hypertensive Response to Exercise is associated with increased Arterial Stiffness in non-diabetic normotensive subjects



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Background: In many studies, hypertensive response to exercise (HRE) is asso-

ciated with an increased incidence of chronic hypertension (HT) during follow-up and has been proposed as a preclinical stage of HT. Recent studies revealed HRE is associated with hypertensive end-organ damage or other cardiovascular complications. Furthermore, arterial stiffness is increasingly recognized as a major determinant of systolic BP and pulse pressure.

However, few studies elucidated the cause of exercise-induced hypertension might be related to arterial stiffness. In this study, the relationship of HRE to arterial stiffness was evaluated by pulse wave velocity (PWV).

Methods: The patients population includes 151 consecutive patients who are randomly selected with undergoing treadmill stress testing between April 2000 to March 2005. Among these patients, we identified 32 patients who showed hypertensive response to exercise (HRE group: >210 mmHg in males and >190 mmHg in female). The clinical, biochemical variables and exercise stress test data of in this group was compared with those of 119 patients who underwent exercise test during same period but showed normal response (control group).

Patients were considered to have sustained hypertension with clinic BP measurements >140/90 mmHg on three or more occasions and daytime ambulatory BP >135/85 mmHg. We also assessed brachial BP and arterial stiffness by brachial-ankle PWV (baPWV: VP-2000 pulse wave unit, Nippon Colin Ltd, Komaki City, Japan).

Results: see Table.

Table 1. Comparison of 2 groups

Variables	Control group	HRE group	p
Sex(M/F)	58/61 (119)	16/16(32)	NS
Age(yrs)	53.8 ± 8.6	58.4 ± 8.2	>0.01
Systolic BP (mmHg)	125.8 ± 14.9	128.3 ± 14.5	NS
Diastolic BP (mmHg)	81.6 ± 10.3	79.1 ± 10.2	NS
Pulse pressure (mmHg)	44.6 ± 10.7	50.3 ± 11.1	0.01
Pulse rate (bpm)	66.4 ± 9.2	64.7 ± 7.5	NS
BMI (kg/m ²)	25.4 ± 2.8	25.8 ± 2.9	NS
Total cholesterol (mg/dL)	192.9 ± 36.7	194.4 ± 41.2	NS
HDL (mg/dL)	46.4 ± 11.3	46.4 ± 10.9	NS
baPWV(cm/sec)	1434.8 ± 156.7	1608.8 ± 303.8	0.004

mean±standard deviation

There was a significant positive correlation between in HRE and baPWV ($\beta = 0.29$, $p = 0.001$) after adjusting for age, sex, pulse pressure and BMI.

Conclusion: Hypertensive response to exercise is independently associated with increased arterial stiffness in patients with essential hypertension. Further studies to determine the prognostic significance of this finding is warranted.

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P1584 Long-term effects of a low dose of grape seed proanthocyanidin extract on blood pressure in a hypertension rat model



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Most studies on the antihypertensive effects of bioflavonoids reflect effects of high concentrations (40-100 mg/kg/d). We were interested to see whether much lower concentrations (which correlates with the average intake of bioflavonoids in humans) could still produce antihypertensive effects. A grape seed proanthocyani-

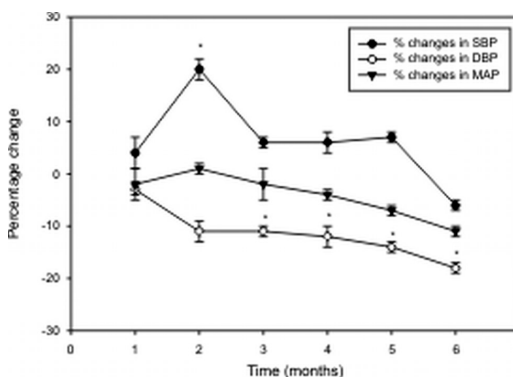


Fig. 1. Effects of grape seed extract.

Table 1. Effects of grape seed extract

Parameter	Control (N = 10)	GSPE treated (N=10)
HR (beats min ⁻¹)	218.0 ± 8.3	215.2 ± 4.1
LVSP (mm Hg)	188.7 ± 5.2	157.3 ± 6.9 **
Dp/dt _{max} (mm Hg s ⁻¹)	2949.3 ± 102.6	2369 ± 238.9 *
Cardiac work (mm Hg/beat/min)	41 143.0 ± 2161.4	32083.6 ± 1048.7 **

Comparison of the cardiodynamic parameters. All values express as mean ± s.e.m. *P < 0.05, **P < 0.01. (HR: heart rate; LVSP: left ventricular systolic pressure; Dp/dt_{max}: the maximum rate of rise in left ventricular pressure.

din extract (GSPE) (4 mg/kg/d) was given to spontaneous hypertensive rats over a 6 month (mo) period. Arterial blood pressure (BP) in these rats was measured monthly using an indirect tail-cuff method and the results were compared to those of a control group (figure). Direct BP from the carotid artery was measured after 3 mo (table) and N-nitro-L-arginine methyl ester was administered. The results suggested that a low concentration of GSPE had antihypertensive effects due to an increase in NO and a reduction of afterload

P1585 Regression of hypertrophy in hypertension is more closely associated with nocturnal blood pressure than with class of antihypertensive agent



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In the regression of left ventricular mass (LVM), the relative importance of blood pressure (BP) lowering versus the class of antihypertensive employed is uncertain. The objective of the study is to evaluate the time-dependent relationship between indexes of LV hypertrophy (LVH) and ambulatory BP as well as between indexes of LVH and the use of the angiotensin-converting enzyme inhibitor (ACEI), enalapril, over a 25 month treatment period.

This was a single-centre, randomized open-label trial. Patients (n=185 at enrollment) with a mean daytime diastolic BP ranging from 90-114 mm Hg off-treatment were randomized to receive either calcium channel blockers, enalapril or a diuretic agent as initial therapy. Doses were increased and additional therapy, including enalapril, added to achieve a target daytime diastolic BP below 90 mm Hg.

At 4, 13 and 25 months of therapy 66, 71 and 72% of patients had BP values within target ranges. LVM index decreased from 118±33 g/m² at baseline to 101±25, 101±23, and 96±22 g/m² at 4, 13 and 25 months of therapy (p<0.0001 compared to baseline). Accounting for effects on ambulatory BP at each time point, the use of enalapril was associated with neither LVM index, nor with LV relative wall thickness over the treatment period. However, in-treatment systolic night-time BP was associated with both LVM index (p=0.026) and LV relative wall thickness (p=0.006). Although 24 hour and daytime BP were not associated with LVM index, both 24 hour (p=0.01) and daytime (p=0.028) BP were associated with in-treatment LV relative wall thickness.

In the treatment of hypertension the use of an ACE inhibitor confers no additional benefits on LVM beyond that produced by effects on nocturnal BP.

P1586 Prognostic power of heart rate recovery after maximal exercise testing in patients with chronic heart disease



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Background: Recent research has demonstrated that the rapidity of heart rate (HR) recovery after exercise testing is related to prognosis in healthy subjects. We sought to determine whether the analysis of HR recovery after maximal exercise testing is superior to the measurements of established respiratory gas indexes in predicting cardiac events in cardiac patients.

Methods: A total of 571 consecutive patients with chronic heart disease (63.6±10.5 years) performed a symptom-limited incremental exercise test on a cycle ergometer. The peak O₂ uptake (VO₂) and the slope of the increase in ventilation to the increase in CO₂ output (VE/VCO₂ slope) were calculated from the respiratory gas analysis. The recovery of HR after exercise testing (ΔHR) was calculated as the difference between HR at peak exercise and HR after 2 minutes of exercise recovery.

Results: A total of 102 cardiovascular-related events were occurred over 736 ± 424 days of prospective follow-up. Peak VO₂, VE/VCO₂ slope, and ΔHR were significant prognostic indices for these events. Multivariate Cox proportional hazards analysis identified three indices of significantly worse prognosis among patients who died of cardiovascular-related causes: lower ΔHR (p=0.03), lower peak VO₂ (p=0.01), and higher VE/VCO₂ slope (p=0.01).

Conclusions: Though respiratory gas analysis during exercise is certainly useful for predicting future events, the rate of HR recovery after maximal exercise testing is an additional and simpler prognostic index of survival in patients with chronic heart disease.

P1587(W) Physician and smoker misperceptions of cardiovascular and other risks from therapeutic nicotine



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Purpose: Tobacco use is the leading preventable cause of death and disease

worldwide. Current projections are that 500 million people alive today will eventually die of tobacco-related causes, including 250 million children. At current rates, tobacco will kill 1 billion people this century. Helping adult smokers quit is the best way to make a near-term impact on this trend.

Many smokers are concerned about their health, and want to quit smoking. Regulatory authorities around the world have approved safe and effective therapeutic nicotine products in gum, patch, and lozenge form to wean smokers off of tobacco; on average, smokers who use these products to help them quit can double their chances of success. Unfortunately, many physicians and smokers harbor misperceptions about the safety of therapeutic nicotine products. These misperceptions often serve as a barrier to use of these products, detracting from overall cessation success. The purpose of this symposium is to address and begin the process of correcting these misperceptions

Methods: This session will cover the following main areas:

– A review of available evidence on the safety of therapeutic nicotine in patients with cardiovascular disease

– A review of recent survey data on the extent to which physicians, including cardiologists, hold profound misperceptions about the safety of therapeutic nicotine products

– A review of similar survey data on smoker misperceptions and implications for likely use of therapeutic nicotine products

– A description of past efforts, and future opportunities, to reach out to physicians to call attention to and correct these misperceptions

– A description of tools for physicians to use when counseling patients about dispelling these misperceptions

– An examination of opportunities for collaboration with the World Heart Federation and other professional societies to address and reverse these misperceptions

Results and Conclusions: This symposium will result in greater physician awareness of the extent of the significant misperceptions regarding the safety of therapeutic nicotine products. Physicians will come away from the session better armed to dispel these same misperceptions that are held by their patients who smoke. It is hoped that this will result in a renewed interest in quitting by patients.

P1588 Variation of Blood Natriuretic Peptide and high sensibility C reactive protein in obese patients



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Background: NT-pro-BNP and high sensibility C reactive protein (CRP) can change according to age, gender and other risk factors. However, obesity can also influence these markers.

Objectives: To evaluate NT-pro-BNP and CRP values in a population of patients with obesity.

Methods: Retrospective study of 738 patients (65±13 years, 57% males), admitted for an elective coronary angiography for suspicion of coronary artery disease. We excluded patients with previous myocardial infarction or heart failure. In all patients, we measured NT-pro-BNP and CRP. Patients were considered obese in the presence of a body mass index (BMI) >=30 kg/m². We compared demographic and risk factors for coronary artery disease.

Results: Obese patients (n=218, mean age 65±10 years, 50% males) had a lower value of NT-pro-BNP and higher CRP values compared to non-obese patients (n=520, 65±14 years, 60% males). There was a negative correlation between NT-pro-BNP and BMI (r=-0.18, p<0.001). Between CRP and BMI there was a correlation coefficient of 0.15 (p=0.001). In both cases, it was a small level of correlation.

(%)	Obese	Non-obese	p
Hypertension	82	72	0.005
Diabetes mellitus	26	20	NS
Hyperlipidemia	51	44	0.08
Smoking	10	15	NS
Waist circumference (cm)	111±89	94±91	<0.001
NT-pro-BNP (pg/ml)	422±722	974±2052	<0.001
CRP (mg/dl)	1.19±4.26	0.76±1.57	<0.001

Conclusions: Obese patients had a lower level of NT-pro-BNP and higher level of CRP, although these parameters had a low level of correlation with BMI.

P1589 The impact of vitamin B12 and folic acid supplementation on atherosclerosis in rural Chinese: A novel strategy for atherosclerosis prevention in China



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Purpose: Vitamin B12 deficiency in vegetarians and folate deficiency in rural northern China are associated with atherosclerosis. This study further tested the micronutrient hypothesis and evaluated the impact of vitamin B12 (B12) and folic acid (FA) supplementation on atherogenic process in northern rural Chinese.

Methods: 38 asymptomatic subjects (29 males) in rural Shanxi (Yu County) were randomized to receive oral B12 (500µg/day) + FA (5mg/day), or image-matched placebos in double-blind 2:1 parallel fashion for 6 months, followed by open label B12+FA for 6 more months. Surrogate atherosclerosis markers flow-mediated dilation of brachial artery (FMD) and carotid intima-media thickness (IMT) were measured by high resolution B-mode ultrasound at baseline, 6 months and 12 months.

Results: Their mean age was 44.7±8.3years. Blood B12 (mean 201.4±101.9pg/l) and folate (mean 9.7±3.3nmol/l) were low at baseline, but significantly increased at 6 months in B12+FA group, and at 12 months in both groups, associated with significant decrease in blood homocysteine and mild lowering of blood pressures (SBP, DBP), but no significant changes in other biochemical profiles. Brachial FMD increased significantly (6.8±1.5 to 7.6±1.5%; p<0.001) in B12+FA group at 6 months, and in both groups at 12 months (6.9±1.4% to 7.7±1.3%; p<0.01), but no changes in carotid IMT were seen after the short double blind or open label treatment period.

Changes in Vascular Markers

	Placebo group (n=12)			B12 + FA group (n=26)		
	Baseline (month-0)	Double-blind (months-6)	Open-label (months-12)	Baseline (month-0)	Double-blind (months-6)	Open-label (months-12)
SBP(mmHg)	123.3±17.6	111.3±13.1**	112.6±10.0*	127.0±15.9	120.4±17.4*	122.3±17.7
DBP(mmHg)	83.2±9.4	73.4±9.8**	73.7±8.9*	83.0±13.4	76.0±15.5**	76.0±13.8**
TC(mmol/l)	3.6±0.5	3.5±0.4	3.6±0.6	3.9±0.7	4.1±0.7*	4.2±0.7*
B12(pg/l)	211.5F	152.7	245.7	196.8	222.7	254.0
	±136.8	±60.9	±99.5**	±84.0	±131.4*	±139.3*
Folate (nmol/l)	9.85±3.3	10.0±3.2	19.4±9.9*	9.68±3.32	21.2±18.5**	19.5±14.1***
Homocysteine (µmol/l)	24.4±16.1	20.0±11.6	13.7±10.8*	23.7±11.7	19.7±12.9*	16.2±10.4***
FMD(%)	6.9±1.3	6.7±1.2	7.8±1.3**	6.8±1.5	7.6±1.5**	7.7±1.3**
IMT(mm ⁻¹)	6.21±0.61	6.21±0.4	6.23±0.47	6.75±0.89	6.67±0.77	6.71±0.73

*p<0.05; **p<0.01; ***p<0.001; TC: Total cholesterol

Conclusions: Vitamin B12 and folic acid supplementation improves atherogenic process in northern rural China, with great implication in atherosclerosis prevention and public health.

P1590 Measurement of baroreflex sensitivity in heart failure patients with frequent episodes of non-sinus rhythm



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Introduction: Noninvasive baroreflex sensitivity (BRS) has prognostic value in chronic heart failure (CHF) and a rehabilitation-induced BRS increase improves prognosis. BRS measurement sessions consist of an ECG and blood pressure recording during several minutes. Later, the longest episode of stationary uninterrupted sinus rhythm is selected for actual BRS computation. CHF patients have frequent arrhythmias, and in practice the longest usable data-segment is often less than a minute. The resulting BRS is then highly unreliable. We have addressed this problem by defining a procedure to compose a session BRS from multiple single-segment BRS values.

Methods and Results: Data were the 9 episodes of uninterrupted sinus rhythm during >7 minutes that were present in our 100 most recently recorded 10-minute BRS sessions of CHF patients, NYHA class II-III. In these 9 episodes we computed BRS by the average transfer function in the 0.05-0.15 Hz band, and the corresponding 95% confidence interval (CI). Subsequently, these episodes were cut into 2, 4, and 8 equal-length segments, and BRS and CI were computed in all segments. Finally, composite BRS and CI values for the whole episode were calculated from the multiple segment BRS and CI values by using the best linear unbiased estimator (BLUE) method. See Table.

Discussion: According to the smallest and the largest segment BRS and CI values, short data segments can yield very unreliable results. Our results underscore the generally accepted rule that a data segment used for BRS calculation should

not be shorter than 4 minutes. However, BRS and CI values that were composed from multiple much shorter 'unreliable' data segments remained within 4% and 8%, respectively, from the value obtained from the complete episodes.

Episode/segment averaged BRS ± CI

Episode or # of segments	1 episode	2 segments	4 segments	8 segments
Segment length [s]	528	264	132	66
Composite BRS [ms/mmHg]	4.68 ± 1.17	4.76 ± 1.19	4.52 ± 1.16	4.62 ± 1.26
Smallest BRS [ms/mmHg]	NA	4.26 ± 1.62	3.17 ± 2.27	2.61 ± 2.77
Highest BRS [ms/mmHg]	NA	5.41 ± 1.80	7.41 ± 2.75	9.33 ± 5.50

Conclusions: BRS computation in patients which fragmented episodes of sinus rhythm can reliably been done by composing a session BRS from multiple segment BRS values by the BLUE method. This solution makes noninvasive BRS measurement feasible in the clinic.

P1591 The prevalence of the Metabolic Syndrome in Venezuela: the MetS-Venezuelan Study



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Background: The Third Report (ATP III) of the National Cholesterol Education Program Expert Panel (NCEP) highlighted the importance of identifying and treating patients with the Metabolic Syndrome (MetS) to prevent cardiovascular disease (CVD) and progression to diabetes mellitus. Limited information is available about the prevalence of MetS, as defined by the NCEP ATP III, in South America, especially in Venezuela.

Objective: To estimate the prevalence of the MetS in Venezuela, The MetS-Venezuelan Study.

Design and participants: A cross-sectional analysis of a representative sample of Venezuelan adults (5174 participants older than 18 years). In all, 4953 subjects were included in the final analysis.

Results: All subjects from the general population were Hispanic-American men (46%) and women (54%), living in urban (n = 5174; 100%) areas. The age-standardized prevalence of the MetS was 33.6% [95% confidence interval (CI): 32.4-35.1%]. This was similar in men (34.2%, 95% CI: 32.3-35.2%) and women (32.8%, 95% CI: 31.4-35.0%) (p = 0.3). The prevalence increased with age in both sexes, 9.7% among participants aged 19-29 years and 33% for participants over 70 years old (p for trend < 0.0001). There was a 17.7-fold increase in odds ratio for having MetS in the age group > 70 years old compared with that of 19-29 years old (p < 0.0001) Most of those with MetS had three components of the Syndrome (61%), 29% had four and 10% had all five components. Abdominal Obesity (62%) Arterial Hypertension (58%) and Hyperinsulinism (37%) were the most common abnormalities in both sexes. The urban venezuelan Community, on a high-saturated fat diet, had the highest prevalence of the MetS, with a low physical activity level. According to the 2001 Census, its possible that about 8.9 million venezuelan may be have the MetS.

Conclusions: These results show that the MetS is highly prevalent in the Venezuelan adult population (33.6%). This may have major implications for the incidence of CVD. Promoting healthy diets, low caloric intake and physical activity, treatment of the comorbidities must be urgently undertaken.

P1592 Trends of cardiovascular risk factors in Chile: prevalence in healthy population and in Acute Myocardial Infarction



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In middle income countries there are few national data about cardiovascular risk factors (CVRF) trends, and their relation with Acute Myocardial Infarction's (AMI) incidence over time.

Objective: To analyze the national changes of CVRF prevalence, in healthy people (without CHD) in the last fifteen years in Chile, and the relation of these findings with the profile of CVRF of people with AMI.

Design: National representative CVRF surveys were conducted in 1989 (n=1,203), in 1999 (n=3,120) and in 2004 (n=12,190). Data from this three independent population studies (ages 30-80 years) were compared to describe national trends of CVRF, and with data from the National Registry of AMI from 1993-94 (n=2,957) and 2004 (n=1,522).

Results: In healthy population the prevalence of hypertension rose from 8.8% in 1989 to 11.1% in 1999, and up to 21.1% in 2004, showing an increase of 140% in 15 years. hypercholesterolemia rose from 46.6% in 1999 to 53.1% in 2004 (an increase of 14%), diabetes rose from 3.9% in 1999 to 5.1% in 2004 (an increase of 29%), and obesity rose from 18.8% in 1989 to 19.7% in 1999 and to 24% in 2004 (an increase of 28%). These increases were observed in both sexes, at all ages, and in all educational levels. The prevalence of current smoking decreased from 46.2% in 1989 to 40.6% in 1999, and to 37.8% in 2004 (a reduction of 23% in the last 15 years). The prevalence of sedentarism change from 82.3% in 1989 to 84.6% in 1999, and to 68.6% in 2004 (a reduction of 20% in this period). In

2004 the average number of risk factor (systolic hypertension, diastolic hypertension, hypercholesterolemia, diabetes, obesity, current smoking, sedentarism and abnormal waist circumference), was 2.62 ± 1.4 in women and 2.49 ± 1.5 in men ($p < 0.0001$). National Registry of AMI, evidenced that hypertension continue to be the most prevalent CVRF associated with AMI (46% in 1993 and 56% in 2004, also showing an increasing trend) and on the opposite, it revealed a decline in the prevalence of smokers (40% to 34%) among the people that suffered an AMI in the same period.

Conclusions: All CVRF evidenced a substantial increase of their prevalence in this period, except current smoking and sedentarism. Particularly important is the increase of hypertension considering that the ten year trend of this RF in the AMI National Registry followed a similar curve. The knowledge of the RF pattern over time and of their burden of risk could help us to better allocate resources in the prevention of CV disease.

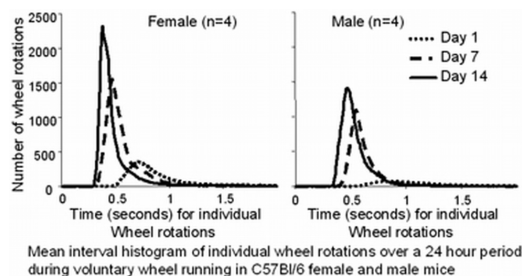
P1593 A novel technique for advanced exercise phenotyping in mouse models



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Regular physical exercise protects against cardiovascular disease. Mouse models have been developed to investigate these beneficial effects at a molecular and genetic level. Many use forced exercise such as swimming or treadmill running. However experimental conditions may be stressful and non-physiological. Voluntary exercise protocols avoid these problems but it has only been possible to monitor simple parameters of wheel running with digital odometers. We describe a novel computerized system capable of continuously recording individual wheel rotations allowing detailed analysis of the running behaviour of individual animals.

Methods and results: C57Bl/6 mice were singly housed with either a fixed or freely rotating running track. Instantaneous wheel rotation speed was monitored continuously by computer and analysed using Spike5 software. Mice ran considerable distances, almost exclusively at night, in short bouts (Mean duration: female 150 ± 17 s, male 134 ± 11 s). An interval histogram of the time taken for individual wheel rotations occurring over a 24 hour period showed that mice ran at a single preferred speed (cruising speed) close to their maximum speed. During training the histogram profile became increasingly left-skewed with increased distance run, increased cruising speed and reduced range of running speeds. There were marked gender specific differences in running performance. Running parameters peaked within 2 weeks in females and 3 weeks in males.



Discussion: These novel parameters of voluntary wheel running provide a highly sophisticated, quantitative assessment of exercise training and performance compared with traditional measures which will improve the utility of exercise training as a physiological phenotyping tool in mouse models of cardiovascular disease.

P1594 Aminoacids intake increases mitochondria and sarcomere in skeletal muscle of old mouse



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Insulin sensitivity, alteration and reduction of contractile proteins and impairment of oxidative enzyme are muscular changes of advanced age. These changes may be responsible of decline in muscle strength in old subjects. Recently it was demonstrated that chronic oral administration of a specific mixture of aminoacids (AAs) stimulate protein synthesis and improve oxidative muscle metabolism. To evaluate the morphometric effects of oral AAs supplementation on mitochondria (Mi) and sarcomere (Sr) of old mouse (14 months) we performed an experiment using two groups of five male animals each. The standard dry food were added with water (controls) or aqueous solution of AAs mixture (1.5g/kg/day) per 90 days. The amount of fluid intake was measured daily. At the end of the treatment animals were killed, the quadriceps were removed, fixed in glutaraldehyde and processed for electron microscopy (EM) technique. For each group, data were collected from about 90 EM photographs (x5,900) randomly taken at different levels of muscle. The morphometric measures were taken twice by three persons

using 5mm-gauge stereological grid. We calculated: the total area of fibres (TotA), the area of sarcoplasm (SpA), Sr (SrA), Mi (MiA), and the number of Mi (MiN). From these data we calculated the ratio SrA/TotA, MiA/SpA, and the MiN/100 m² of SpA. After 90 days there is no difference in fluid intake and body weight: respectively 6.4 ± 1.5 ml and 28 ± 2 g in controls; 5.1 ± 1 ml and 29 ± 1 g in AAs treated. In each group, the total area examined was about 115,000 m². All parameters increased statistically in AAs treated animals. The MiN/100 m² SpA, 15.8 ± 9.1 vs 4.3 ± 2.9 ; the MiA/SpA, 0.32 ± 0.2 vs 0.15 ± 0.05 ; the SrA/TotA, 0.80 ± 0.14 vs 0.57 ± 0.2 .

Conclusion: chronic AAs supplementation improves Mi and muscular functionality, so this data may be of interest in prevention and treatment of sarcopenia and increasing muscle strength in old subjects.

P1595 Nitric oxide production during exercise in acting limb correlates with exercise tolerance



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Background and Objectives: Nitric Oxide (NO) is one of the strongest endothelial cell derived vasodilating substances that regulates the vessel distensibility. We have reported that NO concentration in exhaled air is lower in patients with CHF both at rest and during exercise. However, it is not revealed whether NO concentration in blood is lower or not in those subjects, as well whether it is related with their exercise tolerance. Hereby, we sought to investigate whether plasma NO concentration in acting limb is increased during exercise as comparing with non-acting limb, and if there is any correlation with exercise tolerance.

Method: Eighteen patients with heart failure and three normal subjects were enrolled to this study (Dilated cardiomyopathy (n=7), Ischemic heart disease (n=7), Hypertensive heart disease (n=4), normals (n=3), age: 61 ± 17 years old, LVEF: $39.6 \pm 19.0\%$, Anaerobic threshold: 12.9 ± 4.3 ml/min/kg). Cardiopulmonary exercise testing was performed using a Ramp protocol on a cycle ergometer. We measured NO concentration using a chemiluminescent method, drawing blood by saphenous vein at the lower extremity and median cubital vein at the upper extremity, at rest and at the peak exercise. We divided subjects into two groups according to the value of the peak oxygen uptake (VO₂): subjects whose peak VO₂ was above 80% of normal value were assigned into Group A (n=10) and the rest were into Group B (n=11).

Result: The ratio of increase of NO concentration during exercise in the upper limb (non-acting limb) was not significantly different between Group A and B ($108.2 \pm 15.7\%$ vs. $108.4 \pm 21.8\%$, respectively). Whereas, the ratio of increases of plasma NO concentration in lower limb (acting limb) was significantly ($p=0.024$) higher in Group A ($113.2 \pm 21.6\%$) as compared with Group B ($93.2 \pm 14.0\%$). The ratio of NO increase during exercise of lower over upper limb was higher as exercise tolerance was greater ($r=0.359$).

Conclusion: These data indicate that nitric oxide production in acting limb vessels is attenuated in subjects with impaired exercise tolerance. The ability of nitric oxide production seems to be one of the regulatory factors of exercise tolerance.

P1596 A comparison of the effects of bicycle training and the different antihypertensive drugs on endothelial function in patients with severe hypertension



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The fact that forearm endothelial dysfunction is a marker of future cardiovascular events in patients with hypertension stresses the importance of the clinical evaluation of endothelial function and of the evaluation of the effects of the different antihypertensive drug classes on this parameter. The aim of the study was to investigate the effects of different ways of treatment on endothelial function in patients with severe hypertension.

Methods: The study population included 30 patients with arterial hypertension III degree and 22 healthy volunteers. The hypertensive patients were treated with enalapril, atenolol and diuretic agents (group A: n=12) and the same medicines plus bicycle training (group B: n=9). The intensity of bicycle training was 50% from the individual threshold load detected on the bicycle ergometers during 30 minutes for 14 days. One more group got enalapril, nebilet (nebivolol) and diuretic agents (group C: n=9). The forearm blood flow (FBF) was measured using strain-gauge plethysmography during reactive hyperemia to test endothelium-dependent vasodilatation, and after sublingual nitroglycerin administration - to test endothelium-independent vasodilatation. Two weeks after the treatment the same examinations were performed.

Results: FBF in patients with hypertension during reactive hyperemia was significantly lower than that in control subjects (9.4 ± 1.0 versus $30.9 \pm 1.7\%$, $p < 0.01$). The increases in FBF after nitroglycerin were similar between the hypertensive and normotensive subjects. The treatment with enalapril, atenolol and diuretic agents did not improve FBF during reactive hyperemia ($9.3 \pm 1.7\%$ versus $12.9 \pm 1.9\%$). FBF during reactive hyperemia was significantly increased after bicycle training in combination with medicament treatment compared with the baseline (from $9.4 \pm 1.3\%$ to $18.9 \pm 1.8\%$, $p < 0.05$). Nebilet improved decreased FBF during reactive hyperemia compared with the baseline ($9.7 \pm 1.7\%$ versus $18.5 \pm$

2.0%, $p < 0.01$). The increases in FBF after the sublingual nitroglycerin administration did not differ after treatment in all groups.

Bicycle training and nebilet improve the endothelial function even in severe hypertension. Because endothelial dysfunction plays an integral part in the early atherosclerotic process and are associated with poor outcomes and increased mortality, independent of blood pressure, the ability of nebilet and physical training to enhance release of endothelium-derived NO may have significant clinical implications for the use of this agent in the treatment of hypertension and coronary vascular disease.

P1597 Multifactorial intervention decreases cardiovascular disease in patients with metabolic syndrome



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Background: Metabolic syndrome isn't a disease, but is a cluster of disorders of body's metabolism - including high blood pressure, high insulin levels, excess body weight and abnormal cholesterol levels - that more likely to develop diabetes, heart disease or stroke

Objective: The metabolic syndrome describes a high-risk population having 3 or more of the following clinical characteristics: upper-body obesity, hypertriglyceridemia, hypertension, and abnormal glucose. Cardiovascular morbidity is a major burden in patients with the metabolic syndrome. In this study, we compared the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for cardiovascular disease in patients with metabolic syndrome.

Methods: The primary end point of this open, parallel trial was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary-artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, 160 patients were randomly assigned to receive conventional treatment in accordance with national guidelines and 160 to receive intensive treatment, with a stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, dyslipidemia, and, along with secondary prevention of cardiovascular disease with aspirin.

Results: The mean age of the patients was 55.1 years, and the mean follow-up was 7.8 years. The decline in glycosylated hemoglobin values, systolic and diastolic blood pressure, serum cholesterol and triglyceride levels measured after an overnight fast, were all significantly greater in the intensive therapy group than in the conventional-therapy group. Patients receiving intensive therapy also had a significantly lower risk of cardiovascular disease (hazard ratio, 0.47; 95 percent confidence interval, 0.24 to 0.73), retinopathy (hazard ratio, 0.42; 95 percent confidence interval, 0.21-0.86).

Conclusions: A target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with metabolic syndrome reduces the risk of cardiovascular events by about 50 percent.

P1598 Essential hypertensive patients with exaggerated blood pressure response during treadmill test are characterized by increased levels of C-reactive protein and urinary albumin excretion



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Purpose: The data regarding the association of a hypertensive response to exercise (HRE) with cardiovascular risk are controversial, while low-grade inflammatory processes and urinary albumin excretion are linked to atherosclerosis progression and unfavourable outcome. In this study we examined the correlations between HRE, high-sensitivity C-reactive protein (hs-CRP) and urinary albumin excretion, expressed as the albumin to creatinine ratio (ACR), in essential hypertensives.

Methods: 84 newly diagnosed untreated non-diabetics with stage I to II essential hypertension [58 men, mean age = 52 years, office blood pressure (BP) = 145/93 mmHg] with a negative treadmill exercise test (Bruce protocol) were divided into those with HRE ($n=24$) (peak systolic BP > 210 mmHg in men and > 190 mmHg in women) and to those without HRE ($n=60$). Moreover, in all subjects ACR values were determined as the mean of two non-consecutive morning spot urine samples and venous blood samples were drawn for estimation of metabolic profile and hs-CRP levels according to established techniques.

Results: Patients with HRE compared to those without HRE were older (56 ± 9 vs 50 ± 9 years, $p < 0.05$), had greater 24-h systolic BP (138 ± 14 vs 131 ± 12 mmHg, $p < 0.05$), while did not differ regarding metabolic profile, left ventricular mass index and relative wall thickness ($p=NS$ for all). Furthermore, patients with HRE as compared to those without HRE exhibited higher levels of ACR (71.9 ± 18 vs 14.2 ± 2.6 mg/g, $p < 0.0001$) and hs-CRP (5.1 ± 1.2 vs 2.1 ± 0.8 mg/l, $p < 0.0001$). In the total population, peak systolic BP was related to 24-h systolic BP ($r=0.238$, $p < 0.05$), hs-CRP ($r=0.439$, $p < 0.0001$) and ACR ($r=0.474$, $p < 0.0001$), while hs-CRP was associated with ACR ($r=0.758$, $p < 0.0001$). By analysis of covariance it was revealed that ACR and hs-CRP values remained significantly different between groups after adjustment for confounders ($p < 0.05$).

Conclusions: In the setting of essential hypertension, an HRE is associated with heightened hs-CRP and ACR levels, reflecting diffuse proatherosclerotic pro-

cesses. These findings suggest that HRE may be a useful tool in identifying hypertensive subjects at high cardiovascular risk.

P1599 Exercise cardiac output increase through the Frank Starling mechanism in patients with abnormal force-frequency relationship



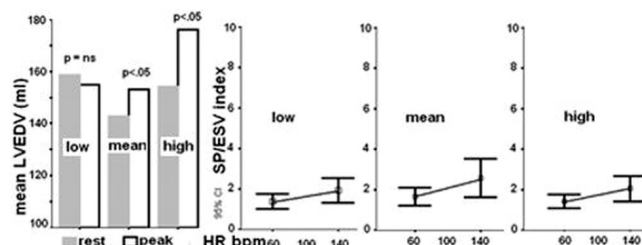
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Background: Goal of the heart during exercise is to increase cardiac output (stroke volume x heart rate) to metabolizing tissues. In LV dysfunction this can be obtained through pump reserve recruitment.

Aim: to assess the relative role of systolic vs. diastolic dysfunction in modulating cardiac output in patients with non-ischemic left ventricular dysfunction.

Methods: We enrolled 51 pts (age 46 ± 15 , 45 males, EF = $36 \pm 9\%$), normal coronary arteries, NYHA class $\geq II$, scheduled for exercise blood pool gating study. To assess the systolic function the Force frequency relationship was built during stress: the force was determined at rest and peak stress as the ratio of the systolic pressure/end-systolic volume. Diastolic performance was assessed by the ability to recruit end-diastolic volume (preload reserve) during stress.

Results: based on stroke volume changes from rest to peak stress low (-2 ± 5 ml), medium ($+10 \pm 4$ ml) and high ($+24 \pm 12$ ml) tertiles, pts were divided in three groups. Systolic reserve assessed with the Pressure Volume Relationship was equally abnormal flat (delta SP/ESV index < 1.5 mmHg/ml) in the three groups (figure). EDV decreased from rest to peak stress in the low, while increased in the medium and high stroke volume subgroups (figure); Peak stress cardiac output was 5.6 ± 2.9 L/min in the low, 8 ± 3 L/min in the medium and 9.1 ± 2 L/min in the high stroke volume subgroups ($p < 0.05$ between groups).



Conclusions: failure of the Frank-Starling mechanism, manifested by an impaired ability to recruit end-diastolic volume (preload reserve) results in greater physiological abnormality that further worsens cardiac output reserve during exercise.

MANAGEMENT OF CORONARY DISEASE

P1600 The gap between preoperative cardiac risk evaluation in clinical practice and current guidelines



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Background: The ACC/AHA guidelines on perioperative care propose an algorithm for a stepwise approach to identify patients at risk and to initiate risk reduction strategies. According to this algorithm, patients scheduled for acute procedures or those who underwent recent cardiac testing without unfavourable results, can undergo surgery without further evaluation. All other patients have to be stratified according to major, intermediate or minor clinical cardiac risk factors. Subsequently, in patients at high cardiac risk, with poor functional capacity or undergoing high risk procedures, additional non-invasive cardiac evaluation is recommended.

Objective: To determine the adherence of the ACC/AHA guidelines on perioperative care in daily clinical practice and its effect on cardiac complications after one year.

Methods: Between May and December 2004, 711 consecutive peripheral vascular surgery patients were included in 11 hospitals in the Netherlands and evaluated for cardiac risk factors and 1-year outcome. This survey was an integrated part of the infrastructure of the Euro Heart Survey Programme. We applied the ACC/AHA guidelines algorithm to the study population and subsequently compared these recommendations with daily clinical practice.

Results: Of the total of 711 patients, 92 patients underwent emergency surgery and 38 patients underwent recent coronary revascularization or evaluation without recurrent symptoms. In accordance with the ACC/AHA guidelines algorithm, the remaining 581 patients were subsequently defined as having major ($n=13$), intermediate ($n=265$) and minor or no clinical risk predictors ($n=303$). Non-invasive testing while not recommended by the guidelines was performed in 9% of those 581 patients. A total of 185 patients fulfilled the ACC/AHA criteria for recommen-

dation of preoperative non-invasive cardiac testing. However, testing was only performed in 21% (n=38) of those cases. Of 16 patients with abnormal test results, beta-blockers were started in 13 patients (82%), but none of the patients were referred for revascularization prior to surgery. There was no significant difference in cardiac complications after one year in patients tested according to the guidelines or not (10.5% vs 9.8%; p-value=.779).

Conclusion: Clinician daily practice in vascular surgery and the ACC/AHA guidelines had a low level of agreement for non-invasive cardiac testing. Despite the poor adherence to the guidelines with respect to performing of non-invasive cardiac testing, this did not result in a higher frequency of cardiac complications after one year.

P1601 Endovascular repair of abdominal aortic aneurysm is associated with reduced perioperative myocardial ischemia during continuous 12-lead electrocardiography, troponin T release and all-cause mortality

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Background: Endovascular abdominal aortic aneurysm (AAA) repair is considered to be minimally invasive and associated with reduced in-hospital complications compared to open repair. Limited information is available whether endovascular repair is associated with reduced myocardial ischemia.

Aim: To determine the incidence of perioperative myocardial ischemia, troponin T release and outcome in patients undergoing endovascular infrarenal AAA repair compared to open repair.

Methods: A total of 129 patients (mean age 69±9 years, 86% male) undergoing open (n=94) or endovascular (n=35) repair of infrarenal AAA were preoperatively screened for cardiac risk factors, stress-induced myocardial ischemia during dobutamine stress echocardiography and cardioprotective medication. Myocardial ischemia was detected by continuous 12-lead electrocardiographic monitoring starting 24 hours before surgery and continued until two days after. Troponin T release was measured on day 1, 3, and 7 postoperatively and before discharge. All-cause mortality during the first 30 days after surgery was recorded.

Results: There were no significant differences in baseline characteristics between patients undergoing open or endovascular AAA repair. Myocardial ischemia, troponin T release (>0.1 ng/mL) and hospital mortality was detected in 49 (38.0%), 25 (19.4%) and 11 (8.5%) patients, respectively. The incidence of myocardial ischemia was significantly higher in the open repair group, compared to the endovascular repair group (50.0% vs 5.7%, p<0.001), also after adjustment for cardiac risk factors, dobutamine stress echocardiography results and cardioprotective medication (OR: 17.3, 95% CI: 2.8-105.4, p=0.002). Positive troponin T levels were also more frequently observed in patients undergoing open repair compared to endovascular repair (26.6% vs 0%, p<0.001). Finally, all-cause mortality occurred more frequently in patients undergoing open repair compared to endovascular repair (11.7% vs 0%, p=0.035).

Conclusion: Endovascular stent grafting for infrarenal abdominal aortic aneurysm is associated with a reduced incidence of perioperative myocardial ischemia during continuous 12-lead electrocardiographic monitoring, troponin T release and perioperative death, compared to open repair.

P1602 Carotid angioplasty and stenting under protection is becoming the gold standard treatment of a carotid stenosis in high and low risk patients

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Background: Recent studies have shown that Carotid Angioplasty and Stenting (C.A.S.) has superior short term outcomes than Carotid Endarterectomy (C.E.A.) in high surgical risk patients (H.R.). It is not clear however, whether low surgical risk patients (L.R.) are also at lower risk. We compared short term outcomes of C.A.S. in H.R. and L.R. patients.

Methods: We analyzed all C.A.S. performed under protection devices. HR factors included age ≥ 80 yrs, post surgical restenosis, prior neck surgery or radiation, contralateral occlusion, low or high anatomic lesion, unstable or severe coronary or hearty diseases, severe comorbidities. Patients were followed for 30 days.

Results: C.A.S. were performed in 597 arteries under protection devices using occlusion balloon (n=334), filters (n=257), reversal flow technique (n=6). 385 (65%) were found to be at HR and 212 (35%) at LR. HR and LR patients had similar success rate of protection device deployment (99% both), and stent placement (100% both).

The 30 day outcomes were as follows:

- High-risk patients:
- TIA: 4 (1%)
- Minor stroke: 2 (0.5%)
- Major stroke: 1 (0.3%)
- Retinol embolism: 1 (0.3%)

- Hyperperfusion syndrome: 2 (0.5%)
- M.I.: 1 (0.5%)
- Death and stroke: 5 (1.3%)
- Embolic events: 8 (2.1%)
- Low-risk patients:
- TIA: 2 (1%)
- Retinal embolism: 2 (1%)
- Hyperperfusion syndrome : 1 (0.5%)
- Death and stroke : 1 (0.5%)
- Embolic events: 3 (1.4%)

There was no statistical difference between occlusion balloon and filter for 30 day death and stroke rate (0.3% vs 0.8%, p=n.s) and embolic events (1.4% vs 1.6%, p=n.s.).

Conclusion: C.A.S. under protection is safe with favourable low event rate in HR and LR patients. LR patients have a trend towards lower death and stroke rate after C.A.S. compared to C.E.A., but it is not statistically significant. C.A.S. should be enlarged to LR patients. C.A.S. is becoming the gold standard treatment of a carotid stenosis.

P1603 Endovascular repair (EVAR) of thoracic and abdominal aortic diseases: a 4-year experience

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Introduction: Thoracic and abdominal aortic diseases are still life-threatening disorders and the optimal management of these diseases continues to be a matter of concern. Aim of our study was to evaluate the safety and efficacy of EVAR over a 4-year experience.

Methods From March 2001 to June 2005, 157 patients (pts) underwent EVAR: 101 pts (64.3%) with abdominal aortic aneurysm(AAA), 51 pts (32.4%) with thoracic aortic diseases, and 5 pts (3.2%) with a combined thoraco-abdominal aneurysm. A comorbid medical illness (ASA III- IV) was observed in 109 pts (69.4%).The thoracic group consisted of: 7 pts (13.7%) with traumatic rupture, 18 pts (35.3%) with a thoracic aortic aneurysm(TAA), and 26 pts (51%) with a type B dissection. An emergency procedure was required in 51 pts (32.4%):35/51 pts(68.6%) in the thoracic group, 13/101 pts in AAA group and 4/5 pts (80%) in the combined group. In AAA group 19/101 pts (18.8%), unfit for open surgery, showed a challenging anatomy because of a severe proximal neck angulation (>60°). The follow-up(F-U) ranged between 6 and 51 months (average 40.7 ± 10.8 months). All pts were clinically followed during hospitalization and they underwent a 2 mm-interval CT-scan 2 weeks, and 6/12 months after discharge and every year.

Results There were no perioperative death, no paraplegia and no open surgical conversion. The average length of intensive care unit and hospital stay was 1.7 ± 0.9 and 6.9 ± 3.0 days, respectively. The intraoperative angiography and CT-scan on discharge showed no significant endoleaks in anypatient. At F-U, there were 3 late deaths (one procedure-related) in the thoracic group and 9 (none procedure-related) in AAA group. A traumatic patient with a type I endoleak was successfully treated by a secondary EVAR 16 months after the first procedure.

Conclusions: In our experience EVAR has shown to be a safe and effective treatment option in pts with aortic diseases, associated with low immediate and late complications, even in pts with an high clinical risk profile and/or challenging anatomy.

P1604 Spanish registry of acute aortic syndrome. The improvement in the diagnosis is not reflected in the reduction of mortality

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The impact of recent advances in management of acute aortic syndrome (AAS) is usually reported by centres with high experience in aortic disease. The Spanish Registry of Acute Aortic Syndrome was established to assess the current results in the management of AAS in a large cohort of hospitals in the same geographical area.

All patients (pts) at 22 hospitals with AAS were enrolled during 2005. 242 pts, (76% men, mean age 61±14 y, range 20-92), 201 with aortic dissection (156 type A, 45 type B), 32 haematoma (12 type A and 20 type B) and 9 penetrating ulcer (2 type A and 7 type B).

CT was the first diagnostic technique used in 77% of cases. Time interval between symptoms and diagnosis was < 24h in 67% of cases (median 5h; P25%:3h and P75%: 10h) and > 72h in 11% of cases. 77% of Type A AAS underwent surgical treatment. Time interval between diagnosis and surgery was <24h in 90% of cases (median 4h; P 25%: 3h and P75%:7h). Type B SAA invasive treatment: 48% (34/71), surgery (n:7) and endovascular treatment (n:27).

Type A mortality during hospitalization was 46.5% (79/170), 39.7% (52/131) in surgically treated and 69.2% (27/39) in medically treated pts ($p=0.002$). Overall mortality in Type B was 22.2% (16/72); endovascular treatment: 14.3%, (4/28) surgically treated pts: 33.3% (2/6) or medically treated pts: 24.3% (9/37) ($p=n.s.$). **Conclusion:** Despite significant advances in Acute Aortic Syndrome diagnosis, hospital mortality remains high. Our data support the need for continued improvement in the management of Acute Aortic Syndrome.

P1605 Management and mortality of type A acute aortic syndrome. Results from the Spanish registry of acute aortic syndrome



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Type A AAS is a clinical emergency associated with high mortality. Although improvement in mortality has been reported by experienced centers, current results of management in a large cohort of hospitals in a specific geographical area is not well known.

170 consecutive pts with type A AAS at 22 hospitals were enrolled during 2005. 44% were transferred from community hospitals. 132 pts (77%) underwent surgical treatment. 15 pts died before surgery. 22 pts were treated medically due to co-morbidity in 6, age in 7, non-complicated intramural haematoma in 4 and patient decision in 5. The interval between symptoms and surgery was 9 h (median; P25%:6h- P75%:16h). Surgery was performed within 24h after the diagnosis in 90% (median 4h, P25%:3 h - P75%: 7h). Surgical treatment employed was: Bentall technique in 25%, valvular replacement with ascending aorta tube graft in 16%, only tube graft in 57%.

Mortality in surgical management was 39.7% (52/131) and in medical management 69.2% (27/39) ($p<0.01$). Complications after surgery were: 23.6% neurological complications, 34.4% renal failure, 10% peripheral or visceral ischaemia. 9 pts required surgical reintervention. The imaging test before discharge showed descending aorta false lumen flow in 64%.

Conclusions: Type A AAS in a large cohort of hospitals of a specific geographical area has a higher morbi-mortality than is reported. A shorter interval between symptoms and treatment, a lower number of transferred patients and the inclusion of non-selected high specialized aorta centres may explain these differences. The results of this study may better represent the real evolution of this severe disease.

P1606 Screening, diagnosis and treatment of renal artery stenosis by Percutaneous Transluminal Renal Angioplasty (PTRA) with stenting, the Haifa experience



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Renal artery stenosis (>50% luminal narrowing) is the most frequent cause for secondary hypertension and is mainly of atherosclerotic origin. Recently renal artery stenting (RAS) was introduced as potential therapy.

Methods: Patients undergoing coronary angiography were screened according to pre-selected criteria to undergo renal arteriography to rule-out renal artery stenosis.

Results: Renal arteriography was performed in 450 patients having coronary angiography according to pre-selected criteria, significant renal artery stenosis was found in 35 patients (7.7%), another 6 patients were referred for RAS by nephrologists. RAS was performed in 41 patients, 27 (64%) were female, age 72±6 years, comorbidities included: ischemic heart disease (76%), diabetes (46%), hyperlipidemia (66%), smokers (20%), peripheral vascular disease (29%), carotid artery disease (22%). Ostial renal stenosis was present in 86%. 40 patients of 41 were treated by RAS, 1 patient found to have fibromuscular dysplasia was treated by angioplasty without stenting, success rate 100%, without procedural and peri-procedural complications. Post-PTRA quantitative analysis revealed 15±5% diameter residual narrowing. During follow up period (median-3 years, range 2 months-4 years), re-PTRA was needed in 2 subjects. Systolic pressure decreased immediately (< 7 days) after PTRA (from 160±18 mmHg to 137±14 mmHg, $p=0.0001$). Diastolic blood pressure also significantly decreased (from 79±13 mmHg to 72±9 mmHg, $p=0.004$). On late follow up both systolic 140±12 and diastolic 75±11 mmHg blood pressure were lower than baseline ($p=0.002$, $p=0.06$ respectively). Creatinine <1.5 mg/dl predicted more sustained decrease in systolic blood pressure ($p=0.003$). In 32% of the patients less antihypertensive drugs as compared to baseline were needed. Plasma creatinine did not change significantly.

Conclusions: 1) Screening method is effective for diagnosis of renal artery stenosis according to pre-selected criteria in patients undergoing coronary angiography. 2) Patients with renal artery stenosis can be treated successfully with RAS. 3) During follow-up period no significant deterioration in renal function was

found. 4) Sustained improvement in blood pressure is achieved especially when renal function is preserved.

P1607 Feasibility of real-time Magnetic Resonance-guided stent-graft placement in a swine model of descending aortic dissection

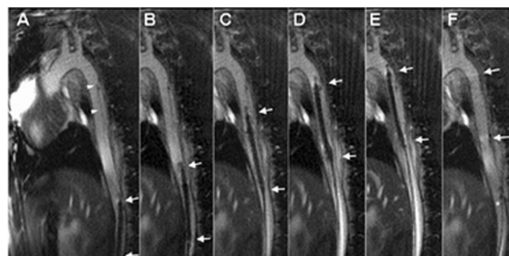


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Background: Endovascular stent-graft placement for thoracic aortic disease is usually performed under x-ray guidance which has several shortcomings beyond radiation exposure and use of nephrotoxic contrast media. It was the aim of the present study to evaluate the preclinical feasibility of real-time MR imaging (rtMRI) to guide stent-graft placement for experimental aortic dissection (AD).

Methods: Using a catheter-based technique, dissections of the descending thoracic aorta were successfully created in 8 domestic pigs. Subsequent implantation of commercially available, nitinol-based stent-grafts was performed entirely under rtMRI guidance.

Results: By pre-interventional MRI, the mean minimal true lumen diameter was 0.9 (0.825-0.975) cm. Real-time MRI permitted not only the successful and safe device navigation within the true lumen from the iliac arteries to the thoracic aorta, but also the precise positioning and deployment of the stent-graft and safe withdrawal of the delivery catheter in 7 of 8 pigs. This was achieved without any other complications. After stent-graft placement, MRI demonstrated complete obliteration of the false lumen which was confirmed at autopsy. All stent-grafts were well expanded resulting in an increase in the size of the true lumen diameter to 2.05 (1.925-2.1) cm ($p=0.066$ vs. baseline).



Conclusions: In experimental AD, rtMRI guided endovascular stent-graft placement is feasible and safe and has the potential for mitigating radiation and contrast-related side effects. Additionally, it allows not only pre-interventional diagnosis and detailed anatomic diagnosis, but also permits immediate post-interventional anatomic and functional delineation of procedure success that may serve as a baseline for future comparison during follow-up.

P1608 Natural history of type B aortic dissection in medical therapy



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Background: Medical therapy is indicated in case of uncomplicated type B aortic dissection (TBD). The present study aimed to define the natural history of TBD patients in medical treatment, with particular focus on long-term survival and descending aortic dilatation in the follow-up.

Methods: Between November 1988 and December 2005, 129 patients with TBD were referred to our tertiary referral Institution: 53 (41.1%) with complicated TBD underwent surgical or endovascular treatment; 76 (58.9%; mean age 59.4±11.6; 77.6% male) with uncomplicated TBD were put on hypotensive therapy with invasive blood pressure monitoring until pressure stabilization. Instrumental follow-up was performed through and transesophageal echocardiography (TEE) and/or CT scan. First admission and follow-up data were entered in a dedicated database and retrospectively analysed.

Results: Twenty-two patients (28.9%) had chronic TBD, 54 (71.1%) acute. History of already known hypertension was present in 73.7% patients, previous aortic surgery (ascending aortic replacement or deoarcctation) in 5.3%, an intramural haematoma in 14.5%. Hospital mortality occurred in 10 patients. Follow-up length of hospital survivors was 32.7±31.8 months (range: 0.33-128.2 months). Eight patients died during the follow-up (for sudden unexplained death or ascertained aortic causes in 50% cases). Female sex ($p<NS$) and presence of dilated ascending aorta (>3.9cm at first admission; $p=0.05$) were associated with lower long-term survival. Patients with intramural haematoma had significantly higher ($p=0.03$) 10-year survival. Among patients with at least 1 year follow-up, mean annual rate of progression of descending aorta diameters was 0.16±0.3, 0.15±0.3, 0.18±0.5 cm/year at 25, 30 and 35 cm from incisors. A correlation was found between progression of aortic diameters in the follow-up and mortality ($p<0.05$). Invasive treatment of TBD was necessary in 7 patients (10.6%), in 4 of whom endovascular treatment was feasible. Patients with ascending aorta dilatation showed a trend towards greater descending diameter changes at 25-30

cm. A high rate of progression was rarely observed with intramural haematoma ($p=0.05$).

Conclusions: Uncomplicated TBD is a multiform entity: some patients have a worse prognosis in terms of late need for operation or mortality in the follow-up. Awareness of the risk of mortality is required for patients with rapid diameter progression. Notwithstanding the small numbers, the present study found different (sex, intramural haematoma, ascending dilatation) subpopulations at different risk.

P1609 Percutaneous transluminal angioplasty and stenting of extracranial vertebral artery stenoses



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Purpose: To evaluate safety and efficiency of angioplasty/stenting in patients with symptomatic vertebral artery (VA) stenosis.

Material and methods: 66 angioplasties attempted in 60 patients (M: 44) mean age 68.4 ± 6.9 years (22-84) right 33 left 33. All patients had multivascular diseases. 64 lesions were atheromatous, 2 inflammatory diseases. Mean lesion length: 9.5 ± 2.5 mm (5-14), mean arterial diameter: 4.6 ± 0.6 mm (4-6). 59 lesions at VO segment (ostium) 5 at V1 segment and 2 at V2 segments. Indications for angioplasty included: dizziness (60), bilateral weakness (9), visual changes (9), diplopia (8), drop attacks (8), TIA (5), ataxia (4). A protection device (filter) was used in 3 patients. 11 subclavian, 3 carotid angioplasties performed during the same procedure.

Results: Technical success 64/66. Clinical success 58/60. 2 failures in elderly patients with very tortuous calcified arteries. 6 lesions were treated by angioplasty alone (3 VO lesions, first 3 patients, 2 V1, 1 V2 lesion). 1 patient with inflammatory disease was treated by cutting balloon alone. 58 lesions stented with balloon, expandable stents (peripheral stents: 18, coronary stents: 37). 3 V1 and 1 V2 lesions were treated with self expandable stents. No per or post-procedure neurological complications. Angiographic success, defined no significant residual stenosis without in hospital emergency surgery, stroke and death: 64/66 lesions (97%).

Post-procedure arterial diameter: 4.55 ± 0.8 mm (4-6). Mean residual stenosis $2.2 \pm 3.5\%$. 4 patients (8%) developed symptomatic restenosis during the follow-up (mean follow-up: 26.5 ± 26.3 months). 3 after PTA alone, 1 after PTA and stent (1 occlusion treated medically, 3 stenoses successfully treated with balloon angioplasty).

Conclusion: Endovascular treatment of VAS can be performed safely and effectively with a high technical success rate, a low complication rate, a low restenosis rate and a durable clinical success in patients with symptomatic VAS. Stents seem to improve immediate and long-term results.

P1610 Substitution of the aortic valve may have better long-term results than preservation in type-A dissection



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Objective: To evaluate and compare the results obtained in patients operated on for type A aortic dissection, with preservation (group 1) or substitution (group 2) of the aortic valve.

Methods: From November 1988 through December 2003, 101 patients, 79 male, mean age 58.9 (12-82) years, were operated on for type A aortic dissection. Of these, 81 had associated aortic valve pathology. The aortic valve was preserved in 78 patients. In 51 of these only a supraaortic prosthetic tube was implanted, in addition with an aortic commissuroplasty in another 16 and surgery of reconstruction of the root in a further 11 patients. In the remaining 23 patients the valve was replaced, by a prosthesis in 19 and by a homograft in 4.

Results: Hospital mortality was 6% in group 1 and 21% in group 2 ($p<0.05$). Post-operative haemorrhage and CVA occurred in 9% and 5%, respectively, in group 1, and 13% and 4%, in group 2 ($p=NS$). The follow-up was almost complete (98%), for a mean period of 7 years (1-15 years). Late mortality was 27% in group 1 and 4% in group 2 ($p<0.05$), the majority of cardiovascular origin or sudden (81% in group 1, 100% in group 2). Late morbidity in group 1 was similar to that of group 2, including rates of haemorrhagic and thromboembolic events of 3% to 5%. In the latest follow-up an echocardiographic evaluation of the valve function was made in all group 1 patients, including those who did not have prior aortic valvulopathy, and showed minimal or very mild aortic regurgitation in 86% of the patients, mild to moderate in 10% and moderate in 4%.

Conclusion: In patients with type A dissection and associated aortic valvulopathy, valve preservation and substitution had identical cumulative short and long-term results, but the preservation group had higher late mortality, the causes of which require clarification. Valve substitution may be a better option in the long term.

P1611 Blood transfusion death and myocardial infarction after elective major vascular surgery



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Purpose: To evaluate whether liberal blood transfusion (BT) after elective major vascular surgery (VS) is associated with death and myocardial infarction (MI) among patients who had been previously risk stratified according to current guidelines. Anemia is a frequent and serious complication after VS. However, retrospective studies reported that BT may be associated with a higher incidence of death. Furthermore, no guidelines exist on BT, and a liberal regimen based on clinician judgment is common practice.

Methods: All consecutive elective major VS candidates were prospectively risk stratified and treated according to the ACC/AHA guidelines for preoperative cardiovascular evaluation for non cardiac surgery. Patients were grouped according to whether they received a BT during the hospitalization. Death and MI at 30 days were blindly assessed by two independent investigators. The association between BT and outcome was assessed using multiple Cox regression models adjusting for possible confounders.

Results: 274 patients were included (mean age 70 ± 8 years, 73% men). At least moderate anemia (haemoglobin < 9 g/dL) was associated with a significantly increased risk of death and MI which was not attenuated after multivariable adjustment for age, gender, diabetes, and BT (HR=6.2, 95%CI 2.0 to 19.5, $p<0.001$). 43 (16%) patients underwent at least 1 BT during their hospitalization. Patients who underwent BT had an increased hazard of MI (HR= 3.2, 95%CI 1.4 to 7.3; $p=0.005$), death (HR=5.3, 95%CI: 1.9 to 14.0; $p=0.001$), and the combined end-point death or MI (HR=3.4, 95%CI: 1.7 to 7.1; $p=0.001$), compared with patients who did not undergo BT. Such association remained even after adjusting for age, gender, and diabetes (HR for death or MI=2.39, 95%CI 1.2 to 4.75, $p=0.004$). There was a significant interaction between BT and anemia ($p<0.001$); therefore we stratified patients according to the presence or absence of anemia. In patients with at least moderate anemia, BT was associated with a reduced risk of death or MI (HR= 0.3, 95% CI 0.1 to 0.9; $p=0.03$). In patients without moderate anemia, BT was associated with a significantly increased risk of death or MI (HR=3.2, 95% CI 1.5 to 6.8; $p=0.003$).

Conclusions: Anemia of at least moderate severity is an independent prognostic marker after major elective VS in patients risk stratified. Our data suggest caution regarding the routine use of liberal BT in patients with less than moderate anemia to maintain arbitrary hematocrit levels in stable patients, while in patients with moderate anemia BT appears to be a useful therapy.

P1612 The influence of statins and aneurysm size on high-sensitive CRP levels in patients with abdominal aortic aneurysms



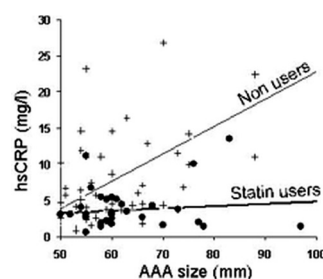
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Background: Pro-inflammatory cytokines are produced locally in abdominal aortic aneurysms (AAAs) and circulating inflammatory markers are related to AAA growth and adverse cardiovascular events. Statins have, in addition to a lipid-lowering effect, anti-inflammatory properties, reflected by a reduction of high-sensitive C-reactive protein (hsCRP) levels. We hypothesized that statins, due to their pleiotropic effects, lower the level of circulating inflammatory markers such as hsCRP in patients with AAA.

Methods: Consecutive patients scheduled for elective AAA repair preoperatively underwent CT angiography to assess the diameter of the AAA. These patients were also screened for cardiac risk factors (age, gender, angina pectoris, myocardial infarction, heart failure, diabetes, stroke, renal failure) and medication use. In all patients serum levels of hsCRP were measured. Linear regression analysis was performed to evaluate the relation between AAA size and hsCRP levels and the influence of statins on hsCRP.

Results: A total of 77 patients (69 males, 73 ± 8 years) were included in the analysis. Their median AAA diameter was 60 mm (range 49 - 97 mm), the median hsCRP level was 4.36 mg/l (range 0.56 - 36.10 mg/l). At the time of hsCRP



measurement 30 (39%) were statin users. As shown in the figure, AAA size was significantly related to hsCRP levels ($p < 0.001$). Statin use was associated with a significantly lower hsCRP level, irrespective of AAA diameter ($p = 0.03$, p -value for interaction with AAA size = 0.006).

Conclusion: AAA size is related to serum levels of hsCRP and statin use is associated with a lower level of hsCRP, irrespective of AAA size.

P1613 Characterization of medically managed patients with acute type A aortic dissection: insights from the international registry of acute aortic dissection (IRAD)



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Background: Optimal treatment for type A acute aortic dissection (TA-AAD) is immediate surgical repair. However, 5-20% of patients are treated medically with very high mortality rates. We characterize the features of medically managed patients with TA-AAD in a large multi-center registry.

Methods: We examined 916 consecutive patients with TA-AAD enrolled in IRAD from 1996 to 2003. Univariate testing followed by multivariable logistic regression was performed to identify independent predictors of being managed medically.

Results: 14.4% (132/916) of patients were managed medically with an in-hospital mortality rate of 64%. Mean age was 67.7 years $\pm$ 15.9 and 47% were female. In-hospital complications (hypotension, CHF, renal failure, mesenteric ischemia, and altered mental status) were increased in patients managed medically compared to those undergoing surgery. Logistic regression identified age > 70 years, female gender, diabetes, mesenteric ischemia, renal failure and altered mental status as independent predictors of being managed medically (Table; Area under receiver operating curve, 0.75).

Table 1. Predictors of Medical Management

Variable	Odds Ratio	95% CI	p-Value
Age > 70	3.10	1.79-5.37	< 0.01
Female Gender	2.06	1.21-3.52	0.01
Diabetes	3.19	1.14-8.98	0.03
Mesenteric Ischemia	3.02	1.0-9.15	0.05
Acute renal failure	2.60	1.11-6.08	0.03
Altered mental status	2.60	1.27-5.30	< 0.01

Conclusions: Medically managed patients with type A aortic dissection are more likely to be older, female, diabetic, and present with malperfusion syndromes placing them at high-risk for in-hospital death. These high risk features and resultant perioperative risk may have precluded them from surgical treatment.

P1614 Prognosis after endovascular repair of thoracic aortic aneurysms: combined clinical and imaging follow-up in 85 patients treated with stent-grafts



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Objective: The endovascular approach may offer an alternative to open surgery in patients with aneurysms of the thoracic aorta. Only few data exists concerning clinical and imaging follow-up in large populations treated by nonsurgical means. This study reviews a single-center experience with 85 consecutive patients after endovascular repair.

Methods: Eighty-five patients (64 males; mean age 68 (43-83) years) with TAA underwent elective stent-graft placement between 10/1998 and 02/2005. A total of 91 commercially available customized stent-grafts were implanted. Technical success was determined by final angiography and aortic imaging on discharge. Serial imaging was obtained 3, 6 and 12 month after endoluminal repair. Follow-up, which averaged 47 (0.5-98) months was 100% complete. Clinical baseline characteristics revealed a high-risk setting with considerable comorbidity in the majority of patients (HT 93%, CAD 62%, COPD 34%, PAD 23%, TIA/Stroke 14%). Forty percent had a history of previous aorto-vascular surgery, including AAA-surgery in 20 and CABG in 15 patients, respectively.

Results: Complete exclusion of the aneurysm (mean diameter 67 mm) was achieved in 72 Patients (85%). None of the patients suffered persisting paraplegia or conversion to open surgery. Early serious complications included stroke in 2 patients (2.3%). During follow-up 8 patients (9.4%) were electively treated with open surgery or additional stent-graft placement for progressive enlargement due to primary endoleaks. Estimated survival rate at 1, 2, 3 and 5 years were 80 $\pm$ 6%, 75 $\pm$ 6%, 67 $\pm$ 7% and 64 $\pm$ 7%, respectively. Overall mortality was 20%, with aortic rupture as underlying cause in only 5 patients. In patients without endoleak serial imaging revealed a shrinkage of thrombus (mean 2mm), while primary endoleaks were associated with progressive enlargement (mean 9mm).

Conclusion: Stent-graft repair is safe and effective with a mortality and morbidity considerable lower than associated with open repair. Given these promising midterm-results the endovascular approach may serve as an encouraging alternative to chest surgery in patients with thoracic aortic aneurysm.

P1615 Detailed transesophageal echocardiographic imaging can identify class 3 (discrete) acute ascending aortic dissection



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Introduction: Little is known about the real comparative diagnostic accuracy of imaging techniques in patients with discrete/subtle aortic dissection, because of the rarity of this entity.

Patients and methods: In a series of 105 consecutive patients who had ascending aortic dissection 8 patients (7.6%) had subtle aortic dissection. Seven patients presented with acute anterior chest pain, three had syncope and one had transient neurologic deficit. One patient had Turner's syndrome, one had bicuspid aortic valve, whereas the other had only hypertension as risk factor for dissection.

Results Transthoracic echocardiography was performed in all patients and identified pericardial effusion in 5, cardiac tamponade in 2, and aortic regurgitation in 4. Two patients had markedly enlarged ascending aorta (5.6 and 6.4 cm, respectively), whereas in the remaining six patients the ascending aorta was normal or only slightly enlarged (mean diameter 4.3 cm). All patients underwent TEE, 4 underwent aortography and 4 underwent CT. This latter was negative in all patients but identified small haematic pericardial effusion in 3. Aortography was negative in all but one patient in whom bulging of the aortic wall was seen just above the left coronary ostium. In all patients TEE identified the dissection on the posterior aspect of the ascending aorta 0.5-3 cm above the left coronary ostium; all patients presented with limited aortic wall hematoma (defined as eccentric increased wall thickness) and pericardial effusion surrounding the aorta. The dissection appeared as a stellate tear of the vessel wall, with the fragmented remnant oscillating in the lumen in three patients, as a "double track" intimal thickening in two patients and a discrete intimal tear with an underlying eccentric and tortuous hematoma in the media in the remaining 4 patients. Two patients observed in 1990 and 1993 were not operated immediately because of the negative CT and angiographic findings. One died of aortic rupture and the other developed class 1 aortic dissection surviving operation with permanent neurologic sequelae. The remaining six were operated in emergency on the basis of the clinical presentation and TEE findings: all survived operation (limited resection of the aortic wall in one patient, and valve-sparing "David procedure" in the remaining five) and were discharged without sequelae after a mean 7.2 $\pm$ 2.8 days.

Conclusions: Clinical suspicion and detailed TEE examination are important for early identification of class 3 type A aortic dissection leading to limited surgery, shorter hospital stay and better outcome.

P1616 Mid-term outcome after carotid artery stenting in poor surgical candidates with concomitant carotid, coronary and peripheral pathology



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Background and Purpose: The optimal treatment of poor surgical candidates with severe carotid stenosis and coexistent coronary and peripheral artery disease is uncertain. A recent and modern approach is to perform carotid artery stenting (CAS) and combined interventional or surgical coronary or peripheral revascularization in one or two sessions. The purpose of this study is to report the efficacy of CAS in such patients in preventing stroke, myocardial infarction and death for the 30-day periprocedural period and stroke ipsilateral to the treated carotid artery during 1-year follow-up period.

Methods: From June 2001 to June 2005 we treated in 142 consecutive patients 168 carotid stenoses $> 70\%$ and simultaneously 97 severe coronary and 48 peripheral artery lesions. The mean age of the patients was 64.3 $\pm$ 2.7 years, 78(54.9%) were symptomatic, 137(96.4%) men. CAS was performed in 156 internal, 4 external, 5 common carotid and 3 vertebral arteries. In 26 cases we performed bilateral CAS and intracoronary stenting (ICS), in 94 unilateral CAS and ICS (in 33 of them peripheral stenting apart), in 38- CAS and CABG, in one-vertebral stenting, CABG and Aortic VR, in 9- CAS and peripheral surgical or endovascular procedure.

Results: Carotid stenting was successful in all lesions. The average CA stenosis was 77.2% preprocedure and 9.4% postprocedure. One fatal cardiogenic shock (0.7%) and one minor stroke (0.7%) occurred during the procedure; two (1.4%) non-Q MI within 30 days. No ipsilateral TIA, strokes or procedure related death occurred during the mean follow-up period of 23 $\pm$ 8 (8 to 29) months. At follow-up 3 stents (1.7%) showed restenosis, treated successfully with re-PTA.

Conclusions: The results suggest a beneficial effect of CAS for patients with high-grade symptomatic carotid and concomitant coronary and peripheral stenoses who are not good surgical candidates. CAS should be considered treatment of choice for the management of these high-risk patients.

P1617 NGAL/MMP-9 complex is highly present in unstable carotid plaques and vascular wall of abdominal aortic aneurysms



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Purpose: Neutrophil gelatinase-associated lipocalin (NGAL) is a protein which could have an important function in atherosclerosis. By means of complex formation it prevents degradation of Matrix metalloproteinase (MMP)-9, which plays an important role in plaque destabilization, expansive remodeling and aneurysm rupture. In this study, we examine NGAL/MMP-9 complex activity in the vascular wall of abdominal aortic aneurysms and carotid plaques, and its relation with unstable plaque characteristics.

Methods: Activity levels of the NGAL/MMP-9 complex (135 kD) were determined by gelatin zymography in protein isolated from 82 carotid endarterectomy specimens and 21 aortic aneurysm wall specimens. Mammary arteries (n=9) and macroscopically normal abdominal aortas obtained from autopsies (n=4) served as a control. The culprit lesions of the carotid plaques were stained for fat, macrophages, smooth muscle cells, collagen, and calcifications. Protein was isolated from the carotid plaques for determination of interleukin (IL)-6 and IL-8 concentrations (Multiplex) and MMP2, MMP-8 and MMP-9 activity (ELISA).

Results: Activity levels of the NGAL/MMP-9 complex were higher in carotid plaques and abdominal aortic aneurysm wall compared to non-diseased aortic wall: 14.4 (p=0.01) and 6.8 (p=0.002) fold increase, respectively. Compared to the mammary arteries, NGAL/MMP-9 activity levels were increased 5.3 fold in carotid plaques (p=0.004) and 2.5 fold in aneurysm wall (p=0.006). In carotid plaques, high NGAL/MMP-9 activity was associated with unstable plaque characteristics: high fat content (p=0.002), high IL-8 levels (p=0.005), and low smooth muscle cell content (p=0.047). MMP activity levels of the NGAL/MMP-9 complex on zymography was strongly related to total MMP-9 activity as determined by ELISA (p=0.001), but not to MMP-2 or MMP-8 activities. There was no relation between NGAL/MMP-9 activity levels and other plaque characteristics.

Conclusion: The NGAL/MMP-9 complex is highly active in unstable carotid plaques and the wall of abdominal aortic aneurysms and shows a strong relation with total MMP-9 activity, suggesting a possible role for NGAL in MMP stabilization and subsequent plaque destabilization and expansive vascular remodeling. Considering the aspecificity of MMP inhibitors, NGAL could be a target for more specific intervention on MMP-9 to increase plaque stability.

P1618 Predictive factors of aortic dilatation in descending aorta dissection by magnetic resonance imaging



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Progressive dilatation of descending aorta after aortic dissection (AD) increases the risk of aortic rupture.

Aim: To define predictor variables of this dilatation could permit select the sub-group of patients (pts) with greater benefit of more aggressive therapy in subacute phase of non-complicated AD.

Methods: 35 patients with descending AD (21 type B and 24 type A after ascending aorta surgery) underwent a MRI study which consisted on multiphasic angiography and phase contrast sequences. Systolic anterograde and diastolic retrograde flow volume in true lumen (TL) and false lumen (FL) in proximal aorta was quantified. Distal aortic communication between FL and TL was assessed by multiphasic angiography. Aortic diameter enlargement during follow-up was evaluated by MRI or CT every 6 months.

Results: Follow-up range: 2-6y (median: 2.8±2.1). Annual aortic dilatation range: 0.1-8mm, median 2.05±1.91mm. Proximal anterograde FL flow volume < 5 ml/beat (10 pts: enlargement <1 mm/y, p<0.01) and distal communication (1.07±0.89 vs 2.88±1.17 mm/y, p<0.01) were protector factors for enlargement. High anterograde flow volume in FL (5ml/beat) with diastolic reverse flow (>50%) in the absence of distal reentry tear was related to progressive dilatation of the FL during follow-up (2.8±1.7 vs 0.9±1.3mm; p<0.01).

Conclusion: MRI evaluation of the flow volume in the false lumen is useful for predicting enlargement of the dissected aorta. This information should be used to improve the risk stratification in subacute aortic dissection.

P1619 Long-term prognosis of ulcer-like images during intramural hematoma evolution



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Localized dissection which produces ulcer-like image (ULI) is one of the main complications of intramural haematoma (IMH). Although some studies suggested they represent a bad prognosis factor, long-term evolution is not well known. Our aim was to assess the evolution of patients with ULI and the progressive changes of these lesions. From 67 consecutive patients with IMH followed-up in our department, 27 pts presented a ULI in the aorta (23 men, age range 56-88).

All of them were located in the descending aorta. Patients were treated by beta-blockers and followed by MRI or CT every 6 months to assess complications, changes in ULI size or aorta wall rebleeding. Follow-up was 2-10 y (m:4.5).

Results: No patients died or presented signs of aortic rupture during follow-up. Two ULI disappeared after a 6 month evolution, 12 presented progressive enlargement, 9 no changes and 4 reduction in size. In this 4 cases, a paradoxical evolution was observed as ULI reduced size but maximum aortic diameter increased becoming a fusiform or saccular aneurysm formation. Endovascular therapy was considered in two cases due to asymptomatic progressive enlargement of the ULI after 3 years of evolution.

Conclusions: Ulcer-like images are frequent in IMH evolution in the descending aorta. They evolve favorably and only in rare cases tend towards slow progressive dilatation. In the absence of early complications or ascending aorta location, early aggressive treatment does not appear to be indicated. After acute phase and blood pressure control most of these lesions tend to be stable and free of complications in long-term follow-up.

P1620 The diagnostic value of circulating D-dimer levels in patients with acute aortic dissection as compared to those with intramural hematoma



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Background The elevation of D-Dimers, final degradation product of fibrin, in acute aortic dissection (AAD) is important, reflecting the thrombogenic character of false lumen. Its value in diagnosis workup of patient with suspected AAD is now established. The aortic intramural haematoma (AIH), localized variant of AAD without patent false lumen (PFL) account for 10% of dissections. The place of D-Dimers testing in primary diagnostic assessment in this sub group is actually unknown.

Method We have retrospectively included 94 consecutive patients admitted to our institution with confirmed AAD and in whom D-Dimer test has been performed at presentation (immunoturbidimetric Liatest Stago® method).

Results Eighty four patients (89%) have been diagnosed with AAD versus 10 patients (11%) with AIH. The mortality was nil for AIH group while being 22% for those with AAD (p=NS). The level of D-Dimers was significantly lower in patients with AIH (median 1230 ng/ml, interquartile range 685 to 2645 ng/ml) as compared to patients with AAD with PFL (median value 9290 ng/ml, interquartile range, 3890 to 20000 ng/ml) (p = 0.008).

The number of segments anatomically involved was significantly lower among patients with AIH as compared to those with PFL (1 ± 0.5 vs 3 ± 1.8 segments, p = 0.0008).

All patients with AAD with PFL had the D-Dimers levels over the upper normal limit (> 400 ng/mL - sensibility 100%), when in AIH patients only one had the D-Dimers' concentration < 400 ng/mL.

Conclusion: The diagnosis efficiency of D-Dimers assay is very high in patients with AAD (sensibility 100%).

Given the localized character of dissection and the absence of false lumen, the plasma levels of D-Dimers were significantly lower in AIH group (sensibility 90%). If we decide to integrate D-dimer test into a diagnostic algorithm of suspected AAD, this limitation should be taken into account.

P1621 Etiology and risk evaluation in prosthetic valve dysfunctions and re-operation



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Purpose: In this study, the etiology, risk evaluation, clinical and echocardiographic characteristics of patients who were followed up in our clinic between 1996-2003 with the diagnosis of prosthetic valve dysfunction (PVD), and who underwent a second valve surgery, were examined.

Methods and Results: Forty nine patients (24 females, mean age: 46±12 years), with the diagnosis of PVD were included in the study during the 7 years period. The majority (89%) of the prosthetic valves were metallic (n=44, 34 mitral and 10 aortic), and 11% were bio-prosthetic valves (n=5, 4 mitral and 1 aortic). Seventy seven percent of PVDs were seen at the mitral and 13% were at aortic prosthetic valves. Transesophageal echocardiography was performed to all patients, it was observed that there was pannus in 20% of the patients, thrombus in 24%, endocarditis in 10%, bio-degeneration in 10%, and dehiscence in 32% of them. The average time of degeneration for bio-prostheses was 8 years. When cases with pannus and thrombus were compared, the rate of insufficient anticoagulation were higher in 80% of patients who had prosthetic thrombus (p=0.01). The period of time right up to re-operation was 9.6±2.1 years for pannus cases, and 2.3±1.8 years for thrombus (p=0.01). The functional capacity in patients with thrombus deteriorated more rapidly, while progression was seen to be slower in pannus patients. In accordance with this, upon echocardiography, systolic pulmonary artery pressure was measured as 49.7±13.5 mmHg in patients with pannus, but 71.5±13.0 mmHg in those with thrombus (p=0.02). There was no significant difference between these two groups regarding mean age and gender distribution. Moreover, in patients diagnosed with pannus by echocardiography during the second valve surgery, small microthrombi were observed in 48% in addition to pannus.

Conclusion: Most frequent cause of re-operation for PVD was dehiscence, followed by thrombus formation and pannus. In patients admitted with a serious clinical condition shortly after the first operation, prothetic valve thrombus should be considered particularly if anticoagulation seems insufficient. Microthrombi should be kept in mind in cases with pannus formation.

P1622 A benign cardiac tumor: a case of papillary fibroelastoma causing stroke and mitral insufficiency



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41 year-old-woman presented with left upper and lower limb weakness. She complaint of effort related dyspnea and ortopnea. She has been having these symptoms for the last 3 years. The transthoracic echocardiography revealed a pedunculated mobile echogenic mass attached to the atrial aspect of the anterior leaflet of the mitral valve with dimensions of 1,75x1,70 cm. The mass was described as irregular shaped and heterogeneous in texture. The mass on the anterior leaflet of the mitral valve was suspected to be either papillary fibroelastoma (PFE) or myxoma with advanced mitral insufficiency. Cranial CT scan showed acute right parietal lobe infarction.

The patient underwent cardiothoracic surgery. Unfortunately the mass was attached tightly to the anterior leaflet of the mitral valve, hence along with the mass the valve was also resected and replaced with a prosthetic valve.



Fig. 1. Echocardiogram showing p. fibroelastoma.

PFEs are rare benign cardiac tumors which usually involve cardiac valves. PFE is usually an incidental finding. They are often asymptomatic. In symptomatic patients the clinical presentations may vary and depend on the location, size and the motility of the tumor. The most feared complication is the systemic embolization. The most common presentation is stroke or transient ischemic attack (TIA). If the tumor is on the aortic valve, the most prevalent manifestations are sudden death and myocardial infarction whereas in mitral valve tumors stroke dominates. Predominant or isolated valvar insufficiency is rare in the literature.

P1623 The surgical management in one procedure of a patient with diagnosis of ascending aorta aneurysm, aortic valve stenosis, mitral regurgitation and aortic coarctation. Report of one case and literature



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Objective: The surgery treatment in the complex cardiac illness it became more common in our hospital, with the development of new surgical strategies and technologies, now we can operate this kind of patients and in some cases in one surgical procedure. This report is presenting our experience in the surgical management of a patient with ascending aorta aneurysm, aortic stenosis, mitral regurgitation and aortic coarctation in one procedure and the literature revision.

Methods: A retrospective clinical review of this case was undertaken using hospital records, clinical and echocardiography, computed tomography and magnetic resonance imaging data. And we made a review of national and international literature.

Results: It is a 54 years old male with diagnosis of ascending aorta aneurysm, aortic valve stenosis, mitral valve regurgitation and aortic coarctation, in the pre-operative analysis the clinical group thought that the patient were out of surgical treatment because the high surgical risk and they used maximum medical treatment. During the next months the patient went worse despite the medical treatment so the surgical group offer a high risk total simultaneous repair through an ascending aorta replacement with composite mechanical valve graft and hemi-Cabrol reconstruction, mitral valve replacement and extra anatomic ascending-descending bypass, with an extracorporeal circulation time of 272 minutes and aortic cross clamp of 120 minutes. The patient had an excellent evolution with early extubation, Intensive Care Therapy discharge was 5 days later and the hospital discharge was in 2 more days. At the moment the patient is on New York Heart Association class I, without any problem. We did an extended search of

any kind of this complex surgery but we could not find any paper with any resemblance experience.

Conclusions: In the recent time the cardiovascular surgeon has to face a very complex cases, having to use of new technologies and surgical techniques what has carried him to be able to resolve illnesses that before were considered not surgical. In this patient is shown that in spite of the fact that the patient was considered without possibility of surgical treatment, he tolerate the procedure without greater complications being obtained an excellent result. AI to be sought a similar case in the universal literature and not to find it, this carries us to give a great importance to this patient, and invites us to try a greater effort in the patients that are considered as not surgical cases.

P1624 Influence of comprehensive cardiac rehabilitation programme on anxiety and depression scores in patients after valvular replacement



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Objectives: Anxiety and depression are frequent in patients with history of surgery and are more acute in those with decreased functional reserve. We assessed the anxiety-depression scores in patients after valvular replacement at admission in a complex cardiac rehabilitation programme and after 3 months (after phase II of rehabilitation). We followed the influence of gender and type of valve.

Material and method: 106 patients with valvular replacement: 60 (56.6%) men, 46 (43.4%) women, mean age: 57±8 years. We considered 2 groups: group I: 56 patients with exercise training programme; group II: 50 patients - control. Following valvular replacements were performed: 53 mitral, 40 aortic and 13 both mitral and aortic replacements. HAD scale was used to assess the anxiety-depression score, both at admission and after 3 months. Patients in group I had a regular exercise training program 3 times/week, 30-40min/meeting to 70-75% from the achieved heart rate at the effort test.

Results and discussions: A significant improvement both in anxiety and depression scores was noticed in group I: 67.85% had normal HAD score (0-7) after phase II vs. 42.85% at baseline, (p11 were 10.71% in group I after phase II vs. 24.99% at baseline (p<0.001) and in group II were 18% after phase II vs. 24% at baseline (p<0.05). Depression was improved more obvious in group I.

Conclusions: Anxiety is more frequent than depression in patients after valvular replacement; cardiac rehabilitation programmes led to effort capacity increase and significant improvement of anxiety and depression scores. Outcome data were better in patients with aortic valvular replacement.

P1625 Elevated serum creatinine one year after heart transplantation is a risk factor for all-cause mortality



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Elevated serum creatinine (Cr) in end-stage heart failure, which in large part is due to deteriorated haemodynamics, is a strong risk factor for all-cause mortality. After heart transplantation (HTx), haemodynamics improve but the predictive value of Cr for survival is unclear. We aimed to assess the relationship between Cr at 12 months post-HTx and survival.

Methods: 386 consecutive HTx recipients above 14 yrs attending their first annual follow-up were retrospectively studied (mean age 50.8±11.8 yrs SD; mean follow-up 8.3±4.8 yrs SD). Data regarding age, gender, smoking, HTx aetiology, hypertension, diabetes, cytomegalovirus infection, immunosuppressive regime, serum Cr and mortality was collected.

Results: A cut-off of 124 µmol/l (local upper reference limit) was used to divide the patients into a normal (n=247) and elevated (n=139) Cr group. 64 (26%) and 62 (45%) patients died in the normal and elevated Cr group, respectively. Kaplan Meier analysis demonstrated significantly decreased survival in the latter group (p<0.001). The number of deaths directly attributable to renal failure were 7 (3%) and 12 (9%) (p=0.01) in the normal and elevated Cr group, respectively. Univariate analysis found age, hypertension, atherosclerosis as aetiology for HTx and elevated Cr to be associated with decreased survival. Multivariate analysis iden-

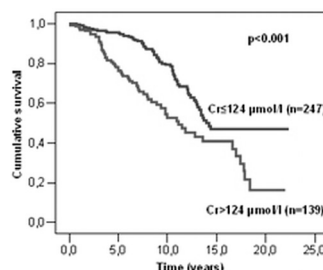


Fig. 1. Creatinine 1 year post-HTx and survival.

tified elevated Cr [hazard ratio (HR) 2.13, 95% confidence interval (CI) 1.50-3.02, $p=0.001$] and atherosclerosis as aetiology for HTx [HR 1.65, 95% CI 1.15-2.36, $p=0.007$] as independent risk factors for mortality.

Conclusion: Elevated Cr at 12 months post-HTx is of prognostic significance as it represents an independent risk factor for all-cause mortality. Cr is routinely measured in HTx patients and elevated levels may warrant a more intensive follow-up regime.

P1626 Plasma NT-proBNP as a marker of cardiac allograft vasculopathy



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Transplant coronary artery disease (TCAD) is a common complication after heart transplantation (HTx) limiting long-term survival. The diagnosis is, however, predominantly based on invasive techniques and non-invasive markers of the disease would be valuable. We aimed to assess the association between plasma N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels and angiographically determined TCAD to help determine its potential role as a biochemical marker of TCAD.

Methods: A total of 107 consecutive, clinically stable HTx recipients with a mean age of 57.1 ± 12.3 yrs SD and 7.1 ± 4.9 yrs SD (range 1-19 yrs) after HTx were studied. All patients received standard triple-drug maintenance immunosuppressive therapy with cyclosporine, prednisolone and azathioprine or mycophenolate mofetil. Data was collected as part of annual routine follow-up. Patients were evaluated by left-sided heart catheterisation including selective coronary angiography. The diagnosis of TCAD was based on the presence of any of the following: stenosis, distal tapering/pruning or loss of tertiary vessels. Blood samples for analysis of NT-proBNP were taken on the same day as angiography.

Results: Altogether 34 (32%) patients had TCAD. Mean NT-proBNP $\pm$ SD was 224.6 ± 243.9 pmol/L (median 115.0 pmol/L) and 58.3 ± 64.1 pmol/L (median 34.0 pmol/L) in patients with and without TCAD, respectively ($p < 0.001$). Univariate analysis identified atherosclerosis as aetiology for HTx, time since HTx, smoking, hypertension, elevated creatinine and NT-proBNP > 100 pmol/L as factors associated with TCAD, while age, gender, cholesterol, HbA1c and cyclosporine levels were not. Variables with a p -value < 0.20 in univariate analysis were entered into a multivariate logistical regression analysis and this identified NT-proBNP > 100 pmol/L ($p=0.04$), together with hypertension ($p=0.003$), time since transplantation ($p=0.008$) and smoking ($p=0.03$) as independent indicators of TCAD.

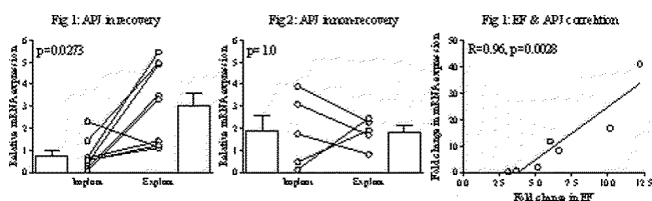
Conclusion: Elevated plasma NT-proBNP levels are common in HTx recipients but levels above 100 pmol/L are strongly associated with angiographically determined TCAD. Thus, measurement of this biochemical marker should be included as part of routine TCAD surveillance.

P1627 The apelin-angiotensin receptor-like 1 (APJ) mRNA levels closely correlate with myocardial recovery in end-stage heart failure patients treated with left ventricular assist devices (LVADs)



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APJ signalling is an important mediator of cardiovascular regulation. APJ mRNA levels are decreased in patients with heart failure (HF) and upregulated in the myocardium from patients treated with LVADs as a bridge to transplantation. The role of APJ gene expression in the clinical recovery observed in HF patients following combined LVAD and pharmacological treatment including the β_2 agonist, clenbuterol (clen) remains unknown. Real-time PCR was used to measure APJ mRNA expression in left ventricular (LV) samples collected at LVAD implant and explant from 7 patients with functional improvement to allow LVAD removal without requiring transplantation (REC) and from 5 patients who failed to recover function and were transplanted (TX). Correlation between ejection fraction (EF) and APJ expression was tested using Spearman's correlation test. Figure 1 and 2 show that APJ gene expression was up-regulated in REC (9.8 ± 4.3 -fold at explant vs. implant; mean $\pm$ SEM) but unchanged in TX (1.4 ± 3.4 -fold at explant vs. implant). Figure 3 shows a close correlation between the change in APJ expression in REC with improvement in EF suggesting a role for APJ in myocardial recovery. To study whether the observed effects are due to mechanical unloading or clen treatment, Lewis rats underwent heterotopic abdominal heart transplantation and were treated with either 2 mg/kg/day clen or saline (sal). Donor unloaded (UNL) and recipient control (C) hearts were collected after 7 days. APJ gene expression



was significantly upregulated in UNL but clen treatment had no effect ($C+sal=1.4 \pm 0.1$; $UNL+sal=2.0 \pm 0.1$; $C+clen=1.6 \pm 0.1$; $UNL+clen=2.0 \pm 0.2$; $n=6$ per group; $p=0.009$). We conclude that APJ may play an important role in functional recovery following mechanical unloading in patients treated with LVADs.

P1628 Increased coronary microcirculatory resistance does contribute to cardiac allograft ischaemia: a pressure wire study



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Purpose: Cardiac allograft vasculopathy (CAV) is commonly attributed to pathologic changes of the large coronary arteries. This investigation sought to evaluate possible microcirculatory alterations in heart transplant recipients.

Methods: In 30 orthotopic cardiac transplant recipients (mean age 58 ± 9 years; mean age at transplantation 56 ± 63 months) without significant coronary artery stenoses, distal pressures were measured in the left and the right coronary artery with a pressure wire. Microvascular resistance was calculated (pressure divided by flow) during peak hyperaemia and the index of microcirculatory resistance (IMR) was derived. Flows were determined by thermodilution. Fractional flow reserve (FFR) and coronary flow reserve (CFR) were measured by the same technique. Standard hemodynamic parameters, including systolic left ventricular pressure (LVP), cardiac index (CI), and pulmonary capillary wedge pressure (PCWP) were recorded.

Results: An abnormal increase of IMR was found to be associated with increased PCWP, borderline reduction of CFR, borderline increase of LVP, and normal FFR and CI (table). Simple regression analysis revealed IMR to directly correlate with PCWP ($r=0.58$; $p < 0.001$) and inversely with CFR ($r=0.54$; $p < 0.005$), but not with LVP and CI.

	CFR	FFR	IMR (U)	LVP (mmHg)	PCWP (mmHg)	CI (L/min ² m ²)
Mean	3.03	0.89	0.29	147	13.0	2.81
SD	1.46	0.16	0.18	25	4.5	0.78

Conclusions: CAV does involve the microcirculation to a functionally significant degree, even if macrovascular disease does not hamper blood flow. Moderate left ventricular backward failure in heart transplant recipients is obviously associated with increased microcirculatory resistance.

P1629 Time-course of interleukin-6 and neopterin after ventricular assist device implantation in heart failure end-stage patients

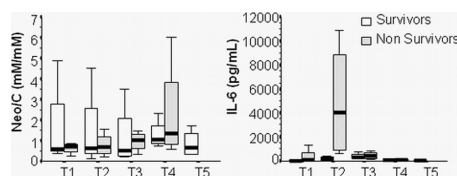


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Purpose: Left ventricular assist device (LVAD) has become a validated therapeutic option for bridging patients with end-stage heart failure (ESHF) to heart transplant. Although the LVAD implantation restores adequate cardiovascular hemodynamics, multi-organ failure syndrome (MOFS) still remains the main cause of adverse outcome in these patients. This is probably related to the activation of an immuno-inflammatory response. Aim of the study was to investigate the time-course of inflammatory status and the impact on clinical outcome.

Methods: Eight male patients (55.1 ± 10.4 yrs) supported by LVAD for ESHF have been enrolled. Urine neopterin/creatinine (Neo/C), a marker of monocyte/macrophages activation, and plasma interleukin-6 (IL6) levels were analysed in samples collected before (T1), 4hrs (T2), 24 hrs (T3), 1 wk (T4), and 4 wks (T5) after LVAD implantation.

Results: Four out of 8 patients died of MOFS between T4 and T5. The IL6 and Neo/C levels were not different between survivors and non survivors at T1. By nonparametric analysis, IL6 and Neo/C levels significantly increased in non survivors ($P=0.021$ and $P=0.027$ from T1 to T5, respectively) but not in alive patients.



Conclusions: These preliminary data suggest that patients with unfavourable outcome have a more pronounced inflammatory response and monocyte/macrophages activation after LVAD implantation, contributing to MOFS development.

P1630 Direct immunosuppressive properties of PARP-inhibition contribute to increased survival after cardiac transplantation



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Recently we showed that inhibition of poly (ADP-ribose) polymerase (PARP) improves cardiac function during untreated acute cardiac rejection. In the present study, the immunosuppressive properties of PARP inhibition and their effects on graft survival were investigated. In isolated human T- and endothelial cells, antigen-dependent (MLR, mixed lymphoid reaction) and independent (PHA, phytohemagglutinin) proliferation and expression of adhesion molecules were investigated by flow cytometry. In addition, graft survival was determined in DA-to-Lewis heterotopic rat cardiac transplants under chronic treatment with placebo, the PARP-inhibitor INO-1001 and/or cyclosporine. INO-1001 dose-dependently reduced PHA and MLR induced proliferation (Figure; values are given as counts/min) and the endothelial cell ICAM-1 expression ($p < 0.05$).

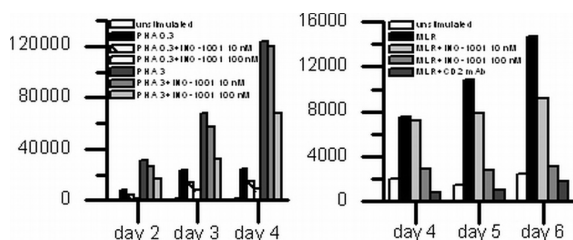


Fig. 1

Mean graft survival was increased by both 1mg/kg/die INO-1001 and 2.5 mg/kg/die cyclosporine in comparison to control (9.1 ± 0.5 vs. 8.9 ± 0.7 vs. 5.8 ± 0.4 days, $p < 0.05$). The combination of both led to a permanent survival comparable to that of 5 mg/kg/die cyclosporine. Thus, chronic treatment with PARP-inhibitors improve graft survival which mediated at least partially by direct immunosuppressive effects. PARP-inhibitors act synergistically with cyclosporine and thereby represent a new concept of immunosuppressive therapy.

P1631 Sirolimus increases a risk of surgical complication early after heart transplantation



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Background: mTOR inhibitors are potent non-nephrotoxic immunosuppressants, however their anti-mitotic properties may impair wound healing early after surgery. The aim of this retrospective analysis was to assess the influence of sirolimus (SIR) administered before or immediately after transplantation on surgical complications in heart transplant recipients. **Material and methods:** Study Group consisted of 28 heart transplant recipients (26F/2M, 49.2 ± 11 y.) receiving 15mg of SIR before operation, 10mg of SIR on the first postoperative day (POD) and thereafter 5mg daily ($n=20$), or 5mg SIR daily starting on POD 2 ($n=8$), till the introduction of cyclosporine-A (CyA). A matched historical Control Group was composed of 28 patients (26M/2F, 49.7 ± 9 y.) receiving CyA from POD 1. We compared a number of surgical re-interventions, volume of drainage and blood products use among groups. A statistical significance was assessed using chi2 test and Mann-Whitney U test.

Results: The overall number of patients requiring surgical re-intervention was 16 (57%) in Study Group vs. 6 (21%) in Control Group ($p=0.014$). Percardial tamponade decompression was performed in 7 (25%) vs. 0 patients, and sternum re-fixation in 7 (25%) vs. 0 patients, respectively ($p=0.015$). None of wounds was infected. Overall drainage volume was 4213 ± 5996 vs. 1911 ± 1728 mL, respectively ($p=NS$). The average use of the red cell concentrate was 7.8 ± 8.6 vs. 3.2 ± 3.1 units ($p=0.006$). Frequency of biopsy-proven rejection and infection occurrence was comparable, except for CMV infection, which was less frequent in Study Group - 3 (11%) vs. 11 (39%) patients ($p=0.023$).

Conclusion: SIR given before, or immediately after heart transplantation, increase the risk of surgical wound healing complications.

P1632 Quilty effect correlates with cellular rejection but not with coronary artery vasculopathy in heart transplant recipients



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The aim of the study was to assess a relation between Quilty effect (QE) and cellular rejection or coronary artery vasculopathy (CAV). We performed a re-reading of all available endomyocardial biopsies (EMBs), obtained in heart transplant recipients since 1986. The overall number of analyzed EMB samples was 5361 (ob-

tained in 429 pts.). QE was observed in 669 EMBs (12.5%); at least 1 EMB with QE was found in 231 pts (53.8%, Quilty group), while QE was absent in 198 pts (Control group). QE was observed in 20.7% of EMBs from Quilty group. The earliest QE appearance was noted from the 1st week to the 56th mo. after the surgery (average 5.5 ± 9 mo.). In 68% of pts from Quilty group, the first occurrence of QE was observed during the first 3 mo. after transplant, however, in 13% of pts the first QE was found later than 1 year post-transplant. The average EMB score in a presence of QE was 2.45 (vs. 1.84 without QE, $p < 0.000001$), the average EMB score in Quilty group was 2.06 (vs. 1.71 in Control group, $p < 0.000001$). Further analysis was performed only in pts with, at least, 1 year follow-up. Quilty group ($n=202$, age 44.8 ± 12 y., M/F-85/15%) and Control group ($n=142$, age 45.4 ± 12 y., M/F-87/13%) had comparable recipient and donor characteristics, and ischemic time. Average number of the acute rejection episodes (ISHLT $\geq 3A$) was 3.4 ± 2.1 in Quilty group vs. 2.3 ± 1.9 in Control group ($p < 0.000001$). Steroid resistant rejection occurred in 18.6% vs. 8.6% of pts. ($p=0.003$). Percentage of pts. without any significant rejection was 4.5% vs. 16.2% ($p=0.002$). Significant rejection over 1y. post-transplantation occurred in 28.2% vs. 15.5% ($p=0.006$). To analyse CAV occurrence we reviewed results of coronary angiographies that were performed, at least, every 24 mo., beginning from the end of the 1st year after transplant. Any CAV lesions were observed in 32% pts. from Quilty group and 30% pts. from Control group. Clinically significant CAV (need for angioplasty, myocardial infarction or death) was observed in 10% vs. 13% of pts., respectively. Additional analysis of Kaplan-Meier curves showed no difference in the time of CAV occurrence. Comparing different protocols of immunosuppression, we were able to show beneficial effect of primary tacrolimus therapy (12.5% of pts. with QE vs. 59.8% in the remaining group, $p=0.02$), and ATG induction (23.1% vs. 60.1% in the remaining group of pts., $p=0.02$).

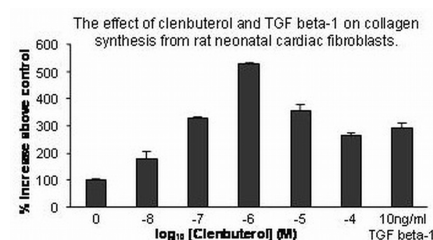
Conclusion: Quilty effect occurrence in transplanted heart biopsies seems to be a marker of the increased immune system activity, that can lead to the significant cellular rejection, however it is not related to CAV development.

P1633 Stimulation of collagen synthesis from cardiac fibroblasts by clenbuterol



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Stimulation of β_2 -adrenoceptors by clenbuterol has been used to augment the reverse remodelling of the myocardium in patients who have received left ventricular assist devices (LVAD). The role of cardiac fibroblasts in mediating this response has not been addressed. We have examined the ability of clenbuterol to stimulate secretion of collagen from cultured rat neonatal cardiac fibroblasts. The ability of clenbuterol (10nM-100 μ M) to stimulate collagen synthesis from cardiac fibroblasts was assessed via the incorporation of [^{3} H]-proline into newly synthesised proteins, following 72 hours incubation with the drug. Incubation with lower concentrations of clenbuterol (10nM-1 μ M) gave a concentration-dependent increase in collagen synthesis and secretion by cardiac fibroblasts. This effect reached a maximum value of $429.7 \pm 22.0\%$ above control at 1 μ M ($p < 0.05$, $n=3$), which was significantly greater than that achieved with 10ng/ml of TGF β 1 ($194 \pm 17.3\%$; $p < 0.05$, $n=3$). At concentrations above 1 μ M, [^{3} H]-proline incorporation remained elevated, but was similar to that induced by TGF β 1 (see figure).



There was no effect on cell viability over the whole concentration range used of clenbuterol, as measured by the Promega CytoTox 96 Non-Radioactive Cytotoxicity Assay. The relevance of these findings could be important when choosing a drug to promote reverse remodelling and requires further investigation.

P1634 Type D personality predicts early onset of allograft rejection after successful heart transplantation



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Background: Type D personality (high emotional distress and behavioural inhibition) predicts clinical events in patients with coronary artery disease, but its influence on post transplant outcome is unknown. We therefore examined the role of Type D personality in acute cellular rejection and mortality following heart transplantation.

Methods: 48 transplant recipients (75% men, mean age = 59 ± 10 yrs) completed

the Type D Scale (DS14) pre-transplantation; 14 (29%) were type D. Endpoints were: rejection score, number of rejections grade $\geq 3A$, time to first rejection, and out-of-hospital mortality.

Results: Type D patients had relatively higher rejection scores than non-Type D patients (mean: 0.80 versus 0.68) and a higher incidence of rejection grade $\geq 3A$ (3.6% versus 2.1% respectively), but these differences were not statistically significant. However, Type D was negatively correlated with the number of days to first rejection ($r = -0.240$, effect size = 0.44) with an average of 15 rejection-free days in recipients with type D personality versus 49 days in non-type D patients ($p = 0.035$). There were 5 out-of-hospital deaths. The mortality rate of Type D patients (4/14 = 29%) was significantly higher than that of non-Type D patients (1/34 = 3%) adjusting for age and gender ($p = 0.008$).

Conclusions: Type D personality predicted earlier onset of allograft rejection after successful heart transplantation. Preliminary data also suggest that Type D may be associated with an increased out-of-hospital mortality risk in heart transplant recipients.

P1635 Coronary artery fistulas post-cardiac transplantation



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Purpose: Endomyocardial biopsies (EMB) post heart transplantation (HTX) is daily practice for surveillance of acute allograft rejection. Possible complications after EMB are coronary artery fistulas. The aim of this study was to evaluate the incidence, natural history and management of coronary fistulas in patients transplanted in our centre.

Methods: The angiographic criterion for a coronary fistula was specified as visualization of a direct confluence from the arterial vascular lumen into a cardiac chamber, independent of size. The diagnosis was typically made by coronary arteriography, which was done, routinely one and four year's after HTX and thereafter only when clinical or scintigraphic evidence of ischemia was present.

Results: The clinical data of all (N=470) orthotopic HTX patients/ca. 9000 EMB, performed at our centre, between the years of 1984 to 2005, were reviewed. Mean follow-up periods after HTX and diagnosis of coronary fistulas were 96 [range 36-231] and 70 [24-145] months respectively. In 21 patients (4.5%) one or more coronary artery fistulas were diagnosed. Sixteen patients (=76%) had fistulas involving the left anterior descending artery and five the right coronary artery (=24%). Five patients (=24%) had two or more coronary fistulas. Six pts (29%) had scintigraphic evidence of ischemia and five typical chest murmurs; one patient presented with angina pectoris and another with acute myocardial infarction directly after EMB, which was immediately treated with covered stent percutaneously. During follow-up, the fistulas were accepted as such in eighteen patients (=86%), one another pt was treated with percutaneous covered stent and one with surgical elimination because of significant shunting (after two attempts of failed percutaneous procedures).

Conclusion: Post HTX, coronary artery fistulas are relatively uncommon complication of surveillance EMB. Most of the cases have a benign clinical course, justifying the conservative attitude of "watchful waiting".

P1636 Serial echocardiography identifies responders to aggressive donor management with the potential for improving retrieval rate for cardiac transplantation



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Purpose: Heart transplantation activity is declining and the retrieval rate from the available donor pool remains at 30%. There is a need to consider and resuscitate borderline hearts to increase retrieval rate. Transthoracic echocardiography (TTE) is difficult in supine ventilated donor and there are few published data on the role of serial studies. The aim of this study was to determine whether serial echocardiography could identify functional changes in response to management that might increase the pool for transplantation.

Methods: 63 potential heart donors undergoing standard resuscitation using pulmonary artery flotation catheter (PAFC), were studied by serial TTE using a Siemens Acuson Cypress portable machine with second harmonic imaging (3.6 MHz probe). Management comprised PAFC guided correction of pre- and after-load and substitution of norepinephrine with vasopressin. TTE was performed at baseline prior to donor management and was repeated after 2 hours. Donor details were anonymised and TTE time order coded. The pictures were analysed off-line by 2 independent blinded observers.

Results: Serial TTE was possible in 44/63 heart donors (70%). Resuscitation was initiated within 2 hours of consent for donation. 19/44 (43%) donors were on high dose inotropic support (norepinephrine [NE] $> 0.06 \mu\text{g/kg/min}$ or epinephrine $> 0.03 \mu\text{g/kg/min}$) at entry into the study. On the first TTE LV function was worse in those on high dose support compared to those with no or minimal support (FS 32.5% [10.6] vs. 21.3% [8.1] $p=0.003$, LVEF 67.1% [15.1] vs. 49.8% [15.8] $p=0.004$, LV-Tei index 0.37 [0.13] vs. 0.62 [0.26] $p<0.001$, LV wall motion score 1.4 [0.59] vs. 2 [0.69] $p=0.027$). Withdrawal of high dose support in those with poor baseline TTE parameters resulted in a significant improvement in LV function in 10/19 donors compared to the remaining 9 who continued on high inotropic support (FS 33.6% [9.5] vs. 23% [15.5] $p=0.026$, LVEF 69% [13.8] vs. 49.5%

[27.6] $p=0.011$, LV wall motion score 1.5 [0.59] vs. 2.1 [0.69] $p=0.043$). In the remaining 25/44 (57%) donors, there were no changes in LV function on TTE. 11/19 dysfunctional hearts ultimately attained transplantable criteria and 8 were used.

Conclusion: In this study, serial TTE could be performed in 70% of donors and identified improvements in donor hearts in response to aggressive management. Donor management allowed maintenance or improvement of function on serial TTE in $> 50\%$ of donors initially on high inotropic support. Substitution of NE with vasopressin was associated with significant functional improvement.

P1637 Experience with the new generation Etlogix and Geoform annuloplasty systems for correction of ischemic MR in patients with CAD and dilated CMP



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Objective: Restrictive mitral annuloplasty and/or chordal cutting have been proposed for repair of ischemic mitral regurgitation (MR). However, the new Etlogix and Geoform Annuloplasty Rings are specifically designed to correct ischemic MR. We report our early experience with these new rings in ischemic and dilated CMP.

Methods: Between January 2004 and February 2006, the Etlogix (ER; n=19) and Geoform ring (GR; n=6) were used for repair of significant ischemic MR (ERO $> 20\text{mm}^3$, RV $> 30\text{ml}$) in 25 patients (age 65 ± 11 years, EF $35 \pm 12\%$, LVEDD $62 \pm 7\text{mm}$, LVESD $49 \pm 8\text{mm}$, EuroScore 7 ± 3). In 24 patients, additional procedures were performed (CABG n=15; tricuspid repair n=8; atrial ablation n=4; aortic valve replacement n=2; carotid endarterectomy n=1).

Results: CPB and AXC were 129 ± 45 and 87 ± 37 min, respectively. ER sized 26 (n=8), 28 (n=8), 30 (n=2) and 32 (n=1) and GR sized 26 (n=2) and 28 (n=3) were used. Mean mitral gradient was 4.6 ± 1.8 and 3.7 ± 2.1 mmHg ($p=.5$) in the ER and GR group, respectively. No residual important MR was observed. Vasoactives were used in 24 patients and IABP in 6 (24%). Ventilatory duration was 27 ± 39 h, ICU and hospital stay 2.9 ± 2.7 and 12.6 ± 6.1 days. No early death or stroke occurred. PMI was seen in 3 patients (12%), arrhythmias in 14 (56%), pacemaker implantation in 1 (4%), renal failure with/without dialysis in 1/4 (20%). During a total observation period of 12.4 ± 6.9 (ER 15.2 ± 5 , GR 3.3 ± 3.1) months, one late death and no reoperation occurred. Echocardiographic controls showed no recurrent MR and improved LV function in most patients.

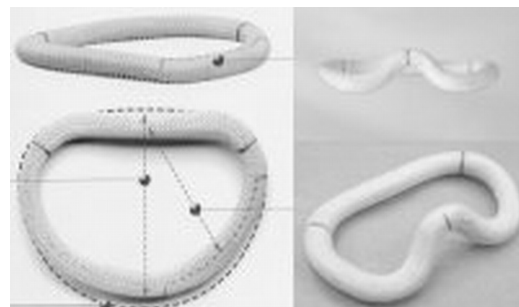


Fig. 1. Etlogix (left) and Geoform (right) rings.

Conclusions: The new Etlogix and Geoform rings allows effective and durable correction of ischemic MR. However, on-going follow-up is needed to assess its impact on long-term survival and cardiac function.

P1638 Mortality predictors in left main disease



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Background: Left main coronary artery (LMCA) disease has a poor short and medium term prognosis if no revascularization is accomplished. Treatment for this condition can be surgical coronary artery by-pass grafting (CABG), percutaneous coronary intervention (PCI) or pharmacological therapy. Risk stratification is especially important for treatment strategy decision. We seek to assess mortality predictors in LMCA disease patients.

Methods: Patients consecutively diagnosed with LMCA stenosis $> 50\%$ from January 2000 to December 2004 in our centre were studied.

Results: 548 patients were included, mean age 68 ± 10.6 years, 81% male, mean ejection fraction (EF) $58 \pm 10.6\%$. Indication for catheterization was: stable angina (SA) 21%, Non ST elevation ACS 63%, ST elevation ACS 4%, dyspnea 8%, other 4%. After catheterization 78% underwent CABG, 9% PCI and 13% received only pharmacologic therapy. After median follow up period of 20.5 months, incidence of major clinical event was: Death 20.3%, non fatal myocardial infarction (MI) 2.6% and revascularization 5.5%. Eight patients presenting in cardiogenic shock had 63% mortality and were not included in regression model analysis. In-

dependent predictors of mortality were assessed through Cox regression model as shown in table below.

	OR	CI	
Serum Creatinin	1.43	1.24 - 1.65	$p < 0.001$
Stable Angina	0.28	0.11 - 0.70	$p = 0.006$
Age	1.04	1.02 - 1.07	$p = 0.001$
EF	0.97	0.96 - 0.99	$p < 0.001$

Conclusion: Despite revascularization, LMCA disease has a high mortality. Main mortality predictors in patients not presenting in cardiogenic shock in our cohort were high creatinine levels, clinical instability, age and low EF.

P1639 The effect of coronary revascularization prior to vascular surgery of high-risk patients with extensive stress-induced ischemia on post operative outcome



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Background: Vascular surgery patients with multiple cardiac risk factors and extensive stress-induced ischemia at preoperative cardiac testing are at high-risk of perioperative and late cardiac events. Preventive coronary revascularization prior to surgery might be considered. However, the benefit on postoperative and long-term outcome compared to optimal medical therapy is ill defined.

Methods: 1476 patients were screened and stratified into low (0 cardiac risk factors), intermediate (1-2 cardiac risk factors), and high-risk (≥ 3 cardiac risk factors). All high-risk patients underwent cardiac testing using dobutamine stress echocardiography (17-segment model) or stress nuclear imaging (6-wall model). Those with extensive stress-induced ischemia (> 4 segments or > 2 walls) were randomly assigned for coronary revascularization. All received beta-blockers aiming at a heart rate of 60-65 bpm, anti-platelet therapy was routinely stopped 1 week prior to surgery. The endpoint was cardiac death or MI at 30-days and during 2-year follow-up.

Results: Of 352 high-risk patients 176 (50%) showed no ischemia, 106 (30%) limited ischemia, and 70 (20%) extensive ischemia. The 70 patients with extensive ischemia were randomly assigned to revascularization (N=38) or no-revascularization (N=32). Coronary angiography showed 2-vessel disease in 10 (26%) and 3-vessel disease in 27 (71%). The median duration of revascularization to operation was 29 (13-39) days in the 13 patients undergoing coronary bypass surgery and 31 (19-65) days in the 25 patients undergoing a percutaneous coronary intervention. Revascularization did not improve 30-day outcome, the incidence of cardiac death or MI was 31.6 vs 9.4%, OR 4.5, 95% CI 1.1 to 18 ($p=0.024$). Also no long-term benefit during 2-year follow-up was observed after coronary revascularization, 43.9 vs 16.3% ($p=0.041$).

Conclusions: Preoperative coronary revascularization in high-risk vascular surgery patients with extensive stress-induced ischemia was not beneficial.

P1640 Cardiovascular risk factors are major determinants of perioperative mortality in noncardiac surgery



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Background: Perioperative mortality in non-cardiac surgery is caused by cardiovascular complications in 25 to 33% of cases. The relationship between cardiovascular risk factors and perioperative mortality is poorly defined.

Methods: Between 1991 and 2002, 871,565 non-cardiac open-surgical procedures were performed in the Netherlands. Type of surgery, cardiovascular risk factors, and in-hospital outcome (dead/alive) were collected. Data were sent to PRISMANT, the institution that is responsible for nation-wide health-care statistics. We applied multivariable logistic regression to evaluate the relation between patient characteristics and perioperative all-cause mortality.

Table 1. Cardiac risk factors and mortality

Characteristic	Mortality	Adjusted OR (95% CI)
Surgical risk type (ACC/AHA)		
Low	0.2%	1
Intermediate	3.7%	6.7 (6.2, 7.4)
High	11.2%	20 (18, 23)
Diabetes mellitus	6.1%	1.3 (1.2, 1.4)
Renal insufficiency	8.2%	2.4 (2.3, 2.5)
Angina pectoris	8.5%	1.3 (1.1, 1.4)
Arrhythmias	15.0%	2.4 (2.3, 2.6)
Valvular disease	10.7%	1.6 (1.4, 1.7)
Pacemaker	10.2%	1.4 (1.1, 1.6)
Myocardial infarction	8.9%	1.2 (1.1, 1.3)
Heart failure	26.4%	4.9 (4.6, 5.2)
Stroke	12.2%	2.6 (2.4, 2.9)

Results: 28,350 (3.3%) patients died during hospital stay. In-hospital mortality did not change during 1991-2002. The 233,533 (24%) patients undergoing low-risk surgery (ACC/AHA classification) had 0.2% in-hospital death, as compared to 3.7% and 11.2% in the 581,389 (70%) and 56,640 (6%) patients undergoing intermediate and high-risk surgery. Cardiovascular risk factors were identified that were associated with increased mortality.

Conclusion: Mortality after non-cardiac surgery is predominantly determined by the surgical risk-type. Cardiovascular risk factors provide additional prognostic information.

P1641 Procalcitonin-based therapeutic strategy to reduce antibiotic use in treatment of patients underwent open heart surgery



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Background: Procalcitonin (PCT) is thyroid gland prohormone, and its serum concentration is elevated in bacterial infections. The prognostic value of elevated serum levels of PCT in patients early after cardiac surgery on cardiopulmonary bypass (CPB) remains unclear. Kerbaul et al. (2002) suggest that PCT concentrations of 5 ng/mL were related to postoperative severe systemic inflammatory response syndrome associated with significantly prolonged mechanical ventilation and length of ICU stay.

Aim: In RCT study, we investigated whether PCT is useful as prognostic marker in cardiac surgery, with respect to mortality, complications and infections, and whether procalcitonin-guidance could reduce antibiotic use in patients subjected to the open heart surgery.

Methods: 203 patients subjected to surgical CABG, valve replacement or combined CABG + valve operations were randomly assigned for procalcitonin-guided treatment (procalcitonin group; n=102) or standard care (control group; n=103) from 02/05 till 08/05. On the basis of serum PCT concentrations, use of antibiotics was encouraged (≥ 0.5 ng/mL) or discouraged. Reevaluation was possible after 6-24-48 hours in both groups. Primary endpoint was use of antibiotics and analysis was by intention to treat. Operation data, laboratory data and clinical outcome: mortality, infections, severe complications were observed.

Results: In the PCT-group, the ICU stay was 5.74 ± 11.49 days and in control group 6.97 ± 11.61 ($p=0.0447$). Hospital stay was 12.08 ± 11.28 v 12.93 ± 10.73 ($p>0.05$) days, respectively. Clinical and laboratory outcome was similar in both groups and favorable in 188 (92.6%). Mortality ratio was 7/95 in experimental and 8/95 ($p=0.8038$) in control group. We have found that complications occurred in 40/62 v 41/62 ($p=0.4837$) while infections appeared in 5/97 v 22/81 (0.0082) cases. The relative risk of antibiotic exposure was in control group compared with the PCT-group 3.81 (95% CI 2.03-7.17; $p<0.00001$). Substantial difference we observed in treatment of urinary infections between PCT and control group: 1/101 v 9/94 ($p=0.0330$). Considering the type of cardiac surgery the antibiotic use was significantly reduced in all diagnostic subgroups.

Discussion: Besides infectious complications, many noninfectious factors could explain the development of a post-CPB inflammatory reaction. We have found that PCT-guided antibiotic treatment is safe and can significantly reduce the cost of postoperative care. Additionally, the antibiotic use during immediate postoperative course should be timely controlled and limited on documented bacterial infections.

P1642 Preoperative evaluation of flow-mediated dilatation in the left radial artery or the right brachial artery, as a predictor of nitric-oxide bioavailability in coronary artery bypass grafts



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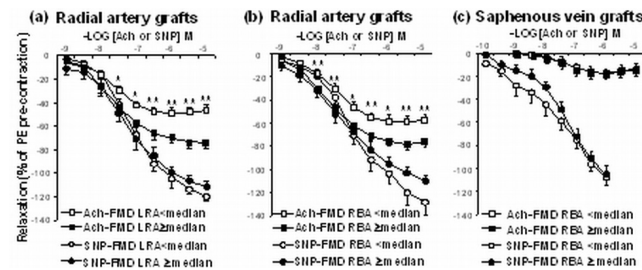
Vascular endothelium may be a key regulator of short- and long-term patency of CABG grafts.

Aim: We examined whether non-invasive preoperative evaluation of endothelial function by using flow-mediated dilation (FMD) in the left radial artery (LRA) and right brachial artery (RBA) can predict nitric oxide (NO) bioavailability in CABG grafts such as LRA or saphenous veins (SV).

Methods: The study population consisted of 50 patients (66.7 ± 1.8 years old) scheduled for CABG. FMD was performed in LRA (FMD-LRA) and RBA (FMD-RBA), one day before CABG. At the day of operation, LRA or SV grafts were obtained, and vasomotor responses to acetylcholine (ACh) and nitroprusside (SNP) were examined.

Results: FMD-LRA was correlated with the maximum relaxations of LRA to ACh ($r=0.534$, $p=0.049$), while patients with FMD-LRA>median had significantly better dose-response curves compared to those with FMD-LRA<median (figure a). Patients with FMD-RBA>median had better vasomotor responses to ACh in LRA compared to those with FMD-RBA<median (figure b). FMD-RBA was also correlated with the maximum relaxation of SV to ACh ($r=0.469$, $p=0.016$), although there was no difference between dose-response curves when median

FMD was used as the cutoff point (figure c). In multivariate linear regression, the only independent predictors of LRA responses to maximal Ach were FMD-RBA ($\beta=0.02$ (SE:0.006), $p=0.004$) and FMD-LRA($\beta=0.020$ (SE:0.008), $p=0.036$). Similarly FMD-RBA was an independent predictor for the vasomotor responses of SV to maximal Ach ($\beta=0.882$ (SE:0.394), $p=0.034$).



Conclusions: Preoperative FMD in the LRA or RBA, is an independent predictor for NO bioavailability in both arterial and (in a smaller degree) venous CABG grafts, suggesting that FMD may be a useful index for pre-operative evaluation of CABG grafts.

P1643 A mechanical connector (PAS-PORT) for proximal vein graft anastomoses: 12-months angiographic and intravascular ultrasound evaluation



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Introduction: The treatment of middle or late stage coronary artery disease (CAD) often requires coronary artery bypass grafting (CABG) as the therapy of choice. The goal of proximal anastomotic coronary devices is to reduce neurological deficits by eliminating the side biting clamp and to improve the ease of performing proximal anastomoses. The objective of this study was to evaluate the patency and restenosis rate of proximal vein graft anastomoses using angiography and intravascular ultrasound analysis (IVUS).

Methods and Results: 21 patients (P) (mean age = 69 years, 19 male) were examined. All P had at least one anastomosis successfully completed with the PAS-PORT TM-device (PPD) and one conventional hand-sutured anastomosis (CA) as well. The CA served as reference. The median time to the previous CABG was 12 months (range 8-16). We calculated the patency and restenosis rate using quantitative coronary analysis (QCA). Moreover we examined IVUS images (motorized pull back 0.5mm/s) of the proximal vein grafts and the proximal anastomoses. Cross sections of the vein grafts were assessed using the following factors: maximum lumen diameter (MaxLD), minimum lumen diameter (MinLD), cross sectional area (CSA), and vessel wall area (VWA). In the control angiography 12 months after surgery 2 connector grafts and 5 CA were occluded (9% versus 23%, respectively; $p=0.002$). Furthermore, one stenosis of about 50% occurred on the site of a connector anastomosis and a hand sewn graft as well. The IVUS examination showed no significant differences. Among the clinical risk factors no significant differences were measured.

Results of IVUS Measurement

	MinLD (mm)	MaxLD (mm)	CSA (mm ²)	VWA (mm ²)
PPD (n=23)	3.1±0.7	3.6±0.7	9.1±3.7	4.6±2.4
CA (n=23)	3.2±0.7	3.6±0.8	9.4±4.7	4.1±2.7
p-value	ns	ns	ns	ns

Conclusion: The PPD appears to be effective and safe as a tool for proximal vein graft anastomoses. The 12-months patency rate compare favourably to the average mid-term graft patency for standard coronary bypass procedures.

P1644 Effect of perioperative nesiritide administration on postoperative renal function and clinical outcomes in patients undergoing cardiothoracic surgery: Results of the NAPA trial



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Purpose: Postoperative renal dysfunction (PRD) is a serious complication after cardiac surgery using cardiopulmonary bypass (CPB). The purpose of this study was to evaluate the impact of nesiritide (NES) on PRD and clinical outcomes in patients undergoing cardiothoracic surgery.

Methods: The Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiothoracic Surgery (NAPA) trial was a prospective, multicenter, randomized, double-blind, pilot trial. Patients undergoing CABG surgery utilizing CPB, with or without mitral valve repair/replacement, and LVEF $\leq 40\%$ were randomized to NES (0.01 mcg/kg/min, no bolus) or placebo (PLB) after induction of anesthesia in addition to usual care and continued for 24-96 hrs. SCr, GFR, and urine output (UO) were measured. PRD was defined as SCr increase >0.5 mg/dL

through hospital discharge or study day 14, whichever came first. Fisher exact test, ANOVA model and Wilcoxon rank-sum test were used for comparisons between treatment groups.

Results: 279 patients from 55 centers were randomized and treated with PLB (n=138) or NES (n=141). Mean age was 64 ± 11 yrs; 78% (219/279) were male; 83% (232/279) Caucasian. PRD occurred in 22% (30/134) of PLB patients and 9% (12/137) of NES patients ($P=0.002$). Mean ($\pm$ SE) peak increase (at hospital discharge or by study day 14) from baseline in SCr was lower in NES-treated patients (0.33 ± 0.04 PLB vs. 0.16 ± 0.03 NES, $P=0.001$); this difference was greater in patients with baseline SCr >1.2 mg/dL (0.48 ± 0.10 PLB vs. 0.02 ± 0.06 NES, $P=0.001$). Worst decrease from baseline in GFR was also lower in NES-treated patients (-16.7 ± 1.9 mL/min/1.73 m² PLB vs. -11.3 ± 1.7 mL/min/1.73 m² NES, $P=0.004$). UO 24 hrs after ICU admission was greater in patients receiving NES (2486 ± 165 mL PLB vs. 3140 ± 225 mL NES, $P=0.02$) while postoperative IV diuretic use was similar (19% PLB vs. 12% NES, $P=NS$). Serious adverse event rate was similar between treatment groups (37.0% [51/138] PLB vs. 29.8% [42/141] NES, $P=NS$). Mean ICU/CCU LOS was not statistically different between PLB and NES groups (102.4 ± 8.8 hrs vs. 79.5 ± 7.9 hrs, $P=0.143$). Patients receiving NES had marginally shorter mean total hospital LOS (11.3 ± 0.8 days vs. 9.2 ± 0.5 days, $P=0.08$).

Conclusion: NES exerted beneficial effects on PRD and outcomes in patients undergoing cardiothoracic surgery; further evaluation is indicated.

P1645 Timing of coronary artery bypass graft surgery following acute myocardial infarction: influence on operative mortality



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Background: It has been well recognized that there was a higher mortality rate involved with an emergent coronary artery bypass graft surgery (CABG) early after acute myocardial infarction (AMI), especially during mechanical complications or cardiogenic shock. On the other hand, there is controversy whether timing of CABG after AMI (TIME) is an independent predictor of outcome in the absence of mechanical complications or cardiogenic shock. The aim of this study is to determine whether TIME is an independent predictor of 30 days postoperative mortality (OM).

Methods: We performed a retrospective analysis of 380 patients who underwent CABG as the sole procedure after AMI between October 2001 and January 2004. Patients were referred for CABG if they had post-infarction angina or positive low-level stress test despite maximal medical therapy. There were 280 men (73.7%) and 100 women (26.3%). The mean age was 61 ± 9 years-old (range, 39-82). There were 80 patients (21.1%) with left ventricular ejection fraction $\leq 40\%$ and, 18 (4.7%) had had CABG before. Emergent or urgent CABG were done in 32 patients (8.4%) and 110 patients (28.9%) had left main coronary disease. TIME was ≤ 7 days in 23 patients (6.1%), between 8 and 21 days in 49 (12.9%) and, greater than 21 days in 308 patients (81.1%).

Results: OM decreased with increasing TIME: 21.7% for ≤ 7 days, 8.2% for 8 and 21 days and 5.5% > 21 days ($p=0.017$). Multivariate logistic regression analyses of 11 potential ($p<0.2$) risk factors have shown that TIME ≤ 7 days was independently associated with higher OM ($p=0.008$, Odds Ratio=5.022; 95% confidence interval= 1.506-16.738).

Conclusion: CABG within 7 days of AMI might be an added risk for OM.

P1646 Differential impact of troponin assay on estimates of six month mortality after Coronary Artery Bypass Graft (CABG) surgery



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We have reported (n=2,918) that progressive elevations of CK-MB after CABG surgery are associated with significant increased 6 month mortality (J Thorac Cardiovasc Surg 2003;126:807-13; J Am Coll Cardiol 2001;38:1070-77). We prospectively confirmed our findings in 5,682 patients enrolled in the Expedition Trial. It is likely that a similar 6-month mortality relationship exists for cardiac troponin I and T after CABG surgery. The Expedition Trial tested the efficacy of Cariporide, a Na⁺/H⁺ exchange inhibitor, in reducing myocardial ischemia or death in a randomized trial of 5,682 high-risk CABG surgery patients. Troponin I and T data were available in 1,592 and 702 patients respectively. We measured patient troponin I and T ratios (Value/Upper Limit of Normal) at baseline, 4, 8, 12, 24, 36 and 48 hours after entry into the ICU. Patients with elevated cardiac troponin at baseline were excluded. Kolmogorov-Smirnov tests were used to evaluate the difference in median troponin levels between patients who died within 6 months of surgery versus those who survived.

Results: Results are shown (table). Median troponin I ratios were much greater than troponin T ratios in non-survivors after entry into the ICU. Optimal prognostic

cut-points to differentiate survivors from non-survivors ranged from 50-100 times upper normal limits for troponin I vs. 15-20 for troponin T.

Median troponin ratios by 6 mo. survival

Hours After Entry Into ICU	Troponin I		P-value	Troponin T		P-value
	Non-Survivor Median (n)	Survivor Median (n)		Non-Survivor Median (n)	Survivor Median (n)	
Baseline	0.17 (88)	0.17 (1,592)	0.34	0.10 (26)	0.10 (702)	0.57
8 Hrs.	15.0 (77)	9.6 (1,519)	<0.05	5.0 (19)	4.2 (663)	0.36
24 Hrs.	16.5 (68)	7.0 (1,485)	<0.001	7.9 (22)	3.1 (657)	<0.05
48 Hrs.	12.7 (63)	4.1 (1,407)	<0.001	4.3 (19)	2.8 (630)	<0.05

Conclusion: Patients who died within 6 months of surgery had significantly higher troponin I and T ratios compared to patients who survived. However, the magnitude of troponin release differed according to the assay method used and thus the predictive value of the ratios to mortality cannot be used interchangeably. Elevated troponin I or T ratios, similar to elevated CK-MB ratios, are early indicators of increased 6 month mortality.

P1647 The relationship among oxidative stress, membrane lipid peroxidation, and ultrastructural damage, in the heart of patients undergoing ischemia/reperfusion at cardiac surgery: a reappraisal

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Background: In experimental models, oxidant formation at postischemic reperfusion triggers a sequence of events known as "oxidative stress". This begins with release of glutathione (GLUT), followed by peroxidation of membrane lipids, and culminates in ultrastructural injury. During cardiac surgery, the hearts of patients (pts) subjected to cardioplegic arrest/reperfusion might similarly undergo oxidative stress. GLUT release has been shown in this setting, and considered evidence of oxidant-mediated injury. However, GLUT formation is an endogenous mechanisms of oxidant removal; thus, although it signals excess oxidant production, it does not equate cell injury, which may not occur if oxidant toxicity does not progress. Indeed, a precise relationship among GLUT release, lipid peroxidation and development of ultrastructural injury has not been established in pts, and value of antioxidant therapy in cardiac surgery is still debated.

Purpose: To systematically investigate in pts the relationship between oxidant formation and development of injury during reperfusion after cardioplegic arrest.

Methods: In 24 pts undergoing elective coronary artery bypass, we evaluated (before cardioplegic arrest and during reperfusion): a) trans-cardiac blood differences (V-A) of GLUT ($\mu\text{Moles/l}$), and lipid peroxides (MDA, $\mu\text{Moles/l}$); b) biopsy concentrations of membrane peroxidation products (MPO, nMoles/mg prot), and of the antioxidants ubiquinone (UBI, nMoles/g); c) ultrastructural injury (ULTR, semiquantitative 0-4 scale). Cardiac arrest lasted 40.9 ± 11.9 min.

Results: Reperfusion was followed by GLUT release and decrease of tissue ubiquinone, indicative of oxidant attack; however, there was no lipid peroxide release in blood nor accumulation in tissue. Furthermore, no major ultrastructural alterations developed. Finally, full recovery of left ventricular function was observed.

Effects of cardiac arrest/reperfusion

	V-A GLUT	V-A MDA	MPO	UBI	ULTR
Pre-ischemia	0.02 ± 0.04	-0.32 ± 0.17	0.99 ± 0.42	144.5 ± 52.0	1.7 ± 0.5
Reperfusion	$1.10 \pm 0.40^*$	-0.05 ± 0.13	0.92 ± 0.37	$97.6 \pm 82.0^*$	1.8 ± 0.4

* $p < 0.05$ vs pre-ischemia

Conclusions: Together, these data document cardiac exposure to oxidants, but not accompanied by evidence of injury. Although oxidant production occurs in pts undergoing cardiac surgery, under our conditions cardiac oxidative stress does not progress further through membrane damage and irreversible injury.

P1648 Angioscopic observation whether neointimal formation occur or not after sirolimus-eluting stent implantation (after 1, 3, 6, 12 months study)

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The aim of this study is to observe the surface of sirolimus-eluting stent (SES) by angioscopy whether or not stent surface neointimal formation over the stent surface occur 1, 3, 6, 12 months after stent implantation. In addition, we also assessed thrombus formation at the stent site. We performed angioscopy to 36 patients 42 lesions after SES implantation. 25 males, 11 females, mean age was 71 ± 8 years old. All patients received double anti-platelet therapy 1 week before stent implantation to follow up examination. The extent of neointimal stent coverage was semiquantitatively evaluated using a 4-point grading system: 0=complete exposure of stent struts; 1=dull light reflex from stent struts; 2=no light reflex but

slightly visible stent struts; 3=complete coverage without vision of the stent struts. We defined that over grade 1 stent coverage score had a neointimal formation. Thrombus formation was classified as follows; none, WT (white thrombus dominant), RT (red thrombus dominant), MT (mixed thrombus or same amount of WT and RT). Rate of neointimal formation at 1, 3, 6, 12 months after stent implantation was 42%, 33%, 57% and 92%. Rate of thrombus formation immediately, 1, 3, 6 and 12 months after PCI was 35%, 71%, 67%, 86%, and 100%. RT existed immediately after PCI but it was decreased in progress of time and WT mainly existed 6 and 12 months after stent implantation. These observations indicated that neointimal coverage 12 months after SES implantation was almost achieved, however, it is difficult to discontinue anti-platelet therapy because of the existence of thrombus.

P1649 Impact of previous PCI revascularization on outcomes after surgical revascularization: insights from the IMAGINE study

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Objective: To determine the impact of previous coronary artery revascularization by percutaneous coronary intervention (PCI) on outcome after subsequent coronary artery bypass grafting (CABG).

Methods: Of the 2553 patients included in the IMAGINE (Ischemia Management with Accupril post bypass Graft via Inhibition of the coNverting Enzyme) trial, 455 had a history of PCI prior to surgery (PCI group), and 2098 were referred to surgery without previous PCI (non-PCI group). Patients were randomized to placebo or quinapril a mean of 4 days post-CABG, and had a median follow-up of 2.95 years. All patients had stable coronary artery disease and a left ventricular ejection fraction ≥ 0.40 .

Results: The last PCI performed prior to CABG was a median of 19 months, range 3 days to 20 years. Of these, 29 patients (6.4%) underwent PCI within 30 days prior to randomization. There was a significant increase in the primary IMAGINE endpoint in the PCI group HR=1.64 [1.28-2.11], $p < 0.0001$. By individual component of the IMAGINE primary endpoint, the results are: cardiovascular death HR=2.04 [0.97-4.3], $p=0.06$, resuscitated cardiac arrest HR=3.1 [0.51-18.5], $p=0.22$, non-fatal myocardial infarction HR=1.5 [0.71-3.17], $p=0.29$, coronary revascularization HR=1.85 [1.17-2.90], $p=0.008$, unstable angina requiring hospitalization HR=2.43 [1.54-3.83], $p=0.0001$, documented angina not requiring hospitalization HR=1.44 [1.01-2.05], $p=0.04$, stroke HR=1.23 [0.5-3.01], $p=0.65$ and congestive heart failure requiring hospitalization HR=2.08 [0.95-4.57], $p=0.07$. Other events such as transient ischemic attack HR=0.78 [0.23-2.68], $p=0.69$, and other cardiovascular event requiring hospitalization HR=1.00 [0.70-1.43], $p=0.99$ were not increased. Adjustment for baseline characteristics (age, sex, history of myocardial infarction or stroke, diabetes or previous CABG, treatment group, or off-pump surgery) did not alter the results, except for documented angina not requiring hospitalization, HR=1.36, [0.95-1.95], $p=0.10$ when adjusted.

Conclusion: Patients with a previous PCI had a worse outcome post-CABG, even after adjusting for baseline cardiovascular risk factors, suggesting that previous PCI is an independent risk factor for poor outcome post-CABG and that previous PCI may even contribute to the poorer outcome.

P1650 Left ventricular geometry changes and actuarial survival one year after surgical ventricular reconstruction with and without mitral valve repair

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The aim of the study was to evaluate left ventricular (LV) geometry changes and actuarial survival one year following surgical ventricular reconstruction (SVR) with or without mitral valve repair (MVR).

Methods: The study group consisted of 102 patients (pts) who underwent CABG with SVR during 2000- 2005 y: 48 pts underwent LV anterior aneurysm reconstruction combined with MVR (I group), 24 pts - posterior aneurysm reconstruction with MVR (II group) and 30 pts - isolated anterior aneurysm reconstruction (III group). The study protocol included evaluation of LV end diastolic volume index (EDVI), LV sphericity, ejection fraction (EF) and mitral regurgitation (MR) grade preoperatively, 10-14 days and 1 year after surgery.

Results: The overall in-hospital postoperative mortality rate was 16, 6%. SVR with or without MVR reduced EDVI from 96.04 ± 21.80 to 84.99 ± 21.13 ml/m² ($p < 0.001$) and improved EF from 27.77 ± 8.03 to $30.37 \pm 7.18\%$ ($p < 0.004$). 1 year after surgery changes in EDVI were similar in all groups, diastolic and systolic sphericity was reduced in group II and remained unchanged in group I and III (Table 1). In group I MR grade was 2.56 ± 0.55 preoperatively and 1.39 ± 0.59 1 year after surgery ($p < 0.001$), in group II -2.72 ± 0.80 and 1.62 ± 0.66

($p < 0.001$), respectively. In group III 10% of pts had mild to moderate MR before SVR and 30% at 1 year follow-up. Actuarial survival was 81,3% at 1 year: 71% in group I, 100% -group II and 82% -group III.

Table 1. LV indices

		I group	II group	III group
End diastolic volume index	pre-op	101,06 ± 22,35 *	92,13 ± 20,45 *	92,30 ± 21,58 *
	1 yr. post-op	86,36 ± 22,24 #	85,30 ± 20,59 #	82,08 ± 20,69 #
Sphericity index diastole	pre-op	0,67 ± 0,08	0,71 ± 0,08 *	0,62 ± 0,10
	1 yr. post-op	0,67 ± 0,09	0,67 ± 0,06 *	0,63 ± 0,09
Sphericity index systole	pre-op	0,54 ± 0,08	0,60 ± 0,09 *	0,49 ± 0,10
	1 yr. post-op	0,57 ± 0,11	0,57 ± 0,06 #	0,50 ± 0,11

* $p < 0,05$ between pre-op and post-op; ** $p < 0,05$ between post-op and 1 yr. post-op; # $p < 0,05$ between pre-op and 1 yr. post-op.

Conclusions: SVR with and without MVR provides significant reduction in LV volumes which is sustained during 1 year with preferable actuarial survival. LV posterior aneurysm reconstruction combined with MVR is associated with most prominent reduction in LV sphericity.

P1651 What is the optimal approach to assess perioperative risk in patients with ischemic left ventricular dysfunction undergoing CABG: EuroSCORE model or myocardial viability?

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Background: Myocardial viability is an important determinant of prognosis in patients with ischemic left ventricular (LV) dysfunction. In the present study, we tested the hypothesis that assessment of myocardial viability will be associated with improved accuracy to assess perioperative risk in patients with ischemic LV dysfunction undergoing CABG.

Methods: The study consisted of 79 patients with ischemic LV dysfunction (age 67 ± 9 y; 83% males; LV ejection fraction $29 \pm 6\%$; logistic EuroSCORE $5.7 \pm 2.8\%$) undergoing CABG. Myocardial viability in dysfunctional segments was assessed by delayed contrast-enhanced magnetic resonance imaging (16-segment model).

Results: Nine (11%) patients had refractory heart failure in the early postoperative period and died within 30 days after CABG. Survivors ($n=70$) showed significantly larger extent of viable myocardium than patients, who died (6.9 ± 3.3 viable segments vs. 2.7 ± 0.9 viable segments, $p < 0.001$). The presence of ≥ 4 viable segments showed the highest accuracy (Area under the curve=0.75) to identify survivors. In contrast, the EuroSCORE ($p=0.11$) and other baseline clinical and echocardiographic characteristics were similar in both groups. Furthermore, absence of myocardial viability quadruplicated the risk of perioperative death from 8.3% according to the EuroSCORE up to 39% (Table 1). In contrast, the presence of substantial viability lowered the risk by 51% from 6.8% to 3.3%. Finally, only 2 patients (18%) with EuroSCORE $\geq 10\%$ and <4 viable segments survived the operation.

Table 1.

	EuroSCORE (%)	Viable myocardium (n=61)	Nonviable myocardium (n=18)
Survived (n=70)	6.8 ± 5.8	59	11
Died (n=9)	10 ± 4.7	2	7

Conclusions: In patients with ischemic LV dysfunction undergoing CABG, assessment of myocardial viability should be combined with an established EuroSCORE model to estimate perioperative risk. Heart surgery should be avoided in patients with high EuroSCORE and nonviable myocardium.

P1652 Initial experience of video-assisted epicardial pulmonary vein isolation off-pump and ablation of ganglionic plexi in patients with atrial fibrillation

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The objective of this study is to assess the feasibility and safety of our initial experience of video-assisted thoracoscopic epicardial pulmonary vein isolation in patients with atrial fibrillation, who failed previous attempts of transvenous pulmonary vein isolation.

Method: Since Nov - 05, eight pts (3 women, 5 men, 44-61 years) with persistent or permanent AF underwent video-assisted thoracoscopic epicardial pulmonary vein isolation. All pts had experienced two unsuccessful endocardial catheter pulmonary vein (PV) isolations.

The epicardial approach included two intercostally 10 mm ports and one working port on each side of the thorax and a video-assisted epicardial PV isolation was performed "off pump" bilaterally on a beating heart. A bipolar radiofrequency device (Atricure) was used to achieve transmural linear lesions and isolation of the PVs. The left atrial appendage (LAA) was excised using a surgical stapler. Vagal ganglionic plexi (GP) were identified using high frequency stimulation 800 bpm, pulse width 9.9 msec, in specific predetermined sites around the PVs. Dur-

ing stimulation, a decrease exceeding 50% of the ventricular rate identified a GP with predominantly vagal innervation which then was ablated using RF-energy. Vagal denervation was confirmed by repeating the GP stimulation after the RF application(s).

Results: PV isolation confirmed by pacing, identification and ablation of vagal GP, and excision of the LAA were successful in each patient. Sternotomy was not required in any case during the procedure. The average post op stay was 7 days. There were no major post op complications. During the first three post op days, 7 pts had an episode of AF which was terminated by pharmacological treatment. During a follow-up of 2 weeks to 3 months no pt has had AF recurrence or any late complications.

Conclusions: Video-assisted thoracoscopic epicardial pulmonary vein isolation "off pump" on a beating heart with ablation of vagal GP and excision of LAA is feasible and well tolerated in AF patients. Our initial experience with the method offers promising results in AF patients which cannot be cured with endocardial catheter ablative technique. Continuing study evaluating the long term safety and efficacy of the method is indicated, especially regarding the necessity and efficacy of vagal denervation.

P1653 Cardiac outcome after elective abdominal aneurysm repair; size does matter

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Background: Abdominal aortic aneurysm (AAA) size and growth is associated with local generation of inflammatory markers such as IL-6. Inflammation also seems to play a pivotal role in perioperative adverse cardiac events. We hypothesized that, based on this mechanism patients with a large AAA might be more prone to adverse cardiac events.

Methods: Consecutive patients who underwent a CTA scan prior to open elective infrarenal AAA repair between 2000 and 2005 at 1 academic and 2 teaching hospitals were analyzed. All patients were screened for clinical risk factors (age, gender, angina pectoris, myocardial infarction, heart failure, diabetes, stroke, renal failure, chronic obstructive pulmonary disease), and cardioprotective medication. Postoperatively data on troponin release, CK/CK-MB, and ECG were collected on day 1, 3, 7, and 30. Outcome was 30-day cardiovascular death or non-fatal MI. Multivariate Cox regression analysis was used to evaluate the influence of AAA size on postoperative cardiac outcome. AAA size was divided in tertiles for Kaplan-Meier curve presentation.

Results: A total of 500 (431 males, 69.8 ± 9.5 years) patients were included in this study. Thirty-one (6.2%) patients suffered from cardiovascular complications, including 16 (3.2%) nonfatal MIs and 15 (3.0%) cardiovascular deaths. After correction for other risk factors (including age and Revised Cardiac Risk Index) and medication use (including beta-blockers and statins) AAA size was independently associated with perioperative nonfatal MI and cardiovascular death (3.2% increase in risk for each mm added, 95% CI 0.9% to 5.6%, $p=0.006$).

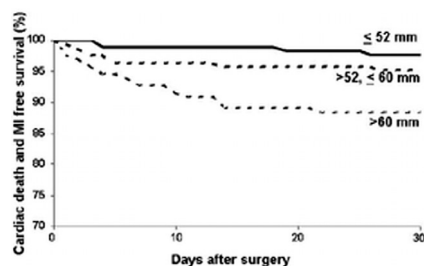


Fig. 1. Cardiac outcome according to AAA size tertiles.

Conclusion: A larger AAA size is independently associated with an increased incidence of perioperative cardiovascular complications after elective.

P1654 Low plasma cholesterol is associated with higher mortality in patients with advanced heart failure undergoing cardiac transplantation

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Purpose: Although low levels of plasma cholesterol (TC) have been associated with adverse outcome in patients with advanced heart failure; their potential impact on post-transplant survival remains undefined. We evaluated the predictive value of low pre-transplant TC in cardiac transplant recipients.

Methods: Of 497 adult cardiac transplant recipients transplanted at Texas Heart Institute from 1990 to 2000, pre-transplant TC levels were <120 mg/dl in 86 (17%) patients (Low TC group), and ≥ 120 mg/dl in 411 (83%) patients (Controls). The

two groups were comparable regarding age (48 ± 13 years in Low TC group vs. 51 ± 11 years in Controls, $P=0.1$), heart failure etiology (ischemic: 48% vs. 51%, $P=0.6$), cardiac index (2.0 ± 0.89 l/min/m² vs. 2.1 ± 0.66 l/min/m², $P=0.94$), and plasma creatinine (1.42 ± 0.75 mg/dl vs. 1.35 ± 0.69 mg/dl, $P=0.58$), but not with regards to AST (116 ± 120 IU/l vs. 58 ± 53 IU/l, $P=0.001$) or ALT (89 ± 78 IU/l vs. 54 ± 56 IU/l, $P=0.04$).

Results: During a 5-year post-transplant follow-up, 42 of 86 (49%) patients from the Low TC group died; compared to 128 of 411 (31%) of Controls ($P=0.002$). Mortality rates were highest in patients in whom TC levels remained low throughout the first post-transplant month: 34 of 59 (58%) died within 5-years. On autopsy, allograft vasculopathy was found in 18 of 42 (43%) patients from the Low TC group; compared to 62 of 128 (48%) of Controls ($P=0.53$).

Conclusions: Low levels of TC in patients with advanced heart failure are related to hepatic dysfunction. They are associated with higher post-transplant mortality, and do not attenuate the development of allograft vasculopathy. To improve hepatic function, assist-bridge to transplant rather than direct transplant may be preferable in this patient cohort.

STEM CELL TRANSPLANTATION: CLINICAL STUDIES

P1655 Feasibility and safety of intracoronary injection of mesenchymal stem cells in severe ischemic cardiomyopathy. Immediate, intermediate and long-term follow-up

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Introduction: Mesenchymal stem cells (MSC) have documented potential of cardiac regeneration in animal models. Data on use of MSC in humans are very rare. The main reason for this is apprehension of MI induction and undesirable transformation of MSC.

Aim: To evaluate safety and feasibility of the intracoronary injection of autologous MSC in patients with ischemic cardiomyopathy.

Patients and methods: Ten heart failure patients (all males, mean age 49.6 ± 4.8 years) with a history of myocardial infarction and severe systolic dysfunction (mean left ventricular ejection fraction (LVEF) $18.7 \pm 7.6\%$) were included. In five of them coronary angiography showed nonsignificant stenoses. Five others had coronary lesions not suitable for any intervention. In 4 of all 10 pts. viable myocardium was detected using SPECT thallium scintigraphy. 30 mL of bone marrow blood from the iliac crest was obtained. The MSC (CD45, CD34, CD 117, CD38, CD71, CD3 negative; CD90, CD44, CD13 positive) were isolated and expanded ex vivo. Standard coronary catheterization was performed using an over-the-wire balloon catheter. Suspension of MSC was injected in four 3 ml boluses during low pressure artery occlusions lasting 3 minutes. Mean number of cells injected was $2.3 \pm 1.0 \times 10^7$. NYHA class, six minutes walking distance (6mWD), peak oxygen consumption (pVO₂), left ventricular end diastolic diameter (LVdD), LVEF, wall motion score (WMS), brain natriuretic peptide (BNP) were evaluated before and 12 weeks after the procedure. Mean follow-up time of the patients was 15 ± 6 months.

Results: No clinical, ECG or humoral signs of acute myocardial lesion were observed. No symptomatic or significant dysrhythmias occurred immediately after the procedure. After 12 weeks there was no significant change in NYHA class, resting LVEF or WMS. Increase of 6mWD (421 ± 112 vs 472 ± 122 m, $p=0.05$) and pVO₂ (16.6 ± 3.2 vs 20.3 ± 5.2 ml/kg/min, $p=0.02$), and decrease of LVdD (63.5 ± 26.5 vs 59.5 ± 25.8 mm, $p=0.02$) and BNP (532 ± 650 vs 359 ± 513 pg/ml, $p=0.02$) were recorded. One patient underwent heart transplantation one year after, 2 died suddenly 7 and 5 months resp., after the MSC intracoronary injection. All others are alive, 3 of them in good clinical condition.

Conclusion: Intracoronary application of MSC in severe ischemic cardiomyopathy is safe and feasible. Changes at 12 weeks after the procedure are promising but more data are needed to evaluate the efficacy and medical benefit of this technique.

P1656 Intracoronary infusion of blood-derived progenitor cells after recanalization of chronic coronary occlusions: long term effects on cardiac function and infarct size

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In a randomised, double-blind, and placebo-controlled study we were able to show that transplantation of blood-derived circulating progenitor cells (CPCs) improves coronary vasomotion and left-ventricular (LV) remodeling in patients (pts) after successful recanalization of a chronic total coronary occlusion (CTO). However, it is unknown so far, whether the short term effects on left ventricular performance documented 3 months after CPC therapy proceed an improvement in

cardiac function at long-term follow-up. Additionally, long-term safety data with regard to CPC therapy in those pts are missing.

Methods: Twenty-six pts after recanalization of CTO were randomised to a treatment group (intracoronary injection of $69.6 \pm 15.5 \times 10^6$ CPCs isolated from 406 ± 13 mL blood) or to a placebo group (intracoronary application of serum). Immediately before, 3, and 15±1 months after study therapy LV function and size as well as volumes of regions with delayed enhancement, which are considered to represent scar tissue, were assessed by magnetic resonance imaging. Pts were monitored with regard to serious adverse events (SAE) defined as life-threatening arrhythmias, acute myocardial infarction, hospitalisation due to worsening of angina pectoris or heart failure.

Results: After 3 months, intracoronary application of CPCs resulted in a significant increase in LV ejection fraction (LV-EF) by 14% (from $52 \pm 4\%$ to $59 \pm 3\%$; $p<0.05$ vs. begin and placebo) and a decrease in left ventricular end-systolic volume (LV-ESV) by 13% (from 72 ± 9 mL to 63 ± 9 mL, $p<0.05$ vs. begin). These beneficial effects on LV function were still evident at long-term follow-up (LV-EF $60 \pm 3\%$, LV-ESV 60 ± 9 mL, $p<0.05$ vs. begin). LV-EF and LV-ESV remained unchanged in the placebo group within the first 3 months and also 15±1 months after study therapy. In the CPC group, the volume of delayed enhancement significantly decreased by 3.1 ± 0.9 mL at 3 months ($p<0.05$ vs. begin and placebo for percentage change) and by 4.3 ± 1.4 mL at 15±1 months ($p<0.05$ vs. begin and placebo for percentage change). Infarct size remained virtually unchanged in the placebo group at all follow-ups. One patient in the placebo group died suddenly 302 days after study therapy, one pt in the CPC group was hospitalized due to heart failure, and one pt in the placebo group due to progressive angina pectoris.

Conclusions: Intracoronary transplantation of CPCs after successful recanalization of CTO seems to exert advantageous long-term effects on left ventricular remodeling and function in the absence of harmful side-effects.

P1657 Intracoronary non-selective transfer of mononuclear bone-marrow cells for large anterior myocardial infarction in subacute phase improves long-term left ventricle function but causes high rate of rest

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Background: There are some weak evidence that intracoronary transfer of bone-marrow mononuclear cells (BM-MNC) through the inflated balloon with repeated arterial wall injury early after STEMI, can cause stenosis and improvement of left ventricle ejection fraction (LVEF) only in patients with large infarction.

The aims of this study were to investigate whether non-selective intracoronary transfer of BM-MNC would have a beneficial effect of long-term left ventricle ejection fraction (LVEF) recovery and to estimate the restenosis rate of such procedure.

Patients and methods. A case-control, single-centre study was conducted in 24 males with the first large (LVEF at 5-th day $<40\%$ due to infarction region akin to anterior acute myocardial infarction (AMI), treated with successful primary PCI on the proximal LAD. Eleven pts represented the experimental group (EG) and 13 pts represented well-matched control group (CG). In the EG, bone-marrow harvest was performed 6-10 days after AMI. After filtration of bone-marrow, cells were processed with separator. Total number of 15.2 ± 3.4 CD34+ cells were then delivered through the diagnostic coronary catheter into the infarct-related coronary artery without use of balloon. Assessment of left ventricular (LV) ejection fraction (EF) by radionuclide ventriculography (RVN), and infarction size (IS) by single-photon emission tomography (SPECT) were performed at two weeks and 6 months after AMI. Coronary angiography was performed in all pts at 6 months.

Results: There were no MACE during 6 month follow-up. Two weeks after AMI, LVEF was similar in the EG and CG (32.8 ± 4.7 vs. $34.5 \pm 5.8\%$, $p=0.469$) as well as IS (27.0 ± 5.9 vs. $25.5 \pm 3.91\%$, $p=0.54$). However, at 6 months, improvement of EF was noticed in EG, as opposed to CG ($6.2 \pm 4.6\%$ vs. $-1.0 \pm 3.5\%$, $p=0.001$). This beneficial change of LVEF in EG was associated with greater reduction of IS, as compared to CG ($7.34 \pm 4.6\%$ vs. $2.4 \pm 3.5\%$, $p=0.04$). Interestingly, unusually high in-stent restenosis rate was found in the EG, as compared to CG (63.6 vs. 23.1% , $p=0.03$) at 6 months.

Conclusion: It appears that non-selective intracoronary transfer of mononuclear bone-marrow cells is associated with the improvement of LV function and reduction of infarct size, but high incidence of in-stent restenosis, 6 months after first anterior AMI.

P1658 Mesenchymal and haematopoietic stem cell mobilization by G-CSF and VEGF gene therapy in patients with stable severe angina pectoris

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Background: We aimed to evaluate the mobilization of non-haematopoietic mesenchymal and haematopoietic stem cells from the bone marrow to peripheral

blood with G-CSF treatment alone and in combination with VEGF gene therapy in patients with severe chronic occlusive coronary artery disease.

Methods: We prospectively treated I) 16 patients with intramyocardial VEGF-A165 gene injections (VEGF-A group), II) 16 patients with intramyocardial placebo injections (Placebo group), III) 13 patients with subcutaneous G-CSF (Neupogen® 5 µg/kg) injections for six days (G-CSF group) and IV) 16 patients with intramyocardial VEGF-A165 gene treatment followed by G-CSF 10 mg/kg for six days (VEGF+G-CSF group).

Results: There was no increase in circulating CD34+ stem cells or mesenchymal stem cells (CD45-CD34-, MSC) after VEGF gene therapy alone. G-CSF treatment led to a significant increase in peripheral circulating CD34+ stem cells, with normalization after one week in both G-CSF and VEGF+G-CSF group. A G-CSF dose dependent mobilization of CD34+ cell into peripheral blood was found on day 7 after 10mg/kg G-CSF treatment in VEGF+G-CSF group when compared to the 5mg/kg in the G-CSF group. Circulating MSC significantly increased in a dose dependent manner after G-CSF treatment and normalized within one month in both G-CSF and VEGF+G-CSF groups. Plasma VEGF-A increased significantly in the two VEGF-A treated groups one week after the intramyocardial injections, and remained unchanged in the placebo and G-CSF treated groups. Neither of the two G-CSF doses had any effect on the VEGF-A levels. Plasma SDF-1 increased one week after intramyocardial injection in placebo group, and tended to be increased in VEGF group. During G-CSF treatment, SDF-1 decreased, and tended to be increased two weeks after G-CSF treatment in the VEGF+G-CSF group.

Conclusions: The present results demonstrated that G-CSF might mobilize not only haematopoietic stem cells but also non-haematopoietic mesenchymal stem cells in a dose-dependent manner. VEGF-A165 plasmid therapy did not mobilize stem cells from bone marrow. Therefore, to improve stem cell mobilization therapy for vasculogenesis in patients with chronic ischemic heart disease, one should consider addition of myocardial SDF-1 gene therapy to increase the homing of circulating stem cells.

P1659 Effects of mobilization of marrow bone stem cell by granulocyte-colony stimulating factor in Heart Failure: a comparison between mobilization and mobilization associated to intracoronary infusion

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Background: Bone marrow stem cell (BMSC) transplantation is gaining interest as a potential new means to treat HF. We tested prospectively the safety and efficacy of cytokine granulocyte-monocyte colony-stimulating factor (G-CSF) in determining BMSC mobilization (evaluated by CD34+) and improvement in HF with non-ischemic etiology.

Methods: In phase I it was included three groups: 82 normal subjects who received G-CSF, 17 HF patients waiting heart transplantation, and 23 HF patients that received G-CSF. G-CSF HF patients were randomized in two arms: BMSC mobilization by G-CSF, or BMSC mobilization by G-CSF followed by intracoronary infusion of an obtained concentrate by apheresis rich in CD34+ cells. BMSC were mobilized by G-CSF on the dose of 600 µg/day subcutaneous until CD34+ cells > 7 cells/mm³. In phase II, G-CSF were repeated monthly by three times in HF.

Findings: In phase I, G-CSF induced leukocyte count peaks (per mm³) in HF (42746 ± 12377), and in normal control (41711 ± 10127) (p=ns). HF CD34+ cell peaks (per mm³) were lower than control CD34+ cell peaks. (19±12 versus 60±20, p=0.003). In HF G-CSF group LVEF(%) (MUGA) increased from 21±6 to 24±7 (p=.02), peak Vo₂ (in ml/kg/min) from 10±2 to 12±3 (p=.04), and BNP from 430±418 to 612±639 (p=.03). In Doppler tissue imaging (DTI) improvement was more higher in septal and inferior segments. In both mobilization and intracoronary infusion groups was observed improvement in LVEF. LVEF did not change in the HF waiting heart transplantation. In phase II during the 468±374 day follow-up 7 patients died. Causes of death were: pulmonary embolism (1 patient); progressive HF (2 patients); and sudden death (4 patients). LVEF (29±8, p=.001), right VEF (31±10 versus 36±10, p=0.01), DTI velocities, and peak Vo₂ (13±4, p=0.4) improved after the 4th G-CSF administration versus baseline. LV end diastolic diameters did not change. Functional class and quality of life improved in the G-CSF group, whereas did not change in the HT waiting heart transplantation. Arrhythmias evaluated by 24-holter monitoring did not change after G-CSF administration. Side effects were transitory and did not determine withdrawal of the G-CSF administration treatment. One specific event was hair growth in 3 patients.

Interpretation: Mobilization of bone marrow cells is impaired in HF. Mobilization of bone marrow cells monitored by CD34+ can improve left and right cardiac function, exercise capacity, functional class, and quality of life in HF. Mechanisms leading to increment in BNP would be clarified. Intracoronary infusion of concentrate rich in CD34+ could not determine additional benefits.

P1660 Beneficial effects of combined (intramyocardial and intracoronary) bone marrow-derived stem cells therapy in patients with ischemic heart disease and severely depressed left ventricular function

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Purpose: Implantation of bone marrow-derived stem cells (BM-SCs) into the failing heart may be a promising approach for cardiac regeneration in heart failure secondary to severe coronary artery disease. The aim of the present study was to determine the effects of the combined (intramyocardial and intracoronary) percutaneous administration of autologous non-selected BM-SCs therapy on reducing myocardial ischaemia, and left ventricular function in no option patients with ischemic heart disease and severely depressed left ventricular function.

Methods: Eighteen patients (94% men, mean age: 55.4 ± 10.5 years) with previous myocardial infarction and left ventricular ejection fraction less than 35% under optimal medical treatment received combined [NOGA-guided intramyocardial (4.0 ± 0.6 ml) plus intracoronary (30.2 ± 13.8 ml)] autologous BM-SCs therapy (total cell number: 2.82x10⁹ ± 3.39 x10⁹; CD34+ cell number: 4.60x10⁷ ± 4.41x10⁷). Baseline and 6-month follow up 99m-Tc-MIBI-persantin-perfusion scintigraphy for determination of size of resting and stress-induced perfusion defects (expressed as % of the entire myocardium), NOGA endocardial mapping for assessment of myocardial viability, contrast ventriculography for calculating of global left ventricular ejection fraction (EF), left ventricular end-systolic (ESV) and end-diastolic volume (EDV) were performed in all patients.

Results: The clinical status of the patients improved (NYHA functional class from 2.69 ± 0.96 to 1.74 ± 0.95; p=0.001, CCS from 2.31 ± 1.10 to 1.43 ± 0.79; p=0.04). A trend to smaller stress-induced (from 37.3 ± 12.0% to 32.9 ± 11.6%; p=0.07) and resting (from 34.3 ± 11.6% to 30.5 ± 10.1%; p=0.18) perfusion defects was measured. Accordingly, the global left ventricular ejection fraction increased (from 32.9 ± 5.4% to 41.0 ± 8.2%; p=0.01) and ESV decreased (from 153.9 ± 37.6 ml to 145.7 ± 57.0 ml; p=0.05), significantly. Significant increase in mean unipolar voltage value of injected area measured by NOGA endocardial mapping (from 7.24 ± 2.33 mV to 8.43 ± 2.70 mV; p=0.007) (normal value > 15 mV) was observed after 6-month combined application form of BM-SCs therapy.

Conclusion: Combined (intramyocardial and intracoronary) autologous BM-SCs implantation induces reduction of the size of chronic ischemia with significant improvement of clinical status and increase in left ventricular function in patients with ischemic heart disease and severely depressed left ventricular function.

P1661 Late observations on arrhythmia after skeletal myoblast transplantation in patients with heart failure. Safety issues from two Phase I trials

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As evidenced by experimental data and suggested by initial clinical observations, transplantation of autologous skeletal myoblasts (ASM) may improve both systolic and diastolic function after MI. Disturbing the postinfarction scar electromechanical homogeneity by cells as well as lack of connexin 43 expression by skeletal myoblasts could both induce arrhythmias. We summarized data from two Phase I clinical trials performed by non-profit research and academic institutions to evaluating the use of ASM transplantation performed during coronary artery bypass grafting (CABG) and by percutaneous approach as a sole therapy. In both studies patients with postinfarction heart failure and an akinetic or dyskinetic area of the left ventricle, were screened by dobutamine stress echocardiography and included into the studies when no viable myocardium was detected. The skeletal myocardial biopsy specimens were obtained from vastus lateralis. After isolation, the cells were cultured for 3-4 weeks and up to 100 million myoblasts per patients were grown. In surgical study (A), including 10 patients scheduled for CABG, myoblast injection into the akinetic area was done after constriction of the anastomoses during CABG procedure. In percutaneous study (B) myoblast injections were performed in 9 patients via trans-coronary-venous approach under IVUS guidance using TransVascular® catheter system. In study A, sustained ventricular tachycardia (sVT) was observed in two patients in early postoperative period and in other two patients during Holter monitoring at two weeks follow up visit. Amiodarone administration prevented recurrence of sVT episodes and no amiodarone treatment was needed 3 months after ASM transplantation, since all patients remained in Lown class 0 or 1 throughout 4 years follow-up. In study B, patients were treated with prophylactic amiodarone infusion before and during the procedure, except one patient reporting allergic reaction to amiodarone in the past. All patients were free from VT throughout 10-16 days of continuous ecg monitoring except of one patient, not receiving prophylactic amiodarone, who had episodes of sVT and experienced 3 shots from his internal defibrillator at day 8 post procedure. Lown class 0 or was observed throughout 2 years follow-up. The data suggest possible arrhythmogenic effect of ASM transplantation, however

ventricular arrhythmias post procedure seem to be well controlled by amiodarone. Lack of late arrhythmia suggests that possible arrhythmogenic effect of skeletal myoblasts is not related to the differences in electromechanical coupling with host cardiac myocytes.

P1662 Bone marrow-derived cell therapy in dilated cardiomyopathy



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Growing evidence suggests that bone marrow derived stem cells can positively influence the outcome of ischemic heart disease in patients. Animal models have suggested that therapy with bone marrow cells may also improve cardiac function in the setting of dilated cardiomyopathy. Given the limited therapeutic options for refractory dilated cardiomyopathy we decided to perform a phase I clinical trial using bone marrow derived mononuclear cells in patients with functional classes II and IV of the NYHA. In addition, inclusion criteria required EF% (Simpson) < 35%, VO₂ max < 16 kg.ml/min and signed informed consent. Main exclusion criteria were: other serious co-morbidities or other cardiomyopathies, excessive use of alcohol or use of illicit drugs, pregnancy and the presence of ventricular arrhythmias. After enrollment patients were subject to the following exams at baseline, 2 and 6 months after cell therapy: 12 lead ECG and 24 hs holter, echocardiography, chest X-ray, blood biochemistry, BNP, ergoespirometry, MRI and Minnesota Questionnaire. Patients were subject to bone marrow aspiration (80-100 mL) under sedation and local anesthesia and mononuclear cells were obtained after Ficoll gradient centrifugation. A mean of 94 million cells diluted in 20 ml of saline were slowly delivered through catheterization in the coronary arteries (10 ml in LAD, 5 ml in RC, 5 ml in CX). After the procedure patients remained hospitalized for 48 hs. We report the results of the first 10 patients that completed the 6 months follow-up period. No adverse effects related to the procedure were observed, nor were arrhythmias detected after cell delivery. There was a significant improvement in NYHA functional class and quality of life according to the Minnesota Questionnaire at 2 and 6 months ($p < 0.03$ and $p < 0.007$, respectively). There were no statistically significant changes in EF%, EDV or ESV as measured by MRI. Maximal oxygen consumption showed an increasing trend although not reaching significance, but both exercise distance and duration showed a significant increase both at 2 and 6 months. BNP levels were not significantly altered. When observed individually, 4 of the 10 patients showed an increase in EF% by MRI $\geq 5\%$, 4 did not change EF% and 2 decreased EF% by $> 5\%$. We conclude that cell therapy with bone marrow derived cells is safe and may bring benefits to some patients, thus justifying further studies in larger randomized trials.

P1663 Improvement of cardiomyocyte function after transplantation of autologous bone marrow mesenchymal stem cells in patients with non-acute ischemic heart disease



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Objective: Human adult bone marrow contains both hematopoietic stem cells and nonhematopoietic (mesenchymal) stem cells (MSCs). The effectiveness of intracoronary delivery of autologous mesenchymal stem cells in patients with non-acute ischemic heart disease still remains unclear.

Methods: A culture of mesenchymal stem cells was initiated from bone marrow mononuclear cells (BMMs). MSCs were isolated and cultured with in vitro cell culture technique. The phenotypes of MSCs were identified by flow cytometry and immunohistochemistry. Sixty-nine patients with non-acute ischemic heart disease were randomly divided into intracoronary injection of MSCs ($n = 18$), bone marrow mononuclear cells ($n = 38$), and control ($n = 13$; only contrast medium during coronary angiography) groups. Serial positron emissive tomography (PET), SPECT, cardiac echo study were done at the designed time intervals until 12 months after transplantation of MSC or injection of bone marrow mononuclear cells.

Results: We observed clinical improvement in all of 18 patients (patients with intracoronary injection of MSCs), and all of 38 patients (patients with intracoronary injection of bone marrow mononuclear cells). A significant reduction in the number of angina episodes and nitroglycerin consumption was noted. Stabilization in clinical and PET data was observed after 9- months follow-up. SPECT study revealed significant improvements in the previously non- or hypoperfused myocardium. PET scanning demonstrated improvement in myocardial viability and perfusion in patients after 6-9 months follow-up. Echocardiography revealed dimension of end-diastolic and end-systolic volume of LV and augmentation of global LV ejection fraction in patients with previously dilated LV. Twenty-four-hour electrocardiographic monitoring demonstrated no arrhythmias occurred at 12-months follow-up.

Conclusions: The transplantation of BMMs and MSCs might improve the cardiac function and it is safe and feasible with no deaths or malignant arrhythmias.

P1664 Efficacy of therapeutic neovascularization for critical limb ischemia: what is the best way to confirm new blood vessel formation?



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Background: Recent reports of early phase clinical trials indicate significant efficacy of therapeutic neovascularization for critical limb ischemia (CLI). However, feasible, sensitive and reproducible evaluation of limb blood flow has never been established. We have been conducting a clinical trial regarding transplantation of autologous CD34 positive cells in patients with CLI and have started systematic and functional evaluation of leg ischemia in our vascular laboratory. The purpose of this study was to investigate what is the best way to assess severity of CLI and efficacy of the therapeutic neovascularization.

Methods: Study subjects were 14 patients with CLI (4 patients with peripheral arterial disease (PAD) and 10 patients with Burger disease), who underwent transplantation of autologous CD34 positive cells. We assessed pain rating scale, walking distance by treadmill, ankle brachial pressure index (ABPI), toe brachial pressure index (TBPI), skin perfusion pressure (SPP) using laser Doppler system (Laser Dopp PV2000, Vasamedics), transcutaneous tissue oxygen pressure (TcPO₂), and X-ray angiogram at baseline and 12 weeks after the treatment.

Results: Ischemic leg pain and skin ulcer were completely healed except in one patient, and maximum walking distance was significantly improved following the cell therapy (baseline, 461 ± 103 m; 12w, 771 ± 102 m, $p = 0.003$). ABPI did not change significantly (baseline, 0.93 ± 0.08 ; 12w, 0.96 ± 0.08 , $p = 0.250$), as it may underestimate the severity of limb ischemia because of severe medial calcification in PAD or obstruction in the more distal vessels in foot in Burger disease. Although it was impossible to evaluate TBPI in 6 of 14 patients because of presence of toe ulcer or undetectable pulse wave (too low toe pressure), TBPI significantly improved in the remaining patients (baseline, 0.23 ± 0.06 ; 12w, 0.43 ± 0.09 , $p = 0.020$). SPP and TcPO₂ could be assessed in all patients and showed significant improvement from baseline to 12 week follow-up (SPP baseline, 12 ± 2 mmHg; 12w, 21 ± 3 mmHg, $p = 0.004$; TcPO₂ baseline 19 ± 5 mmHg; 12w 44 ± 6 mmHg, $p < 0.0005$). In two patients with Burger disease, reconstitution of distal portion of peripheral arteries was observed on X-ray angiogram, although no significant improvement was seen in the other patients.

Conclusion: Our preliminary results suggest that CD34 positive cell transplantation may mainly contribute to regeneration of microvessels which are angiographically invisible. SPP and TcPO₂ which are to assess microcirculatory perfusion may be useful for feasible and sensitive evaluation of therapeutic neovascularization.

P1665 Improvement of heart function in chronic coronary heart disease with chronic myocardial infarction: controlled study with intracoronary autologous mononuclear bone marrow cell transplantation



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Introduction: Remodeling of the left ventricle (LV) after myocardial infarction (MI) represents a major cause of infarct-related heart failure and death. After acute myocardial infarction transplantation of bone marrow cells (BMCs) improve cardiac function. We investigated cardiac performance of intracoronary transplantation of autologous BMCs in patients with chronic ischemic heart disease, suffered from transmural myocardial infarction.

Methods and Results: We treated 35 consecutive patients (48 ± 13 years) with chronic myocardial infarction (6 months to $8 \frac{1}{2}$ years old) by intracoronary transplantation of autologous bone marrow mononuclear cells (BMCs) and compared them with a consecutive enrolled representative control group ($n = 20$, 52 ± 10 years). A myocardial infarction had been treated acutely with percutaneous transluminal coronary angioplasty and most of the patients needed stent implantation. Bone marrow was harvested from the hip (~ 80 ml). The median number of mononuclear cells harvested after overnight culture was 102 million. After 3 months in the transplantation group, infarct size was reduced by 28%, and global left ventricular ejection fraction ($+13\%$) as well as infarction wall movement velocity ($+48\%$) increased significantly ($p < 0.05$), while in the randomized control group no significant changes were observed during 3 months follow-up in infarct size (27 ± 9 to $26 \pm 9\%$), in left ventricular ejection fraction (51 ± 10 to $52 \pm 10\%$) and in wall movement velocity of infarcted area (1.88 ± 0.76 to 1.91 ± 0.79 cm/s). PTCA alone had no effect on left ventricular function in this chronic coronary patients. After bone marrow cell transplantation, there was an improvement of maximum oxygen uptake (VO₂max, $+12\%$) and of regional ¹⁸F-Fluor-Desoxy-Glucose (FDG) uptake (PET) into infarcted tissue ($+14\%$).

Conclusions: These results demonstrate that regeneration of infarcted and chronically avital tissue can be realized in humans by selective intracoronary bone

marrow mononuclear cell transplantation. This regeneration is most probably due to neogenesis of cardiac tissue, of both myocytes and of coronary blood vessels.

P1666 In-vivo echocardiographic imaging of transplanted human adult stem cells in the myocardium labelled with clinically applicable CliniMACS nano-particles



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Objectives: Intra-myocardial transplantation of bone marrow derived cells is currently under clinical evaluation as a therapy of heart failure. A major limitation of all clinical studies dealing with myocardial cell engraftment is the inability to track the fate of the transplanted cells. We present a clinically applicable technique using transesophageal echocardiography of CliniMACS[®] - nano-particle labelled transplanted CD-133+ cells in ischemic hearts.

Methods and Results: CD133+ cells were isolated from human bone marrow by CliniMACS[®] magnetic bead selection. Positive cells (5 x 10⁶ cells) were transplanted into porcine ischemic myocardium (n = 6). Control animals (n = 5) received medium injection. TEE was performed to demonstrate the distribution of the cells during and 8 weeks after the procedure. Accumulations of labelled CD133+ cells of adjacent injections in the myocardium were discriminatively identified by TEE.

Conclusions: TEE is an elegant method for real-time documentation of successful transplantation and cell colony localization of magnetically labelled CD133+ cells in the ischemic myocardium. Our method should be of special interest for TEE-guided trans-catheter injection of cells.

P1667 Mobilization of EPC with high dose statins after AMI



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Background: statins improve lipid profile and event free-survival in primary and secondary prevention. Recent data suggest a potential favorable effect on left ventricular function in patients with post-ischemic and non-ischemic heart failure. Moreover statins are known to mobilize from bone marrow Endothelial Progenitor Cells (EPC), which could contribute to myocardial regeneration. Despite statin therapy is currently recommended after acute myocardial infarction the starting point, the most efficient dose and the effect on left ventricular remodeling are currently poorly understood. Aim of our study: comparing the effect on mobilization of EPC and left ventricular function of an early and high dose vs a late and low dose atorvastatin therapy.

Methods: 24 (of 40 pts planned) STEMI patients undergone primary PCI were randomly assigned to receive, in addition to conventional therapy, Atorvastatin 80 mg from the admission (Group A) or Atorvastatin 20 mg (Group B) from the day of the discharge. CD 34+/KDR+ cell count by flow cytometry and LV function by Echocardiography was measured at discharge and at 4 month FU.

Results: EPC count was similar in group A and B at discharge (7.92 [2.64-42.92] cells/ml vs 11.26 [4.06-16.67] cells/ml), while patients enrolled in the Group A showed higher levels of EPC at 4 months compare to patients in the Group B (5.76 [0.8-7.11] vs 1.20 [0.18-10.34]). LV function was not correlated with EPC count in both Groups.

Conclusion: These early findings suggest that an aggressive approach with statins at high dose could maintain persistently high levels of circulating EPC. However considering the recently well-described favorable effect of high EPC levels on the recurrence of MACE an aggressive approach with Atorvastatin 80 mg from the admission could be beneficial even for its mobilizing effect on EPC. Further studies on larger numbers are warranted to establish whether EPC mobilization translates in a better outcome.

P1668 6-month and 12-month follow-up results on safety: autologous bone marrow mononuclear cells implantation in patients with acute myocardial infarction



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Background: The purpose of this prospective, randomized, controlled study was to investigate the safety of autologous bone marrow mononuclear cell (BM-MNCs) transplantation by intracoronary infusion in patients with acute myocardial infarction (AMI) during 6-month and 12-month follow-up.

Methods and Results: 184 patients admitted within 7 days after the onset of first AMI were randomly allocated to receive intracoronary autologous BM-MNCs (n=92) or sodium chloride concluding heparin (controls, n=92) via microtubular. In the process of the intracoronary infusion of BM-MNCs, the complications should be recorded, which were aberration reflect (including of pale, syncope, nausea, hypotension and shock), chest pain, heart failure or arrhythmias (including of

bradycardia, sinus arrest or atrial ventricular block or ventricular fibrillation), hypotension, embolism etc. Body temperature, blood pressure and heart rates should be monitored during the first week after transplantation. Holter and coronary arteriography were performed at the designed time points. Main heart accidents, restenosis and tumor were recorded within 12-month follow-up. And the end point was death. All patients were followed up within 14.5±8.1 months. There were total 26 cases with complications during the intracoronary infusion of BM-MNCs. The incidence of complications was 8.7% (8/92) in bone marrow puncturation, 3.3% (3/92) in cell transplantation, 4.3% (4/92) in ambo-operation, 3.5% (3/85) in 3-month follow-up and 11.7% (8/68) in 6 to 30-month follow-up. There was no case with death, tumor embolism or malignant arrhythmias in all patients.

Conclusions: In patients with AMI, intracoronary infusion of BM-MNCs is feasible and safe in long term follow-up.

P1669 Effect of the autologous transplantation of endothelial progenitor cells after acute myocardial infarction



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Recent experimental and clinical studies suggested that intracoronary infusion of either circulating endothelial (EPC) or bone marrow-derived (BMC) progenitor cells may contribute to regeneration of infarcted myocardium after acute myocardial infarction (AMI). In this study, we aimed to evaluate the beneficial effect of intracoronary infusion of EPC after AMI.

Methods: After successfully percutaneous coronary intervention (PCI) for anterior AMI, 21 patients were eligible for EPC therapy. Eleven of them accepted the EPC, but 10 patients were not, and these patients constituted the control group (CG). Both group received optimum medical therapy, but study group received intracoronary infusion of EPC, 5 days after PCI. All patients were evaluated by Doppler echocardiography, myocardial gated scintigraphy, rhythm analysis at post PCI, third and sixth months, and control angiography was performed at sixth month. Image analysis were done by two investigators blinded for treatment assignment. Sixth month control was completed for 17 patients. Comparing the EPC and CG, baseline left ventricular ejection fraction (LVEF) was 43.1±6.9 vs 46.3±7.8 respectively (p>0.05). Third month LVEF increased by 17.8±5.2% in the EPC and 3.3±13.6% in the CG (p<0.05). Comparing the baseline and sixth month, LVEF increased by 19.1±3.1% in the EPC and -4.0±18.4% in the CG (p<0.05). Baseline, third and sixth month infarcted area on scintigraphy image were 19±18%, 10±11%, 13±13% in the EPC and 27±21%, 25±18%, 26±19% in the CG (p=0.48, p=0.21, p=0.04) respectively. Decrease in infarct size between baseline and third month was 54% and -3% in EPC and CG respectively (p=0.001). Decrease in infarct size between baseline and sixth month was 28% and -64% in EPC and CG respectively. EPC transfer did not increase the risk of clinical events, instent restenosis or arrhythmia.

Conclusion: Intracoronary infusion of EPC after AMI beneficially effects post-MI remodeling process and improves left ventricular systolic function.

P1670 Intramyocardial bone marrow stem cells transplantation improves LV function in non-ischemic dilated cardiomyopathy, but does it last?



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Background - A study on safety, feasibility and efficacy of transthoracic intramyocardial mononuclear autologous bone marrow stem cells transplantation for improvement of LV function in end-stage non-ischemic dilated cardiomyopathy (NIDC) is being conducted. This paper reports results after 8 months follow-up.

Method - From Dec/04 to Jun/05, 6 patients (pts) (2 fem), age 42.3±14.1 years, NYHA Class III/IV and left ventricular ejection fraction (LVEF) <35% were enrolled. All pts underwent clinical, echocardiography (ECO) and nuclear magnetic resonance (NMR) assessment. Cells were collected from the iliac bone, isolated, washed and suspended, resulting in a mean of 9.6±2.6 x 10⁷ (1.5±0.7% CD34+) cells in 5 ml saline. These were injected, through a small 5-6 cm left thoracotomy, at 20 points of the ±free left ventricular wall with a 21F Butterfly needle. Pts were followed up to 8 months.

Results: There were no immediate major complications or mortality. Seven months post-op, one patient died from sepsis related to knee infection. The baseline x 2 months x 8 months follow-up results were: NYHA Functional Class = IV-2, III-4 to I-5, II-1 and I-2, II-3 pts, respectively. Quality of life evaluated by Living with Heart Failure Questionnaire (mean±SD) = 65.4±7.6 x 24.8±18.6 x 23.6±18.3 points (p=0.02; p<0.01, respectively). Six-Minute Walk Test = 323.5±79.8 x 362.2±82.2 x 435.2±47.6 m (p=0.45; p=0.12). ECO: LVEF = 22.9±4.1 x 31.7±11.2 x 23.0±7% (p=0.11; 0.97); LV short'n fract = 11.0±2.0 x 15.84±5.8 x 11.08±3.5% (p=0.11; p=0.96); end diastolic volume (EDV) = 250.5±107.6 x 200.0±73.1 x 207.8±68.2 ml (p=0.13; p=0.26); end systolic volume (ESV) = 250.5±107.6 x 143.0±74.4 x 163.0±65.9 ml (p=0.11; p=0.29). NMR: LVEF = 21.8±17.6 x 26.5±17.7 x 19.6±11.4% (p=0.02; p=0.66); EDV = 467.6±218.8 x 454.6±251.0 x 498.4±249.1 ml (p=0.23; p=0.23); ESV = 391.8±236.3 x 367.6±250.8 x 419.4±251.8 ml (p=0.06; p=0.2); stroke volume = 75.6±34.5 x 87.0±13.6 x 78.8±25.1 ml (p=0.24; p=0.84).

Conclusions: This study suggests that transthoracic intramyocardial bone marrow stem cell transplantation is feasible and safe through a minithoracotomy. There were early improvements on symptoms, quality of life and LV performance. Medium-term (8 months) evaluation, however, revealed deterioration of LV function near to pre-op levels, although maintaining improved functional class.

P1671 Percutaneous transvenous transplantation of autologous myoblasts in the treatment of postinfarction heart failure: late follow-up of the POZNAN trial

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Background: Autologous skeletal myoblast (ASM) transplantation into the area of postinfarction left ventricular injury is suggested to result in increased contractility of injured segments.

Objectives: A phase I clinical trial to evaluate the feasibility and safety of ASM transplantation performed with percutaneous trans- coronary veins approach in patients with postinfarction left ventricular dysfunction has been established. The procedures were performed using a catheter system enabling intra-myocardial injections from the lumen of cardiac veins under intravascular ultrasound guidance.

Methods: Patients (n=10) with the presence of an akinetic of dyskinetic postinfarction injury with no viable myocardium; heart failure NYHA class 2 or 3 were included. Skeletal myoblasts were obtained from a biopsy specimen and grown in cell culture. Patients were treated with prophylactic amiodarone infusion before and during the procedure, except one patient on ICD.

Results: In one patients the procedure was not performed due to inability of appropriate coronary sinus catheter positioning across the venous valve. ASM transplantations were performed uneventfully in nine patients using TransAccess[®] catheter system. In 5 patients anterior interventricular vein and in 4 patients the middle cardiac vein was used to access the myocardium. The injections were performed in 2-4 channels 1.5-4.5 cm deep within the myocardial injured area, delivering up to 100 million cells in 0.8 - 2.5 ml of saline. Patients were free from ventricular arrhythmia throughout 10-16 days, except of one patient, not receiving prophylactic amiodarone, who had episodes of ventricular tachycardia and experienced 3 shots from his ICD at day 8 post procedure. During 6 months follow-up NYHA class improved in all patients by 1-2 classes and ejection fraction increased 3-8 percent in 6 out of 9 cases. This effect maintained throughout 2 years follow-up and no important ventricular arrhythmia were noted.

Conclusion: Feasibility and procedural safety of myoblast transplantation performed with trans-cardiac vein approach using Trans Access[®] catheter system is shown. Lack of late arrhythmia suggests that possible arrhythmogenic effect of skeletal myoblasts is not related to the differences in electromechanical coupling with host cardiac myocytes. Phase two trial is needed to evaluate the efficacy of this method.

P1672 Meta-analysis of randomized control trials using adult haemopoietic stem cells in the setting of acute myocardial infarction

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Aim: Cell-based therapy for acute myocardial infarction(AMI) has used various approaches with regard to cell type and delivery method. Most randomized control trials(RCTs) have utilized haemopoietic stem cells(HSC). It is unclear from individual trials which approach is optimal and if clinically significant improvements in ejection fraction(EF) are attainable. We therefore performed a meta-analysis. **METHODS:** RCTs were identified via MEDLINE and abstract publications. Trials needed at least 20 patients with post-AMI EF data (mean±SD) recorded before therapy and at 4-6 months. Results were pooled using the Cohen method.

Results: Six trials, with a total of 494 patients, met the specified criteria. EF was measured by MRI in 3 trials, echocardiography in 2 and ventriculography in one. Five trials used intracoronary autologous mononuclear bone marrow cells(mBMC), and one used endogenous mobilization of HSC via subcutaneous granulocyte colony-stimulating factor(G-CSF). Baseline EF of patients were well matched between intervention and control groups, and relatively well preserved. Change in EF (%) with HSC are shown in Fig. 1. Mean weighted difference in EF (%) of control groups in all trials and in mBMC trials was -0.1 (-1.8 to 1.6) and 1.6 (-0.9 to 4.2) respectively. Statistical differences were observed via z-test between intervention and control groups for all trials (p<0.001) as well as the sub-category of 5 trials involving mBMC (p=0.047). No statistical significance was observed when results for the intervention group of mBMC therapy were compared to G-CSF (p=0.094).

Conclusion: This meta-analysis shows, that in present RCTs, HSC-based therapy post-AMI results in a significant improvement in EF. There appeared to be no

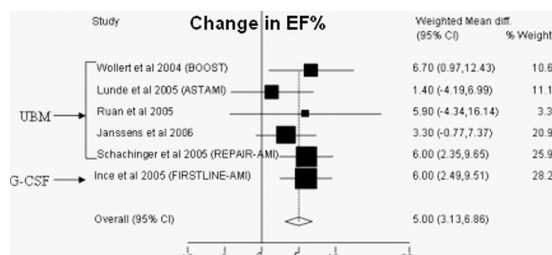


Fig. 1. Change in LVEF(%) with active treatment

added benefit of intracoronary mBMC administration over subcutaneous G-CSF treatment alone.

P1673 Autologous bone marrow mononuclear cells transplantation can not improve cardiac function in patients with idiopathic dilated cardiomyopathy

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Background: The aim of this study is to identify short-term result of cell transplantation in idiopathic dilated cardiomyopathy (IDC) patients who were treated by intracoronary transplantation of autologous mononuclear bone marrow cells (BMCs) in addition to standard therapy.

Method Based on given standard therapy, eighteen patients with idiopathic dilated cardiomyopathy were enrolled and divided into transplantation group and control group. The clinical characteristics of two groups were comparable. Among these patients, 10 patients were performed percutaneous coronary autologous BMCs transplantation. Blood routine test, hepatic function, renal function, glucose, triglyceride (TG), cholesterol, low density cholesterol (LDL), high density cholesterol (HDL), uric acid(UA) and high sensitive C-reactive protein (hsCRP) were measured at the time point of pre-operation and some time after transplantation. All patients were monitored under ultrasonic cardiography, Holter, six-minute-walk test and magnetic resonance imaging over a period of at least 6 months. Annual hospital days were recorded during two-year follow-up.

Results: Blood routine test, hepatic function, renal function, glucose, TG, cholesterol, LDL, HDL, UA and hsCRP had no significant differences among 48 hours, 3 months and 6 months after transplantation compared with control and pre-transplantation (P>0.05). Six-minute-walk distance elevated significantly six months after BMCs transplantation compared with control and pre-transplantation (494.3m ±62.8m vs 307.2±75.0m, 321.5m ±63.7m, P0.05). Myocardium lesion area measured by (MRI) seemed decrease in transplantation group compared with that of control and pre-operation (4.96cm²±0.47cm² vs 5.12cm²±0.54cm², 5.02cm²±0.39cm², P>0.05), but there was no significance. None of proarrhythmias and side effects had been observed around transplantation and 2 years follow-up. There was no significant difference in survival between two groups in 2 years follow-up. Interestingly, annual hospital day in BMCs transplantation patients was significantly shorter than that in control group (30.2d ±11.2d vs 43.6d ±9.8d, P<0.05).

Conclusion: Autologous bone marrow mononuclear cells transplantation can prolong six-minute-walk, decrease re-hospitalization rate, elevate exercise ability and help to improve cardiac function in patients with IDC. In addition, it was demonstrated that cell transplantation is safe.

P1674 Recombinant human granulocyte-colony stimulating factor (G-CSF) and intracoronary CD133 cell infusion in 'no-option' patients with end stage chronic refractory ischemic heart disease

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G-CSF is a novel therapy for ischaemic heart disease patients (IHDPs) and may promote angiogenesis via stem cell or cytokine-related pathways. However, the safety and efficacy of G-CSF, in acute or chronic IHDPs (CIHDPs), is unclear. **Aims:** To assess the safety and efficacy of G-CSF in 20 CIHDPs.

Methods: After baseline cardiac assessment (CA) [Seattle-angina-questionnaire, exercise stress test (EST), persantin-sestamibi and dobutamine-echocardiographic imaging], stable 'no-option' CIHDPs receive open-label G-CSF commencing at 10µg/kg for 5 days, with an EST on days 4 and 6 (to facilitate myocardial cytokine generation and stem cell trafficking). After 3 months, CA and the same regimen of G-CSF and ESTs is repeated, but in addition, leucopheresis and a randomized double-blinded intracoronary-infusion of CD133+ or unselected cells is performed. Final CA is 3 months thereafter.

Results: Eighteen male (2 female) CIHDPs (mean age 62) were enrolled. With

the trial virtually complete, 8 events have fulfilled pre-specified 'adverse event' criteria: 4 ischaemic (troponin-I+) episodes (all non-Q-wave events), 2 episodes of transient thrombocytopenia (1 profound, but both without sequelae), 1 of gout and 1 unscheduled hospitalisation for exhaustion. Troponin-I was positive on 9 further occasions (all CK-MB negative), however, at these instances angina was identical to baseline. Intracoronary cell infusion was consistently uneventful. There were significant improvements in angina, nitrate use and EST performance (all $p < 0.01$), with analysis of imaging data imminent.

Conclusions: Administering G-CSF to CIHDPs warrants careful monitoring, but improves angina, although troponin-I+ events are frequent. Whether G-CSF exacerbates background ischaemia in CIHDPs is unknown.

P1675

Combined cytokine therapy (G-CSF and GM-CSF) in acute myocardial infarction stimulates monocyte-derived pro-angiogenic cells and improves myocardial perfusion



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Aims: Mobilization of endothelial progenitor cells has been suggested to contribute to neo-vascularization of ischemic organs. Aim of this study, on bone marrow stem cells (BMC) mobilization induced by a combined cytokine therapy (G-CSF and GM-CSF) in patients (pts) with acute myocardial infarction (AMI), was to verify feasibility, safety and clinical effects of this therapy and to investigate whether this treatment induced a population of circulating KDR+ endothelial precursors.

Methods and results: Eight male pts (median age: 50.5 years) treated with a primary PTCA were enrolled. The mobilization regimen consisted of G-CSF 5 $\mu\text{g/kg/12h}$ and GM-CSF 2.5 $\mu\text{g/kg/24h}$. During hospital stay all pts showed increased values of WBC and circulating CD34+ following cytokine administration and no major adverse events occurred. KDR+ cells significantly increased in AMI pts treated with G-CSF and GM-CSF, in respect to untreated patients. The increase of KDR+ cells was sustained by CD14+ cells rather than by CD34+ or CD133+ cells. KDR+CD14+ cells were also obtained in vitro by culturing mononuclear cells from healthy donors in a rotary microgravity system in the presence of the combination of G-CSF and GM-CSF but not in the presence of the individual growth factors. This cell population co-expressed haematopoietic (CD45, CD14) and endothelial markers (CD31, CD105, VE-cadherin), expressed several genes related to angiogenesis and endothelial cell survival, stimulated the organization of human microvascular endothelial cell in tubular structures on Matrigel and integrated in these structures. In vivo treated but not untreated monocytes, stimulated human microvascular endothelial cells to form functional vessels in the Matrigel-based angiogenic assay in SCID mice. Six-months follow-up clinical results: target lesion revascularization rate was 12.5%, target vessel revascularization rate was 37.5%, angiographic mean ejection fraction increased from 49.8 $\pm$ 11.9 to 55.4 $\pm$ 8.7 (p =NS), mean coronary flow reserve from 1.63 $\pm$ 0.42 to 2.5 $\pm$ 0.4 (p =0.001), mean Thallium uptake raised from 55.56 $\pm$ 16.42% to 67.56 $\pm$ 13.66% (p =0.01), and normally perfused segments from 16% to 52% (p =0.01). Twelve-months follow up results: no further clinical events occurred and all patients were free of symptoms.

Conclusion: Cytokine-induced BMC mobilization is feasible in AMI pts. The combination of G-CSF and GM-CSF induced a KDR+CD14+ cell population with potential pro-angiogenic properties. Improvements of myocardial perfusion could be expected after PTCA associated with G-CSF and GM-CSF induced BMC-mobilization.

P1676

Autologous bone marrow stem cell transplant after myocardial infarction. In-hospital and long-term follow-up results of the randomized argentina trial (STAR AMI)



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Purpose: Evaluate the effect, of intracoronary implantation of bone marrow stem cells (BMSC), after acute myocardial infarction (AMI) in left ventricular ejection fraction (LVEF).

Methods: From February 2004 to September 2005, 34 patients treated with primary PCI after AMI, were randomized to intracoronary injection of BMSC or control. The BMSC were injected between the 4th and 6 th days after primary PCI. Patients with cardiogenic shock and older than 75 years old, were excluded. The primary end point was to evaluate the mean change in LVEF by angiography at baseline and 4 month follow up between BMSC and control groups.

Results: Baseline demographic, clinical and angiographic characteristics were similar in both groups. However, patients in BMSC group had a significant lower baseline LVEF than control group ($p=0.005$). Follow up angiography was performed in 88% of the patients (30/34). LVFE at follow up, in both groups were similar, ($p=0.68$). However, BMSC group had a significant increase of LVEF compared to baseline (44.5 $\pm$ 6.2% to 55.9 $\pm$ 12% $p=0.002$), whereas control group

showed no significant differences compared with baseline (51.8 $\pm$ 5.5% to 54.8 $\pm$ 15.7% $p=0.48$) meaning an increase of 25.8% and 5.8% in BMSC and control group respectively. Three pts in control versus four in BMSC group had restenosis at follow up. No ventricular arrhythmias were detected during the follow-up. **Conclusion:** In this randomized trial, intracoronary injection of BMSC after AMI, resulted in a significant improvement of LVEF.

P1677

Autologous Bone Marrow Mononuclear Cell (ABMMC) transplantation labeled with Tc99m-HMPAO following acute myocardial infarction: engraftment evaluation according to different delivery techniques



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Purpose: Dynamic behavior of transplanted ABMMC is probably a crucial determinant of its beneficial effects. We aimed to indirectly evaluate cell engraftment of labeled cells and its correlation with two different delivery techniques and with Magnetic Resonance (MRI) data.

Methods: Up to 5 days after ST Acute Myocardial Infarction 40 pts were randomly assigned to Intracoronary group (ICG - N=20) or Intravenous Retrograde Delivery group (IVRG - N=10) of ABMMC vs control group (CG - N=10). Bone Marrow was harvested from iliac crest. ABMMC were selected by Ficoll gradient, diluted in 10cc saline and injected through IC or IVR approach in treated groups. Twelve pts from IC and 5 from IVR techniques received Tc99m-HMPAO Radio-labelled cells. Early capitation (EC) images were obtained 3.58 $\pm$ 1h in ICG and 3.8 $\pm$ 1.3h in IVRG; late capitation (LC) images were obtained 21.16 $\pm$ 4h in ICG and 26.6 $\pm$ 2.4h in IVRG after injection procedure. %EC, %LC and Washout/hour $\{[(\%EC - \%LC)/\%EC]/(\text{Time LC} - \text{Time EC})\}$ were calculated. MRI was performed to evaluate microcirculation obstruction and AMI transmural (MIT) before transplant.

Results: There was no difference in demographic among groups. %EC; %LC; washout/hour and times to EC and LC are shown in table 1. Late enhancement > 75% by MRI was present in 75% of ICG and 80% of IVRG (p = ns). Microcirculation obstruction pattern was present in 50% of ICG and 60% of IVRG (p = ns). There was no difference on %EC, %LC and washout/hour regarding presence or absence of microcirculation obstruction (11.4 $\pm$ 8.4 vs 14 $\pm$ 8% $\pm$ 8; 7.7 $\pm$ 7 vs 8.7 $\pm$ 6 and 2 $\pm$ 1 vs 2 $\pm$ 0.8, respectively) or transmural > 75% (11 $\pm$ 7 vs 18 $\pm$ 9; 7 $\pm$ 6 vs 13 $\pm$ 7 and 2 $\pm$ 1 vs 1.8 $\pm$ 0.7).

	ICG	IVRG	p
%EC	16 $\pm$ 7	4.2 $\pm$ 1.2	<0.001
%LC	10 $\pm$ 6	3 $\pm$ 1.1	0.002
Time to EC	3.6 $\pm$ 1	3.8 $\pm$ 1.3	0.75
Time to LC	21 $\pm$ 4	26.6 $\pm$ 2.4	0.005
Washout/hour	2.2 $\pm$ 0.9	1.24 $\pm$ 0.65	0.03

Conclusions: Engraftment of autologous bone marrow mononuclear cells was higher in the intracoronary delivery than in the retrograde intravenous approach. However, these results seem to be independent of myocardial infarction transmural extension or microcirculation obstruction.

P1678

Autologous bone-marrow stem cell mobilization induced by G-CSF after sub-acute ST segment elevation myocardial infarction undergoing late revascularisation



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Purpose: This investigator driven, prospective, randomized, double-blinded, placebo-controlled Phase II study compares the effects of G-CSF on the improvement of myocardial function in patients undergoing delayed percutaneous coronary intervention (PCI) for ST segment elevation myocardial infarction (STEMI).

Methods: Forty-four patients with late revascularised sub-acute STEMI (mean angina to PCI interval 41 $\pm$ 49 hours) were treated either with G-CSF (10 $\mu\text{g/kg/d}$), or placebo over 5 days after successful PCI. Mobilized stem cell populations were characterized using flow cytometry. Safety parameters were monitored up to 12 months including 6-months angiography. Myocardial function and perfusion was assessed by magnetic resonance imaging from baseline to 3 months after PCI.

Findings: G-CSF treatment resulted in mobilization of endothelial progenitor cell populations (CD34+/CD31+, CD34+/CD133+) and was well tolerated with a similar rate of target lesion revascularisation from in-stent restenosis (G-CSF: 21%, Placebo: 29%). In both groups major adverse cardiovascular events occurred in a comparable frequency. Global myocardial function from baseline to 3 months improved in both groups (Dejection fraction 6.2 $\pm$ 9.0 vs. 5.3 $\pm$ 9.8%). G-CSF was not superior to placebo. G-CSF resulted in significant improvement of myocardial perfusion at baseline and 1 month follow-up.

Interpretation: G-CSF treatment after PCI in sub-acute STEMI is feasible and relatively safe. It results in improved myocardial perfusion of the infarcted area, which may reflect enhanced neovascularisation. However, patients with sub-acute

STEMI do not benefit from G-CSF when PCI was performed late. To evaluate efficiency of G-CSF treatment larger multi-centre trials in patients with rather acute STEMI and early PCI are required.

P1679 Autologous bone marrow cell injection into small coronary arteries may lead to coronary microembolism



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Selective intracoronary delivery of autologous bone marrow cells (BMC), an effective approach for the repair of infarcted myocardium, may impair myocardial microcirculation, as shown in experimental studies. The aim of our study was to evaluate the occurrence of myocardial microembolisation during intracoronary BMC injection in humans.

Our study group consisted of nine patients (seven men, mean age 58.4±8 years) with chronic heart failure (mean LVEF 30.8±11%) due to previous MI. The patients underwent intracoronary BMC administration into 14 coronary arteries supplying regions with perfusion defects shown in Tc-99 SPECT MPS. We determined the defective myocardial perfusion due to coronary microembolism with two separate scintigraphic examinations using intracoronary administration of Tc-99 macroaggregated albumin (MAA). The baseline examination was performed two days before the intracoronary BMC delivery and the second one immediately after the procedure. An additional impairment of the tracer uptake detected by the second MAA examination was considered to be due to myocardial microembolism resulting from the procedure. Beyond demographic, clinical and procedural variables, quantitative estimation of coronary vessel diameter at the site of BMC injection was performed to determine predictors of coronary microembolism.

Compared with the initial findings, MAA scintigraphy, performed after the procedure, showed defective tracer uptake in the 13 myocardial segments of five coronary arteries of five patients. Demographic, clinical and procedural variables did not differ between patients with and without coronary microembolism. However, the mean diameter of coronary vessels supplying myocardial segments with microembolism was significantly smaller than the mean coronary artery diameter supplying territories without this finding [1.62±0.2mm (1.30mm to 1.80mm) vs. 2.35±0.6mm (1.90mm to 3.90mm); p=0.027]. Elevated troponin I and CK-MB levels were observed in one patient with microembolism. However, Tc-99 SPECT MPS, performed six days after the procedure, revealed no additional impairment of myocardial perfusion compared with initial SPECT MPS examination. All of the patients were free of symptoms during entire hospital stay.

Our study revealed that autologous BMC administration into coronary arteries may cause coronary microembolisation when site of BMC injection in coronary vessel is <1.9 mm in diameter. Coronary microembolism may lead to an elevation of cardiac biomarkers. However, this finding is not necessarily associated with impairment of myocardial viability.

P1680 Effects on functional capacity and quality of life by intracoronary injections of autologous mononuclear bone marrow cells in acute myocardial infarction



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Background: Intracoronary injections of autologous mononuclear bone marrow cells (mBMC) in the acute phase of myocardial infarction (MI) may have the potential to improve myocardial function. However, the effect of this treatment on functional capacity and quality of life remains unknown.

Methods: 100 pts with acute anterior wall ST-elevation MI as defined by typical ECG pattern, CK-MB mass >3x upper reference level, and significant anterior wall motion abnormalities on echocardiography (>2 segments), were included in the study. All had PCI with stent on culprit lesion in proximal or mid LAD 2-12 hours after start of symptoms, none had previous Q-wave MI. Pts were randomized to either intracoronary injections of mBMC (mean (SD) cell number 87 (47.7)×10⁶ in LAD 6 (1.3) days after MI (n=50), or control (n=50). Physical capacity assessed by maximum symptom limited cycle ergometer exercise test and

Table 1

	2-3 weeks		6 months		Change*		P
	mBMC	Control	mBMC	Control	mBMC	Control	
Cycle ergometer exercise test							
Peak VO ₂ (ml/kg/min)	20.0 (6.2)	18.8 (6.5)	22.4 (7.2)	20.9 (6.3)	2.8 (4.0)	2.4 (3.5)	0.58
Max load (Watt)	133 (41)	137 (55)	154 (51)	149 (53)	23 (24)	13 (16)	<0.05
Quality of life (SF-36)							
Physical component							
summary	40.9 (11.1)	42.0 (7.4)	47.4 (8.9)	47.7 (9.1)	5.8 (11.2)	6.0 (9.3)	0.66
Mental component							
summary	48.4 (10.9)	48.2 (11.6)	51.2 (10.7)	50.6 (8.8)	1.2 (11.4)	2.1 (11.9)	0.86

*complete pairs, P=ANCOVA for difference in change between groups.

quality of life assessed by the SF-36 health survey, were performed 2-3 weeks and 6 months after acute PCI.

Results: Baseline characteristics of the groups were not different with age 57.4 (9.1) years, 16% females, max CK-MB mass (median) 369 µg/L, and LVEF by SPECT 41.9 (11.0) %.

Conclusion: Compared to the control group, patients randomized to mBMC treatment improved physical capacity measured as maximum work load, but not peak VO₂ in this open-labeled study. There were no differences between groups for change in quality of life.

P1681 Characterization of endothelial progenitor cells: a study of patients with stable coronary artery disease with long term pravastatin treatment



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Purpose: Previous studies have shown that early and outgrowth endothelial progenitor cells (EPCs) can be detected in the peripheral blood. Furthermore, statin therapy can increase EPC mobilization into the peripheral blood. However there are no data concerning the long term effects of statin treatment on this phenomenon. The aim of this study was to investigate whether EPCs can be detected and characterized in patients with at least 4 weeks statin therapy.

Methods: Two groups of patients were matched for sex, age and treatment. The statin (+) group (n=7) included patients with stable coronary artery disease (CAD) treated with pravastatin 40 mg for at least 4 weeks. The statin (-) group (n=7) included patients with stable angina without statin therapy. Mononuclear cells from all patients were assessed for progenitor cell (CD34, CD34/CD144 and CD34/CD117) and endothelial phenotype (VEGF-R2, CD31) by flow cytometry and were cultured to determine the number and the type of EPCs.

Results: Table 1 shows the percent of positive circulating progenitor cells CD34+, CD34+/CD144+ and CD34+/CD117+. There was a significantly higher number of circulating progenitor cells in the statin (+) group. The culture showed that circulating early EPCs were CD146+ and CD45+ and were also significantly higher in the statin (-) group. Surprisingly, circulating outgrowth EPCs were only found in the statin (-) group. Phenotyping of cultured cells showed that cells from outgrowth EPC colonies clearly had an endothelial phenotype CD31+, VEGF-R2+, CD34+ in contrast to cells from early EPC colonies (VEGF-R2low, CD34-, CD45+).

Table 1

Antigens	Statin (+) group	Statin (-) group	p
CD34+	1.3±0.1	0.7±0.1	<0.001
CD34+/CD144+	0.9±0.2	0.1±0.05	<0.001
CD34+/CD117+	0.5±0.2	0.1±0.02	<0.005
CD146+	0.5±0.1	2.1±0.5	<0.001

Conclusions: These results show that, (i) EPCs can be found in the peripheral blood of CAD patients treated up to 4 weeks with 40 mg of pravastatin, (ii) long term statin therapy raises EPC levels by increasing outgrowth EPC population without affecting early population levels and (iii) the phenotype of early EPC is different from that of outgrowth EPCs suggesting that early EPCs are not endothelial but hematopoietic in origin.

P1682 Selective intracoronary infusion of bone marrow-derived progenitor cells in patients with non-ischaemic dilated cardiomyopathy: initial results of the TOPCARE-DCM trial



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Initial clinical pilot trials suggested that intracoronary infusion of bone marrow-derived progenitor cells (BMC) may enhance left ventricular functional recovery in patients with acute myocardial infarction. It is unknown, however, whether such a strategy might also be applicable to patients with non-ischemic dilated cardiomyopathy (DCM). Therefore, we initiated the TOPCARE-DCM trial aiming to regionally improve left ventricular (LV) contractility by selective infusion of BMC into the left anterior descending (LAD) coronary artery of 20 patients with non-ischemic DCM (age 53.4 ± 11.4 years, duration of heart failure 8-173 months, median 72). Intracoronary cell infusion via balloon-occlusion technique for 3 x 3 minutes was well tolerated. A mean cell number of 325 ± 105 million BMC, isolated out of 50 ml bone marrow aspirate was infused. No increase in troponin T level was observed. After 4 months, global LV ejection fraction (by quantitative angiography) significantly increased from 29.0 ± 12.4 to 32.4 ± 12.3% (p<0.01). Improved LV-EF was exclusively due to a significantly decreased extent of hypokinesia in the LAD territory (LV area targeted by cell infusion) from 62.3 ± 20.8 to 56.2 ± 23.9% circumference (p<0.01). The LV endsystolic volumes showed a trend towards reduction after stem cell therapy (from 166 ± 94 to 154 ± 84 ml, p=0.07), whereas the enddiastolic volumes did not change (from 233 ± 96 to 224 ± 87 ml, p=0.37). Serum NT-proANP levels (4653 ± 2830 fmol/ml, n=19) remained unchanged after the first 4 months, but were dramatically reduced one year after stem cell treatment in those 8 patients who as yet completed their 1-year follow-up (2256 ± 1165

fmol/ml, $n=8$, $p<0.05$). Importantly, there was a significant association between the improvement of hypokinesia and the hematopoietic colony forming capacity of the infused BMC ($r = -0.58$, $p<0.01$). There were no cases of death, syncope, newly diagnosed life-threatening arrhythmias, or rehospitalisation for progression of heart failure during 4 months follow-up. Intracoronary infusion of bone marrow-derived progenitor cells is feasible and safe in patients with non-ischemic dilated cardiomyopathy and is associated with significant improvements in regional contractility of the targeted LV area after 4 months.

P1683 One year follow up of heart failure patients surgically implanted with human fetal stem cells in myocardium



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Background: End-stage heart failure (HF) is refractory to current standard medical therapy. Studies suggest autologous stem cell therapy may regenerate cardiomyocytes, stimulate neovascularization, and improve cardiac function and clinical status. Although human fetal-derived stem cells (HFDSCs) have been studied in the treatment of a variety of conditions, no clinical studies have been reported to date on their use in treating HF. We injected human fetal liver stem cells preparation containing: CD34+ cells = $0.89 \pm 0.09\%$; CD45+ cells = $2.33 \pm 0.25\%$; CD34+CD45+ cell fraction $0.82 \pm 0.09\%$; Gly-A+ cells $90.0 \pm 2.54\%$ and CD133+ $0.39 \pm 0.07\%$, >70% of the CD133+ cells co-expressed CD34.

Methods and Results: Direct myocardial transplantation of HFDSCs by open chest surgical procedure was performed in 10 patients with HF. No changes were done in preoperative doses of medications. 2 NYHA class IV patients died at 5 and 8 months. The former provided autopsy, finding positive expression of CD 34, CD 117, Actine smooth muscle, Vimentin, and Myogenin.

The rest of the cohort controls at baseline, 7 months and 1 year respectively show, mean $\pm$ SD: NYHA class: 3.5 ± 0.5 to 2 ± 0.7 to 1.63 ± 0.74 ; %E F: 28.3 ± 4.4 to 35 ± 6.2 to 31.8 ± 5.1 ; LVEDD: $6.67 \text{ cm} \pm 0.64$ to 6.09 ± 0.55 to 6.89 ± 0.73 ; Minnesota Test score: 74.5 ± 22.4 to 14.6 ± 22.72 to 20.7 ± 26.5 ; ETT: $2.35 \text{ Mets} \pm 0.9$ to 5.63 ± 1.3 to 6.14 ± 1.07 ; 6 MWTest: $237 \text{ seconds} \pm 113.1$ to 360 ± 0 to 360 ± 0.0 and 275 meters ± 152 to 467.5 ± 90 to 478.5 ± 67.2 .

None of the tumoral markers searched (PSA free and total, CEA, Alfa-Fetoprotein, CA125, CA19-9, CA 72-4, CA 15-3, CYFRA 21-1) expressed positively at 1 year. From the immunologic profile assessed (C3, C4, Ig A, Ig E, Ig G, Ig M, Antinuclear antibody, Anti-DNA, C Reactive Protein) the only change seen was that 4 patients showed increased IgE. The WBC count of the entire cohort remained within normal range. Neither kidney nor liver dysfunctions nor skin rushes were seen along one year follow up.

Conclusion: 8 out of 10 patients survived at 1 year. The dead were NYHA class IV patients. Although these initial findings suggest direct myocardial implantation of HFDSCs is feasible, safe, improves cardiac function in HF patients at 1 year, and no malignancies or rejection reactions were seen as of this writing, more clinical research and longer follow-up is required to confirm these observations.

P1684 Increase in cardiac function, regional metabolism in the infarcted zone after intracoronary transplantation of autologous bone marrow cells in patients with chronic myocardial infarction



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After myocardial infarction (MI) necrotic cardiomyocytes are irrecoverable and represents a major cause of infarct-related heart failure and death. In experimental infarction in animal models transplantation of bone marrow cells (BMCs) leads to regeneration of infarcted zones due to neovascularization and regeneration of myocardium. Both mechanisms have led to amelioration of cardiac function and perfusion. We assessed the hypothesis that intracoronary transplantation (i.c. TPx) of autologous, mononuclear BMCs may increase perfusion and metabolism in chronic ischemic heart disease after chronic infarcted myocardium in humans.

Methods: 20 patients (age 51 ± 13 year's) received an i.c. transplantation of BMCs more than 5 months to $8\frac{1}{2}$ years after acute transmural MI. Transplantation was performed via the intracoronary administration route using 4-6 fractional infusions parallel to balloon inflation over 2-4 min of 2-5 ml of cell suspension in the open infarct vessel with an average of 102 million mononuclear cells. We conducted [¹⁸F]-FDG-PET and Tc-99m-Tetrafosmin SPECT before and 3 months after BMC transplantation. Myocardial glucose metabolism and perfusion were analyzed, using standardized, individually adjusted regions of interest (ROIs).

Results: The first PET scan demonstrated in all patients extended scars of the left ventricular myocardium. In the second scan three months later the normalized 18F-FDG uptake in the infarcted area had increased from $44 \pm 8\%$ to $52 \pm 12\%$ ($p<0.05$) and the mean number of scar regions decreased from 16 ± 7 to 12 ± 8 regions per patient ($p<0.05$). These results were accompanied by improved

global left ventricular (LV) ejection fraction ($p<0.05$). The perfusion of the infarct remained unchanged.

Conclusions: These results demonstrate that even in long standing myocardial scars an i.c. transplantation of BMCs leads to significant increase in cardiac function, regional metabolism in the infarcted zone as indication for BMC-induced myocardial regeneration and neovascularization. These changes are interpreted as partly revitalization of the infarcted tissue.

P1685 Natural mobilisation of progenitor stem cells into peripheral blood across the spectrum of the acute coronary syndrome



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Background: Adult stem cells can contribute to myocardial regeneration after ischemic injury. Previous studies have shown a marked mobilisation of progenitor stem cells into peripheral blood in patients with ST elevation acute myocardial infarction in comparison with healthy control subjects. The aim of this study was to assess the dynamics and magnitude of the mobilisation of progenitor stem cells into peripheral blood in relation to the degree of necrosis and the inflammatory response across the spectrum of the acute coronary syndrome (ACS).

Methods: Thirty patients with ACS (10 with ST elevation myocardial infarction [STEMI], 10 patients with non-ST elevation myocardial infarction [NSTEMI], and 10 patients with unstable angina [AI]), 10 with stable angina, and 10 healthy control subjects were enrolled. The number of the progenitor stem cells (CD 34+, CD 133+ and CD 117+) was assessed by use of a flow cytometer on admission, daily during the first week, and after 14, 21 and 30 days. Data are expressed as the number of cells per mL of blood (median).

Results: Although, the number of CD34+ (4.06 vs 2.78 vs 1.78 , $p<0.01$), CD133+ (3.86 vs 1.93 vs 1.2 , $p<0.01$) and CD117+ (5.19 vs 2.26 vs 1.81 , $p<0.01$) stem cells in peripheral blood were significantly higher in patients with ACS than in stable angina and healthy subjects, no significant differences were documented, in patients with STEMI, NSTEMI and AI, respectively; neither on admission (CD34: 2.52 vs 2.26 vs 2.08 , $p=0.72$; CD117 2.47 vs 2.5 vs 2.02 , $p=0.97$; CD133 1.94 vs 2.04 vs 1.16 , $p=0.74$), nor the maximal concentration reached during the study (CD34 4.61 vs 3.96 vs 5.67 , $p=0.9$; CD117 5.92 vs 4.89 vs 5.54 , $p=0.76$; CD133 4.35 vs 4.01 vs 3.45 , $p=0.43$). Moreover, though spontaneous mobilisation of progenitor stem cells occurs within the first days from the onset of symptoms, peaking on day 4, and is detectable until 1 month, the correlation between the degree of necrosis (determined by the maximum troponin T levels) and the inflammatory response (determined by the maximum C reactive protein levels) was weak and no significant.

Conclusions: Although mobilisation of progenitor stem cells into peripheral blood occurred across the spectrum of acute coronary syndrome, no correlation with the amount of myocardial damage and the degree of inflammation was found. This data confirms that the natural progenitor stem cell mobilisation response to myocardial damage is not sufficient to prevent left ventricular remodelling as it probably falls short of replacement of necrotic cardiac myocytes.

P1686 Longterm follow-up of improvement of human infarcted heart muscle by intracoronary autologous mononuclear bone marrow cells in chronic coronary artery disease. (IACT-Study)



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Background: Experimental and clinical study suggest that transplantation of autologous bone marrow mononuclear cells fraction has a salutary effect after postinfarcted remodeling in acute myocardial infarction and also in chronic coronary artery disease with regional left ventricular dysfunction. We evaluate the longterm effects on the ventricular remodeling process and the safety of this therapy.

Methods: 15 patients (age 48.6 ± 12.7 years) had a stable chronic artery heart disease and suffered from a transmural infarction (27 ± 31 months) before intracoronary transplantation of autologous bone marrow cells into the infarct-related artery. We compared them with a consecutive enrolled representative control group $n=15$ (age 51.2 ± 14.7 years). Myocardial infarction had been treated acutely with percutaneous transluminal coronary angioplasty and most of the patients needed stent implantation. Bone marrow was harvested from the hip (~ 80 ml) and mononuclear cells were identified. The median number of mononuclear cells harvested after overnight culture was $98 \times$ million. All patients received a standard postinfarcted medication before and after cell therapy. All patients have been re-evaluated 12 month after cell transplantation by coronary angiography, left ventriculography, electrocardiography and 24h Holter-ECG, spiroergometry, laboratory parameters and abdominal sonography.

Results: After 3 and 12 months in the transplantation group, infarct size was reduced by 27% and after 12 month by 29% increased significantly ($p<0.05$). Global left ventricular ejection fraction increase by 14% and after 12 month in total by +15% as well as infarction wall movement velocity by +55% and then after 12 months by 56% increased significantly ($p<0.05$), while in the randomized con-

trol group no significant changes were observed during 3 and after 12 months follow-up in infarct size (26 ± 9 to $25 \pm 9\%$), in left ventricular ejection fraction (53 ± 10 to $52 \pm 10\%$) and in wall movement velocity of infarcted area (1.91 ± 0.79 to 1.93 ± 0.69 cm/s). After bone marrow cell transplantation, there was an improvement of maximum oxygen uptake in the transplantation group (VO₂max, +10% and after 12 month +11%). There was no significant change in the transplantation group in Lown Class in the long term follow up after 3 and 12 months.

Conclusions: These results demonstrate that intracoronary transplantation of BMCs is highly effective, in reduced infarct size, recovered global ejection fraction and wall movement velocity in chronic artery heart disease. These beneficial effects persist for at least 12 month after cell transplantation.

P1687 Transcortical transplantation of progenitor cells for left ventricular dysfunction after healed myocardial infarction: a direct comparison of different cell types (TOPCARE-CHD crossover trial)

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Background: Pilot studies suggest that intracoronary transplantation of bone marrow-derived (BMC) or circulating blood-derived progenitor cells (CPC) may improve left ventricular function after acute myocardial infarction. The effects of cell transplantation in patients with healed myocardial infarction are unknown.

Methods: After an initial pilot trial involving 17 patients, we randomized in a controlled crossover design 75 patients with stable ischemic heart disease with a previous myocardial infarction at least 3 months previously to receive either no cell infusion (n=23), or infusion of CPC (n=24) or BMC (n=28) into the patent coronary artery supplying the most dyskinetic left ventricular area. The patients in the control group were further randomized to receive CPC or BMC and those patients initially receiving BMC or CPC were crossed over to receive CPC or BMC, respectively, at 3 months follow-up.

Results: The absolute increase in left ventricular ejection fraction was significantly greater in patients receiving BMC (+2.9%) as compared with CPC (-0.4%; p=0.003), or the control group (-1.2%; p<0.001). The increase in global cardiac function was related to a significantly enhanced regional contractility in the area targeted by intracoronary infusion of BMC (change in target chord contractility: control -0.06, CPC -0.03, BMC +0.26 SD/chord, p<0.006). The crossover phase of our study revealed that intracoronary infusion of BMC was associated with a significant increase in global and regional left ventricular function regardless whether patients crossed over from control to BMC (delta ejection fraction -1.2% versus 3.1%; p=0.03) or from CPC to BMC (delta ejection fraction -0.4% versus 1.9%; p=0.01).

Conclusions: Intracoronary infusion of progenitor cells is safe and feasible in patients with healed myocardial infarction. Transplantation of BMC is associated with a significant and persistent improvement in left ventricular ejection fraction after 6 months.

P1688 Age-dependent impairment of endothelial progenitor cells is corrected by growth hormone mediated increase of insulin-like growth factor-1

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Ageing is associated with impairment of endothelial progenitor cells (EPC) and increasing risk for atherosclerosis. Insulin-like growth factor-1 (IGF-1) stimulates angiogenesis and has vascular protective properties, but little is known about its effect on age-related EPC dysfunction. We compared EPC number and function in healthy male volunteers (57.4 ± 1.4 years) before and after a ten day treatment with recombinant growth hormone (0.4 mg/day) with that of younger male subjects (27.5 ± 0.9 years). Older subjects had lower IGF-1 levels which were increased by growth hormone treatment (126.0 ± 7.2 ng/ml vs 241.1 ± 13.8 ng/ml; p<0.0001). In older subjects, circulating CD133+/VEGFR-2+ EPC were significantly lower, EPC function was attenuated and EPC telomerase activity was reduced compared with the younger group. Growth hormone treatment in elderly subjects increased circulating EPC, which displayed improved colony forming and migratory capacity, showed enhanced incorporation into tube-like structures, and increased telomerase activity comparable to that of the younger group. IGF-1 stimulated EPC differentiation, migratory capacity and the ability to incorporate into forming vascular networks in vitro via the IGF-1 receptor. IGF-1 increased telomerase activity, expression, phosphorylation and activity of endothelial nitric oxide synthase in EPC in a phosphoinositide-3-kinase/Akt dependent manner. Growth hormone-mediated IGF-1 reverses EPC dysfunction in the elderly and may be a novel therapeutic strategy against vascular disorders with impairment of EPC.

P1689 Telomere dynamics of mononuclear bone marrow cells in patients with heart failure following myocardial infarction

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Unlike in germ cells, replication and ageing of haematopoietic stem cells leads to telomere shortening. The accelerated attrition of telomere length in peripheral white blood cells occurs under the influence of replicative and oxidative stress and predisposes for increased mortality due to infections and cardiovascular disease. Nevertheless, it remains unclear whether oxidative stress primarily leads to telomere erosion of circulating blood leukocytes or directly affects their progenitors in the bone marrow. The goal of our study was to evaluate the intraindividual distribution of telomere length between bone marrow and peripheral white blood cells. Telomere dynamics were evaluated in patients who developed heart failure following myocardial infarction (n=51; mean left ventricular ejection fraction 38%) and young healthy controls (n=10). To distinguish telomeres from the lymphoid or myeloid subpopulations we employed a previously established flow cytometry method using fluorescence in situ hybridization (flow FISH). Mean telomere length (mTL) of both myeloid (r=0.458, p<0.001) and lymphoid (r=0.512, p<0.001) mononuclear bone marrow cells (MBMCs) correlated with age and did not differ from healthy controls after age-correction. Cardiovascular risk factors did not significantly affect mTL of MBMCs (trend for diabetes), although the variation of telomere length distribution of lymphoid bone marrow cells was significantly smaller in diabetic patients as compared to non-diabetics ($14.9\% \pm 1.6$ vs. $19.4\% \pm 4.0$, p<0.001). Surprisingly, telomeres from peripheral blood cells demonstrated significant telomere attrition (-547 ± 610 base pairs) when compared to MBMCs. Peripheral loss of telomere length correlated significantly with an adverse lipid status in patients (p<0.001) as well as in healthy controls (p=0.024). Our results suggest that oxidative stress associated with elevated serum lipids or severe heart disease causes telomere erosion primarily in peripheral blood leukocytes rather than in their progenitors residing in the bone marrow. While heart failure or diabetes had no influence on telomere dynamics of the myeloid population, they affect telomere length distribution of lymphoid bone marrow cells.

e-POSTER SESSION 3

P1690 Evaluation of coronary endothelial function with 13N-ammonia cardiac positron emission tomography in patients with systemic lupus erythematosus and primary antiphospholipid syndrome

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Introduction: Endothelial dysfunction is one of the first markers of coronary artery disease (CAD). Systemic lupus erythematosus (SLE) and primary antiphospholipid syndrome (PAPS) have been recognized as an endotheliopathy model and are associated with CAD. Positron emission tomography (PET) allows the quantification of myocardial blood flow (MBF) in ml g⁻¹ min using 13N-ammonia as a radiotracer. Endothelial function can be evaluated with the endothelium dependant vasodilation index (EDVI) obtained by dividing the MBF during cold pressor testing (CPT) over MBF at rest, the %ΔMBF is considered the change of the percentage of MBF during CPT compared with rest and the myocardial flow reserve (MFR -MBF during stress over MBF at rest-). A reduction in these parameters indicates endothelial dysfunction.

Objectives: The aim of this study was to evaluate the endothelial function in patients with SLE and PAPS using 13N-ammonia PET.

Methods: We studied 11 patients with SLE and 18 patients with PAPS into a three phase (rest-CPT-stress) PET protocol using 20 mCi of 13N-ammonia for each phase. CPT was performed by immersing one hand in 4°C water for 2 minutes, applying the radiotracer at the end of the first minute. The stress test was performed using adenosine infusion for 6 minutes (140 μg kg min) injecting the radiotracer at the end of the third minute. MBF was measured using the polar flow UCLA program in each phase. MFR, EDVI and %ΔMBF were determined. The results obtained were compared with 18 healthy volunteers (HV) using the program SPSS v.10.

Results: Eleven patients (all females) from the SLE group, 18 patients (14 females and 4 males) from the PAPS group and 18 (11 males and 7 females) from the healthy volunteer (HV) group were included. A significant difference was found in the MFR (SLE: 2.437 ± 0.74 and PAPS: 2.67 ± 0.60 vs HV: 3.47 ± 0.85 , p=0.02); in the EDVI (SLE: 1.183 ± 0.23 and PAPS: 1.10 ± 0.03 vs HV: 1.54 ± 0.39 ; p=0.001); and the %ΔMBF (SLE: $18 \pm 22\%$ and PAPS: $15 \pm 18\%$ vs HV: $53 \pm 22\%$, p=0.001).

Conclusion: SLE and PAPS patients have low MFR, EDVI and %ΔMBF values compared to HV. These decreases are due to endothelial dysfunction. 13N-ammonia positron emission tomography is a non-invasive technique that allows the study of endothelial function in this group of patients.

P1691 Motion free images by dual gating of PET listmode acquisitions



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Cardiac and respiratory motion decrease PET image quality by reducing the observed spatial resolution. Whereas cardiac motion has been corrected using ECG gated acquisitions, respiratory motion is still an unsolved issue. In this work we prove the feasibility of dual gated acquisitions in a clinical setup. The resulting images are evaluated to assess the extent of the respiratory motion.

Methods: The ECG and respiratory signals of the patients were recorded synchronized to the listmode acquisition. The listmode events were sorted according to the cardiac and respiratory phases, and the sinograms were reconstructed into corresponding dual gated images. 12 heart scans were acquired with a Siemens Biograph16 PET/CT, the systolic component of the heart cycle was discarded and reconstructions with 4 and 8 respiratory gates were performed. The respiratory motion of the heart in each of the cases was assessed.

Results: Respiratory motion of the heart could be clearly observed on the gated PET images (see Fig 1). The average displacement of the apex between end inspiration and end expiration phases was 7.0 ± 2.1 mm in the craniocaudal direction. Local motion was 5.6 ± 1.0 mm in the inferior wall and 3.3 ± 1.0 mm in the anterior wall, indicating that the heart has an elastic motion due to respiration.

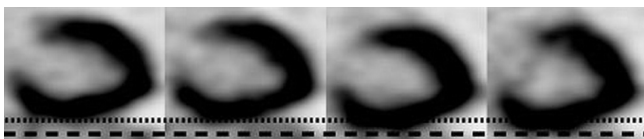


Fig 1. Respiratory motion of the heart.

Conclusions: Dual gated studies were successfully performed with virtually no impact on the clinical workflow. The respiratory motion of the heart was in the same range as the thickness of the normal myocardial wall (7-13 mm) and its correction could improve the observed spatial resolution in myocardial PET. Dual gated acquisitions are particularly promising for hot spot cardiovascular imaging where the targeted structures are likely to be smaller than the motion itself.

P1692 Metabolic management of ischemic heart failure: non-invasive assessment of myocardial perfusion, metabolism and left ventricular function



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Background: Trimetazidine (TMZ) and mildronat represent antianginal drugs shifting myocardial metabolism from fatty acid to glucose oxidation. Previous studies suggested beneficial effects of these drugs in ischemic heart failure.

Methods: 65 patients with heart failure (>6 months after myocardial infarction) and LVEF <40% were randomly assigned to receive for a 6-month period TMZ modified release 35 mg bid (28 patients - T-group) or mildronat 500 mg bid (25 patients - M-group) additionally to standard therapy or usual drug therapy with ACE-inhibitors, b-blockers and diuretics (12 patients- control group). Patients were evaluated at baseline and 6-m with clinical examination, quality of life (MLHF), low dose dobutamine stress-echocardiography (DSE). To assess myocardial perfusion and metabolism at baseline and 6-m 34 patients underwent 99mTc-MIBI SPECT and F18-FDG PET (13 patients T-group, 11-M-group and 10 - control group).

Results: treatment with TMZ and mildronat significantly improved functional status (NYHA and 6-minute walk test) in contrast to control group. Reliable improvement of MLHF and LVEF at rest and peak DSE was found only in T-group. Treatment with TMZ and mildronat resulted in decrease of initially elevated level of glucose metabolism in ischemic segments of left ventricle (T-group 109% [102;120], 101% [97;114] at baseline and 6-m respectively vs M-group 107% [103;112], 97% [89;103]) in contrast to control group (112% [108;127], 119% [107;126]). Treatment with TMZ significantly improved regional contractility assessed by SPECT in hibernated segments of left ventricle in contrast to M-group and control group. Special algorithm was implemented to compare viability results of DSE (any contractility improvement) and radionuclide methods (perfusion/metabolism mismatch). Low sensitivity (50,4%) and negative predictive value (43%) of DSE was found in patients with severe systolic dysfunction and heart failure in comparison with SPECT/PET criteria. At the same time high specificity (85,7%) and positive predictive value (89%) of DSE in detecting hibernated myocardium was confirmed.

Conclusions: Significant functional improvement in patients with ischemic heart failure was observed both in T-group and M-group. PET with F18-FDG showed anti-ischemic action of both drugs in ischemic segments of left ventricle. But significant improvement of regional and global left ventricular function by results of SPECT and DSE was found only with therapy by TMZ. DSE showed low sensitiv-

ity in patients with severe systolic dysfunction and radionuclide viability testing in such patients is recommended.

P1693 Integrated cardiac pet/ct: initial results in patients with ischemic heart disease



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Motivation: Integrated PET/CT imaging devices are a typical domain of oncological imaging. However, with the use of high resolution CT systems, these tomographs offer excellent means towards the often claimed "one-stop-shop" in cardiac imaging. For this purpose, we implemented an acquisition and analysis protocol and evaluated its feasibility.

Methods: Using a combined PET/CT tomograph (Biograph 16), 30 consecutive patients (61 ± 11 y, 25 m) were examined with a low dose CT for attenuation correction and PET N-13 ammonia imaging under resting and adenosine stress conditions. Finally, coronary angiography (CTA) was performed using an iodine based contrast agent. Regional tracer uptake was quantified with a volumetric sampling algorithm providing absolute areas for all polar map elements. CTA images were evaluated using maximum intensity projection and multiplanar reconstruction techniques for degree of stenosis and to assess artefacts. Quantitative analysis of cardiac PET is usually based on standard vascular territories. But coronary anatomy may vary significantly among individuals. Thus, CTA data was finally used to assign the 17 segments from the AHA model to individual supply areas of LAD, LCX or RCA. Reformatted CTA short axis images were used to automatically segment the LV and color coded the wall with the corresponding perfusion studies in order to avoid blurring of the details the CTA studies by the co-visualized PET data.

Results: 58% of all vessels could be evaluated for degree of stenosis. Comparing these data to abnormal PET perfusion results, sensitivity and specificity was 77% and 85%. The distribution of CTA artefacts which hampered the analysis were motion (23%), calcification (14%), low opacification (9%) and stents (4%). The mean segment areas for LAD, LCX and RCA in units of % LV were 50, 26 and 24 (standard vessel supply layout) and 51 ± 8 , 25 ± 7 and 23 ± 5 for the individually adjusted vessel beds. Small, but statistically significant differences ($p < 0.05$) for mean uptake and vessel supply areas were found for the LAD and RCA. The absolute deviations were $|\Delta \text{Uptake}| = 1.5 \pm 0.5\%$ and $|\Delta \% \text{LVI}| = 5.5 \pm 0.7\%$.

Conclusions: Cardiac PET/CT provides complementary information and allows the characterization of myocardial tissue in a routine setting. The effects of individual vessel supply beds using CTA is a feasible approach. In the investigated patient group, the effects are modest but suggest that perfusion defects as well as the hemodynamical relevance of stenosis can be more clearly defined.

P1694 Impact of scar tissue on response to cardiac resynchronization therapy in ischemic heart failure patients



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Background: At present, 20-30% of patients do not respond to cardiac resynchronization therapy (CRT). Preliminary data suggest that the presence of scar tissue may be important for non-response to CRT. Moreover, pacing the left ventricle (LV) in scarred myocardium may result in ineffective pacing and non-response after 6 months. In the present study the extent and location of scar tissue were related to response to cardiac resynchronization therapy.

Methods: Fifty-one consecutive patients with ischemic heart failure and substantial LV dyssynchrony eligible for CRT were included. All patients underwent nuclear imaging with technetium-99m tetrofosmin SPECT before implant to determine the extent and location of scar tissue. Clinical and echocardiographic parameters were assessed at baseline and after 6 months of CRT.

Results: The improvement in echocardiographic parameters after 6 months of CRT was inversely related to the extent of scar tissue. Furthermore, fifteen pa-

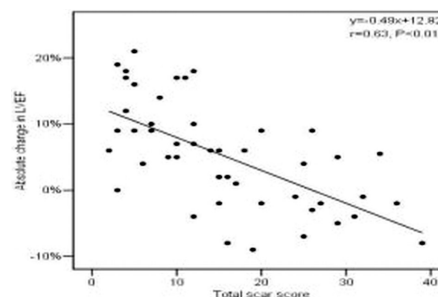


Fig. 1. Relation scar score vs change in LVEF

tients (29%) had transmural scar tissue (<50% tracer activity on SPECT) in the region where the LV pacing lead was positioned. These patients showed neither clinical nor echocardiographic improvement after 6 months, whereas patients without scar tissue in the LV pacing lead region improved significantly.

Conclusion: Scar formation is frequently observed in patients with ischemic cardiomyopathy and is inversely related to the response to CRT. In addition, scar tissue in the region of the LV pacing lead may prohibit response to CRT. Evaluation for scar tissue may be considered in the selection process for CRT.

P1695 Myocardial perfusion SPECT with Tc 99m-labeled Tetrofosmin in diabetic patients with known or suspected coronary artery disease: the European Multicenter Registry

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Diabetic patients with coronary artery disease (CAD) have a high probability of cardiac events. CAD is the leading cause of death among patients with DM. Therefore, accurate risk stratification is needed in this population. Myocardial perfusion scintigraphy (MPS) can provide information on individual risk, consecutively improving patient management with lower morbidity and mortality.

Purpose: The Multicenter European Registry has been intended to evaluate the prognostic power of MPS. Furthermore, the relation of myocardial perfusion abnormalities to clinical risk factors within a follow-up of 2 years in a non selected population of diabetic patients with known or suspected CAD was also a topic of interest.

Patients and Methods: Diabetic patients with known/suspected CAD were prospectively recruited in 17 nuclear medicine centres from 6 European countries. All patients underwent a rest/stress perfusion Tc-99m-labeled tetrofosmin gated SPECT examination. The results of visual interpretations along with those of semiquantitative data analysis were collected in a central database via internet. All baseline clinical and technical parameters were recorded in electronic case report forms as well. Collection of the 2 year follow-up safety data is under way and will run until end of 2007. Univariate and multivariate analyses were performed to identify independent predictors of abnormal MPS among clinical and technical variables at baseline.

Results: 539 diabetic patients (340 males and 199 females) were included. Mean age was 64.0 ± 9.8 (mean $\pm$ SD) years. DM of type II was present in 454 patients (84.2%) and mean duration of DM was 11.9 ± 9.7 years. 189 patients (35.1%) presented a family history of DM and 131 patients (24.3%) a family history of CAD. Among risk factors were smoking (30.4%), dyslipidemia (61.2%), hypertension (78.1%), alcohol consumption (28.4%), cardiovascular history (50.3%) and microalbuminuria (14.8%). MPS was rated as abnormal for 256 patients (47.5%). 509 patients were eligible to enter the multivariate model. History of cardiovascular disease, male gender, BMI (≥ 25), alcohol consumption and type of DM (type II) were found to be independent predictors of abnormal MPS (Odds Ratio of 4.17, 1.97, 1.78, 1.73 and 2.14 respectively).

Conclusion: At time of inclusion we found a high correlation between main risk factors for CAD and a pathologic MPS. Therefore, myocardial perfusion SPECT with Tc-99m-labeled Tetrofosmin seems to be a useful method to stratify patients, adding incremental information to the process of risk stratification in diabetic patients.

P1696 Exercise treadmill stress test with dual isotope studies documents the second window of preconditioning in humans

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Ischemic preconditioning is the phenomenon whereby brief sub-lethal episodes of ischemia renders the heart more tolerant to a subsequent prolonged and potentially lethal ischemic insult. There are two windows of protection: one lasting in 1-2 hours and a second one (SWOP) which starts in 24h and lasts in 3-4 days. There are several indications from indirect surrogate end-points that the both windows exist in humans.

Purpose: To determine if there is a SWOP in humans, using the radio - label scintigraphy as an objective method of imaging.

Methods: Twenty male patients (pts), mean aged 62 ± 7.4 years, with documented coronary artery disease, stable angina and left ventricular ejection fraction $53.1 \pm 9.9\%$ underwent two treadmill exercise tests (at baseline and 30 hours later) and three tomographic perfusion studies (during the first exercise test, during the redistribution phase in 4 hours and during the second exercise test) with

two different isotopes. Thallium-201 (TL) was used for the assessment of the first and redistribution phase, whereas tetrofosmin Tc 99m (TET) was used 30 hours later for the evaluation of SWOP. Both exercise tests terminated at the same time point and the TL and TET were injected as in the every day clinical practice. The distribution of TL and TET uptake was analyzed qualitatively as follows: anterior, septal, apical, inferior and lateral segment. The images were graded on a 5-point scale, 0: normal uptake, 1: equivocal, 2: moderately diminished uptake, 3: severely diminished uptake and 4: no uptake. The score was derived by summing the uptake of the segments.

Results: There was no difference between the first and the second exercise test in maximum ST depression (2.2 ± 1.04 vs 2.2 ± 1.03 mV) whilst there was significant difference in the time of ischemic changes onset (282 ± 152 vs 328 ± 152 sec, $P=0.01$) and the time of angina onset (228 ± 94 vs 265 ± 103 sec, $P<0.001$). Most of the pts (75%) had completely reversible defects and the remaining partially reversible. Significantly fewer perfusion abnormalities were observed in the last perfusion study in comparison to the first: perfusion score 14.2 ± 5.8 vs 21.0 ± 7.4 ($P<0.01$).

Conclusion: The perfusion improvement during the last scintigraphic study denotes better myocardial isotope uptake. This evidence implicates objectively the existence of SWOP in humans.

P1697 Comprehensive cardiac assessment with MSCT: evaluation of LV function and perfusion in addition to coronary anatomy in patients with previous myocardial infarction

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Purpose: To evaluate a comprehensive multi-slice computed tomography (MSCT) protocol in patients with previous infarction, including assessment of coronary artery stenoses, left ventricular (LV) function and perfusion. Currently, different imaging modalities are needed to provide the information, but MSCT may be able to provide all information from a single data set.

Methods: 16-slice MSCT was performed in 21 patients with previous infarction; from the MSCT data, coronary artery stenoses, (regional and global) LV function and perfusion were assessed. Invasive coronary angiography and gated single photon emission computed tomography (SPECT) served as the gold standard for coronary artery stenoses and LV function/perfusion respectively. Regional wall motion and resting myocardial perfusion were assessed using a 17-segment model. A 3-point scale was used to assign to each segment a wall motion score (1=normokinesia, 2=hypokinesia, 3=a- or dyskinesia). Myocardial perfusion was assessed on MSCT by using a 5-point scale (0=no perfusion defect, 1=transmurality 1-25%, 2=transmurality 26-50%, 3=transmurality 51-75%, and 4=transmurality >75%) and on SPECT by using a 4-point scale (0= $\geq 75\%$ of maximum tracer activity, 1=50-75% of maximum tracer activity, 2=25-50% of maximum tracer activity, and 3= $\leq 25\%$ of maximum tracer activity).

Results: In total, 236 of 241 (98%) coronary artery segments were interpretable on MSCT. The sensitivity and specificity for detection of stenoses were 91% and 97%.

Pearson's correlation showed excellent agreement for assessment of LV ejection fraction between MSCT and SPECT, respectively $49 \pm 13\%$ vs $53 \pm 12\%$, $r=0.85$. Agreement for assessment of regional wall motion was excellent (92%, κ statistic 0.77). Finally, in 68 of 73 (93%) segments, MSCT correctly identified a perfusion defect as compared to SPECT, whereas the absence of perfusion defects was correctly detected in 277 of 284 (98%) segments.

Conclusions: MSCT permits accurate, non-invasive assessment of coronary artery stenoses, LV function and perfusion in patients with previous infarction. All parameters can be assessed from a single data set.

P1698 Regional distribution of regeneration of the infarcted myocardium after autologous intracoronary bone marrow mononuclear cell transplantation in humans

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Regeneration of damaged myocardium represents one of the major goals in the treatment of acute myocardial infarction. Bone marrow-derived and blood-derived progenitor cells affect the postinfarction remodeling process. To understand the mechanisms for preventing the remodeling in humans and to evaluate the regional distribution of regeneration in the infarction (borderzone vs. infarcted zone), we performed SPECT and positron emission tomography (PET) analysis in patients with acute myocardial infarction, treated intracoronarily with bone marrow-derived progenitor cells, for analyzing the myocardial perfusion and metabolic condition (glucose uptake) within the infarcted tissue.

Methods and Results: In 13 patients with reperfused acute myocardial infarction (AMI), bone marrow-derived progenitor cells were transplanted into the infarct-related artery 8 ± 3 days after acute myocardial infarction. SPECT and PET investigations were performed initially and 3 months later after intracoronary

bone marrow-derived progenitor cell transplantation (Flow Chart). SPECT analysis demonstrated a recovery of the myocardial perfusion after infarction from 44 ± 4 to $51 \pm 9\%$ of relative ^{99m}Tc -Tetrofosmin-uptake ($p=0.02$). Additionally, PET analysis revealed a significant increase of glucose metabolism in the damaged myocardium 3 months after therapy from 42 ± 5 to $52 \pm 12\%$ relative ^{18}F -FDG-uptake ($p=0.03$). The comparison of the regional distribution of both, myocardial perfusion (56 ± 5 to $63 \pm 9\%$, $p=0.011$) and glucose uptake (53 ± 6 to $61 \pm 9\%$, $p=0.023$), demonstrated an increase for both parameter within the borderzone of the infarction. Also, there is a rise in perfusion (37 ± 5 to $46 \pm 11\%$, $p=0.009$) and in glucose uptake (34 ± 6 to $44 \pm 15\%$, $p=0.05$) in the inner center of the infarcted area. In addition, global ejection fraction significantly improved after infarction from 48 ± 8 to $56 \pm 10\%$ ($p=0.002$), and the infarction wall movement velocity increased from 1.8 ± 1.4 to $3.0 \pm 2.1\text{cm/s}$ ($p=0.015$), while the infarct size decreased from 33 ± 11 to $20 \pm 11\%$, $p=0.002$.

Conclusions: Both, analysis of SPECT and PET images in parallel to hemodynamic parameters, suggests that intracoronary transplantation of adult mononuclear bone marrow-derived progenitor cells in patients with acute myocardial infarction may prevent the remodeling process (possibly by neovascularisation and neomyogenesis or by preserved cardiac cells from apoptotic cell death) in the borderzone and in the inner center of the infarcted tissue.

P1699 Determinants of exercise-induced myocardial stunning in patients with coronary artery disease



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Background: The development of quantitative gated SPECT using $\text{Tc-}^{99\text{m}}$ sestamibi facilitates the evaluation of both myocardial perfusion during stress and wall motion >30 min after the stress, which enables to assess not only exercise-induced myocardial ischemia but also the development of myocardial stunning. On the other hand, no study evaluates the correlation between exercise-induced myocardial stunning and pressure-derived fractional flow reserve (FFR), though $\text{FFR} < 0.75$ indicates stress-induced myocardial ischemia.

Purpose: To elucidate the determinants of exercise-induced myocardial stunning, electrocardiographic and scintigraphic parameters as well as FFR, which assesses functional severity of coronary-artery stenosis, were evaluated.

Methods: Sixty consecutive patients who underwent intracoronary pressure measurements for anatomically intermediate stenosis of coronary arteries were evaluated. Electrocardiogram-gated $\text{Tc-}^{99\text{m}}$ -sestamibi SPECT was acquired >30 min after the stress and 4 hours later, and myocardial perfusion and LV wall motion were analyzed. The extent and severity of myocardial ischemia were assessed using summed difference score (SDS).

Results: Exercise-induced myocardial stunning was observed in 13 patients (22%). The incidences of chest pain (31 vs 4% ; $p < 0.01$) and ST-segment depression (62 vs 30% ; $p < 0.05$) during exercise were higher in patients with stunning than in those without, whereas exercise duration (8.0 ± 2.9 vs 7.6 ± 3.5 min; $p = \text{NS}$) and rate pressure product at peak exercise (27611 ± 5184 vs 27683 ± 5711 ; $p = \text{NS}$) were similar. In patients with stunning, regional SDS (6.1 ± 3.8 vs 1.1 ± 1.4 ; $p < 0.0001$) and changes in LVEF after exercise (-7.3 ± 6.7 vs $-2.5 \pm 5.4\%$; $p < 0.01$) were greater than in those without, while FFR reduced significantly (0.53 ± 0.15 vs 0.87 ± 0.08 ; $p < 0.0001$). Furthermore, multivariate analysis revealed that $\text{FFR} < 0.65$ and regional SDS > 2.0 were the most important determinants for exercise-induced myocardial stunning ($P < 0.0001$).

Conclusion: Myocardial stunning often develops after exercise in patients with coronary artery disease, particularly, in those who has severely reduced FFR.

P1700 Multivessel Coronary Artery Disease is poorly predicted by the presence of multiple myocardial perfusion defects on stress SPECT



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Introduction: Coronary revascularization improves outcomes in patients with multivessel coronary artery disease (CAD). Myocardial perfusion defects in multiple territories, especially when stress-induced, are commonly used as predictors of multivessel CAD on non-invasive testing. The validity of this approach has not been systematically evaluated in a large patient population.

Methods: We compared the results of gated SPECT (Single Photon Emission Computed Tomography) with coronary angiography in 562 patients in a large academic practice. We assessed the sensitivity and specificity of perfusion defects (fixed and reversible) in multiple vascular territories in predicting significant multivessel CAD as diagnosed by angiography. Stenoses of $\geq 50\%$ of the left main coronary artery and $\geq 70\%$ of other vessels were considered significant.

Results: The patient population consisted of 562 subjects (mean age 61 ± 10 years, 74% men). 192 subjects (34%) had multivessel CAD (65% two- and 35% three-vessel disease). Presence of both fixed and reversible perfusion defects in multiple vascular territories had a poor sensitivity (56%) and specificity (70%) in detection of angiographic multivessel disease. The sensitivity of reversible perfusion defects in detecting significant CAD varied with vascular territories (62%

for left anterior descending territory, 49% for right coronary artery territory and 32% for circumflex artery territory). Adding patients' age and traditional CAD risk factors (hypertension, diabetes mellitus, dyslipidemia and smoking) as predictors of multivessel CAD modestly increased the sensitivity of SPECT (68%) at the expense of reduced specificity (53%).

Conclusions: In clinical practice non-invasive assessment by stress SPECT may underestimate the extent of coronary disease in at least 1/3 of the patients. Coronary angiography needs to be considered in presence of high clinical likelihood of multivessel coronary disease regardless of the results of SPECT myocardial perfusion imaging.

P1701 Comparison of 64-slice spiral CT angiography and myocardial perfusion imaging in noninvasive evaluation of functionally relevant coronary stenoses



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Objectives: We prospectively compared the accuracy of 64-slice CT angiography with myocardial perfusion imaging (MPI) using $^{99\text{m}}\text{Tc}$ -tetrofosmin-SPECT as gold standard for the detection of functionally relevant coronary lesions. **BACKGROUND:** Multislice spiral computed tomography offers a valuable alternative for the diagnosis of coronary artery disease (CAD) but its value in the detection of functionally relevant coronary stenoses remains uncertain.

Methods: MPI and 64-slice CT were performed in 62 consecutive patients. In CT images coronary arteries were visually assessed and relevant coronary stenoses with a luminal narrowing $> 50\%$ and $> 75\%$ were characterized and compared to the MPI findings.

Results: A total of 247 coronary arteries and 858 segments was analyzed. Seventy-five segments (9%) in 21 coronary arteries of 9 patients were excluded due to insufficient image quality. In the remaining 783 segments CT revealed stenoses $> 50\%$ in 40 of 226 coronary arteries (18%) and stenoses $> 75\%$ in 18 (8%) coronary arteries. Sensitivity, specificity, and negative (NPV) and positive predictive value (PPV) for MSCT to detect fixed and reversible MPI defects were 75%, 86%, 98%, and 23% for stenoses $> 50\%$ and 67%, 95%, 98%, and 44%, respectively for stenoses $> 75\%$.

Accuracy of 64-slice CTA in the detection of both fixed and reversible perfusion defects in corresponding target areas on MPI

	Sens (%)	Spec (%)	NPV (%)	PPV (%)	Acc (%)
Per coronary artery analysis					
$\geq 50\%$ stenosis	75	86	98	23	85
$\geq 75\%$ stenosis	67	95	98	44	94
Per patient analysis					
$\geq 50\%$ stenosis	91	67	97	42	72
$\geq 75\%$ stenosis	63	85	90	54	81

Sens, Spec; sensitivity and specificity; NPV, PPV; negative and positive predictive value; Acc; accuracy

Conclusions: 64-slice CT angiography yielded a low PPV for the detection of functionally relevant stenoses in a non-selected study population. However, NPV was high indicating that CT is a reliable tool for evaluating a low- to intermediate-risk population.

P1702 Silent myocardial ischemia and subclinical peripheral artery disease in patients with lacunar and large-vessel non-cardioembolic stroke referred for myocardial perfusion scintigraphy



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Background: Stroke is often associated with coronary artery disease (CAD) and peripheral artery disease (PAD). However, the prevalence of silent myocardial ischemia (SMI) and PAD in patients with lacunar stroke (LS) versus large-vessel non-cardioembolic stroke (LVS) has not been evaluated sufficiently. The aims of this study were to estimate the prevalence of SMI and subclinical PAD in patients with LS and LVS without known CAD and to identify the risk factors associated with its presence.

Methods: During a 1 year period, 102 patients with large vessel or lacunar stroke who had no symptoms of CAD or PAD were included. Exclusion criteria were a potential cardioembolic source or a modified Rankin scale > 4 . Demographic data and relevant medical history were collected. Diagnosis of SMI was established by dipyridamole stress-induced perfusion defects on myocardial perfusion SPECT imaging (MPI). PAD was detected using the ankle-brachial index (ABI). Patients were divided in groups according to their subtype of stroke (LS versus LVS).

Results: We included 69 patients with LS and 33 with LVS. Overall, SMI was detected in 35 patients (34%) including 30% of patients with LS and 42% of patients with LVS ($p=0.23$). 6 (5%) patients had a high risk MPI, 2 (6%) had a moderate risk MPI and 27 (77%) had low risk MPI. Hypertension was significantly more prevalent in patients with LS (LS=78% versus LVS=45%, $p=0.001$), however only diabetes was independently associated with SMI ($p=0.032$). Finally, 26% of pa-

tients had an abnormal ABI however differences between groups were not significant.

Conclusions: We have demonstrated a high prevalence of SMI and subclinical PAD in patients with lacunar and large-vessel stroke and prevalence was no different between the subtype of stroke. Based on our findings, MPI for diabetic and non-cardioembolic stroke patients may be adequate. Further studies are necessary to confirm our results.

P1703 Myocardial Sympathetic Denervation In Patients With Impaired Glucose Tolerance. Relationship To Subclinical Inflammation



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Purpose: This study was designed to assess cardiac adrenergic nerve activity, using iodine (I)-123 labeled metaiodobenzylguanidine (MIBG), in patients with impaired glucose tolerance (IGT) and its relationship to circulating levels of proinflammatory cytokines.

Methods: We studied twenty-two patients with IGT, aged 34-68 years, and 18 age-matched healthy controls, using I-123 MIBG cardiac imaging. Static images were obtained 10 min, 1 hour and 4 hours after the intravenous injection of 5 mCi of the radiotracer. SPECT images were also performed. Results were based on qualitative, semi quantitative and quantitative analyses, using washout rate (WR). From blood samples of patients and controls, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a) and its soluble receptor (sTNFRII) were calculated by immunoassay.

Results: MIBG uptake was lower in patients than in control subjects (1.60 ± 0.14 vs 2.85 ± 0.43 , $p < 0.001$), while WR was higher (6.68 ± 3.31 vs 2.11 ± 0.96 , $p < 0.001$). The qualitative and semi quantitative analysis showed innervation defects in twenty out of the twenty-two patients. The majority of them (45.4%), showed severe adrenergic innervation defects both in the inferior wall and the apex, fewer in the inferior-septal (18.2%), the inferior-lateral wall (13.6%), the inferior-lateral wall and the apex (9.1%) and just one (4.5%), in the anterior wall. Regarding cytokines, patients showed significantly elevated circulating levels of TNF-a, sTNFRII, and IL-6, compared to controls. Pearson Correlation analysis showed that IL-6 and sTNFRII were positively correlated with WR ($r: 0.47$, $p=0.03$ and $r: 0.45$, $p=0.03$, respectively).

Conclusion: Patients with IGT show regional abnormalities of cardiac sympathetic innervation. The severity of these changes could be correlated with elevated cytokine levels and may be considered as indexes of early atherosclerotic process in those patients.

P1704 Comparative study between the therapeutic outcome of surgical myocardial revascularization and coronary angioplasty: analysis through myocardial scintigraphy 99mTc-Sestamibi



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Background: The most appropriate treatment to patients with multivessel coronary artery disease (CAD) remains matter of debate. Approximately 60 percent of patients treated with coronary angioplasty (PCI) or surgical myocardial revascularization (CABG) have multivessel CAD that could be treated by either procedure. This study evaluated the myocardial ischemic load (clinical and scintigraphic parameters) before and after CABG.

Methods: Myocardial scintigraphy 99mTc-Sestamibi was performed before and after the procedures both (PCI and CABG). All patients were randomized with multivessel CAD, stable angina, preserved left ventricular function and exercise-induced myocardial ischemia was treated with CABG or PCI.

Results: A total of 96 patients were randomized assigned to either a CABG (n=50) or PCI (n=46) group. The CABG determined a significant greater index of complete revascularization ($p=0.001$), increase in the number of maximum ergometric tests ($p=0.001$) and reduction in the number of positive ergometric tests with exercise angina ($p=0.018$). Both procedures provided an important improvement in the functional class of angina ($p=0.001$), an increase in the average value of heart peak rate ($p=0.007$), double peak product ($p=0.009$), metabolic equivalent level ($p < 0.001$), oxygen peak consumption ($p < 0.001$) and the time of exercise tolerance ($p < 0.001$), besides the reduction in the average value of the left ventricle ejection fraction ($p=0.025$), summed stress score ($p < 0.001$) and summed difference score ($p < 0.001$) in both groups.

Conclusions: Surgical myocardial revascularization and coronary angioplasty did not differ significantly concerning the reduction of myocardial ischemic load 6 months after the procedure. The myocardial revascularization was more complete with CABG than PCI, but it didn't represent a significant factor for reducing myocardial ischemic load appraised 6 months after the intervention.

P1705 Attenuation correction in myocardial SPECT using multislice computed tomography-derived attenuation maps from coronary calcium scoring



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Objectives: To prospectively provide a qualitative and quantitative comparison of attenuation-corrected SPECT images produced by a SPECT-CT device with high-resolution attenuation maps from coronary calcium scoring (CCS), generated with a 64-slice CT scanner.

Methods: Thirty patients (mean age 65 ± 11 years) underwent 99mTc-tetrofosmin gated SPECT and CT angiography on a 64-slice CT (GE Medical Systems). SPECT data were acquired using the Infinia Hawkeye SPECT-CT device (GE Medical Systems). Attenuation correction (AC) was performed using 3 different methods: (1) AC using the "Hawkeye" low-resolution X-ray CT facility attached to the Infinia camera (IRAC); (2) AC using the CCS scan data acquired on a 64-slice CT scanner during maximal inspiration (ACINSP), and (3) during normal expiration (ACEXSP). Automatically determined QPS scores (QPS, Cedars Medical Sinai), providing the percentage counts radiotracer uptake of each segment of a 20-segment model, were used. The 3 AC methods for 5 regions of the left ventricle (apex, anterior, septal, lateral, and inferior) were compared.

Results: CT AC with ACINSP and ACEXSP showed identical findings to IRAC by visual analysis. A good correlation and agreement for uptake values between IRAC and ACINSP was found (apex; $r = 0.93$; anterior, $r = 0.86$; septal, $r = 0.92$; lateral, $r = 0.86$; inferior, $r = 0.90$; all $p < 0.0001$), with little bias, except for the apex, were a moderate systematic overestimation for uptake values using ACINSP was seen. An even better correlation and agreement was found for uptake values between IRAC and ACEXSP with negligible bias (apex; $r = 0.97$; anterior, $r = 0.91$; septal, $r = 0.95$; lateral, $r = 0.92$; inferior, $r = 0.97$; all $p < 0.0001$).

Conclusions: Multislice CT data from CCS provide accurate results for AC of SPECT images. The quality of final attenuation-corrected SPECT images obtained with ACEXSP was higher than that obtained during deep inspiration, and, hence, we believe that using CT data from CCS during normal expiration might be a valuable alternative for AC of cardiac SPECT images.

P1706 Reversible perfusion defects and multiple risk factors influence event-free survival of anginal patients with normal coronary arteries



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Aims: there are currently few data to support a role for stress imaging techniques in anginal patients with normal coronary arteries and multiple cardiovascular risk factors. The aim of this study was to assess the prognostic value of stress myocardial perfusion imaging (MPI) in predicting event-free survival of these patients.

Methods and results: we studied 135 patients symptomatic for angina (78 male; age 65 ± 12) by exercise or dipyridamole MPI. Ischemia was quantified by summed differential score (SDS). All patients had hypertension, 120/135 HDL value below 40mg/dl, 115/135 were currently smokers, 95/135 were obese (body mass index > 29.9 kg/m²) and 60 had diabetes. All patients showed normal coronary arteries at angiography and normal ejection fraction. A normal scan was detected in 61 pts (Group 1, 45%). Reversible perfusion defects (SDS >4) were found in 74 pts (Group 2, 55%). Group 2 patients showed an average of 3.5 ± 0.6 risk factors ($p < .01$ vs Group 1) and 42/74 patients had diabetes. During a median follow-up of 36 months (range 25-56 months) 1 patient died, 2 patients were hospitalized for pulmonary edema and 7 patients were revascularized by angioplasty. The worse event-free survival was observed in Group 2 (72 vs 20% at 48 months of follow-up, respectively in Group 2 and Group 1, $P < 0.0001$). In a multivariate analysis, SDS (HR = 4.1, 95% CI = 1.2-14.4) and presence of diabetes (HR = 6.7, 95% CI = 1.4-17.7) were independent predictors of event-free survival. Moreover, the association SDS + risk factors showed the most significant impact on adverse events (HR = 1.7, 95% CI = 1.02-2.6).

Conclusions: In patients with angina and normal coronary arteries, a positive MPI in association to multiple risk factors should be carefully evaluated as adverse markers of event-free survival.

P1707 Role of myocardial sympathetic nerve dysfunction in arrhythmia associated with mitral valve prolapse



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Mitral regurgitation is well-established risk factor in patients with mitral valve prolapse (MVP) and also a factor for sudden death. In the absence of mitral regurgitation, a relationship between ventricular arrhythmias, sudden death and MVP is not that clear. Evaluation of myocardial sympathetic nerve function by Iodine 123-metaiodobenzylguanidine myocardial scintigraphy (MIBG) may explain arrhythmia associated with MVP.

Methods: We examined 46 patients with symptomatic MVP without mitral regurgitation; mean age 34 ± 8 years and 65% females. They underwent clinical, echocardiographic examination, 24-hour ECG ambulatory holter monitoring, sig-

nal averaged ECG and myocardial scintigraphy with (123)I-labeled metaiodobenzylguanidine (MIBG). Early and delayed images were obtained in 15 minutes and 5 hours after administration of (123)I-MIBG. The heart to mediastinum ratio for (123)I-MIBG activity was calculated (H/M). The myocardial washout ratio (WOR) was determined as percent change in activity from 15 minutes to 5 hours after isotope administration as well as the extent score and severity score. Patients were divided into group (A) with ventricular arrhythmia 28 patients and group (B) without arrhythmia 18 patients.

Results: Holter monitor showed ventricular premature beats in 60% of group A patients of the left bundle branch morphology and complex ventricular arrhythmia of Lown grade > 3 in 40% with positive late ventricular potential in 74%. Leaflet thickening >5mm was present in 85% of group A compared with 48% for group B. Group A patients showed increased WOR (8.3 ± 3.6 versus 3.2 ± 2.3 , $p=0.01$) for group B. The WOR was higher at inferoposterior and septal segments in patients with anterior leaflet prolapse and at the inferoposterior and lateral segments in patients with posterior leaflet prolapse in group A compared with group B with significant $p=0.01$. There was also increased WOR in apical and posteroseptal basal segments in group A compared with group B and this was significant, $p=0.02$. There was positive correlation between grades of arrhythmia and leaflet thickening >5mm and WOR ($r=0.005$, $p=0.01$ and $r=0.003$, $p=0.01$ respectively). There was no significant difference in the H/M ratio between both groups, $p=0.1$. In group A H/M ratio did not correlate with arrhythmia ($r=0.2$, $p=0.65$).

Conclusion: Cardiac sympathetic nerve dysfunction may contribute to arrhythmia and sudden death in symptomatic MVP patients. Myocardial scintigraphy with (123) I-MIBG can be used for risk stratification and assessment of localized myocardial sympathetic nerve dysfunction in MVP patients.

P1708 Prognostic value of exercise stress 99m technetium tetrofosmin myocardial perfusion imaging in patients with normal baseline electrocardiogram

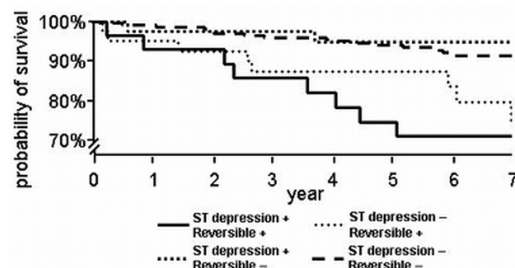


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Background: Exercise stress electrocardiography is the recommended method for cardiac evaluation of patients with normal electrocardiogram (EKG). There are no data to indicate an independent value of myocardial perfusion imaging (MPI) in predicting mortality in these patients. The aim of this study was to assess the value of exercise stress MPI, in predicting mortality in patients with normal baseline EKG.

Methods and results: We studied 319 patients (age = 55 ± 10 year, 180 men) with normal EKG by exercise stress 99m technetium tetrofosmin MPI. End points during follow up were cardiac and all cause mortality and hard cardiac events. A normal scan was detected in 190 (60%) patients. Myocardial perfusion abnormalities were fixed in 59 (18%) patients, and reversible in 70 (23%) patients. During a mean follow-up period of 7 ± 1.2 years, 46 (14%) patients died. Death was considered cardiac in 28 (9%) patients. Nonfatal myocardial infarction occurred in 12 (4%) patients. The annual cardiac death rate was 0.4% in patients with normal perfusion, and 2.7% in patients with reversible defects. Survival curves based on combinations of perfusion and EKG response are shown in figure. The annual total mortality rate was 1.1% in patients with normal perfusion and 3.4% in patients with reversible defects. In a multivariate analysis model, reversible perfusion abnormalities were associated with cardiac death (risk ratio = 2.8, CI 1.6-5.1), and hard cardiac events (risk ratio = 2.7, CI 1.5-4.5).



Conclusion: Stress 99m technetium tetrofosmin MPI provides independent information for predicting cardiac and overall mortality in patients with normal EKG. Reversible perfusion abnormalities, but not ischemic EKG changes are predictive of outcome in these patients.

P1709 Myocardial perfusion profile in young population with and without known Coronary Artery Disease



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The referral of young population for detection of CAD is increasing, however the value of MPI in this population is indeterminate. The aim of this study was to evaluate the clinical characteristics and predictors of ischemia in pts under age of 51 referred for Myocardial Perfusion Imaging (MPI).

Methods: Since 3.02 to 9.05 we recruited 1,765 consecutive patients under age 51 in 2 medical centers who were referred for stress/rest MPI study. Clinical variables including age, gender, risk factors, MI, CABG, PCI, MPI parameters including stress variables, ischemia/extent score, scar, global risk signs. Patients with and without known CAD were compared.

Results: There were 1346(76%) men and 419(24%) women, mean age was 44 ± 6 . There were 450(25%) pts with known CAD and 1487(75%) without CAD. The referral reason for MPI was chest pain or equivalent angina in 851(65%) pts. Definitive MI in 278 (16%), CABG was in 98 (5.5%), PCI in 271(15.3%) pts. Only 341 (19%) were free of CAD risk factors. In stress MPI variables: Stress induced ischemia was in 321(18.2%), marked ischemia in 131(7.5%), LV dilatation (fixed or transient) was in 242(13.5%), increased lung uptake in 209(12%). Comparison between asymptomatic non CAD pts versus symptomatic non CAD pts showed similar prevalence of ischemia and of degree of ischemia. The independent predictors of ischemia were: high cholesterol, diabetes, angina during stress, significant ST depression and smoking ($p<0.0001$).

Conclusions: The prevalence of known CAD as well as stress induced ischemia are quite significant in young patients. Furthermore, the incidence of ischemia in young patients without known CAD was unrelated to referral symptoms and was predicted by CAD risk factors and exercise variables.

P1710 QTc duration is rather linked with evidence of myocardial disease than diabetes per se



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Background: Prolonged QTc intervals have been linked to increased mortality. Little is known about the comparison of QTc in diabetic (DP) versus non-diabetic patients (NDP). Study aim: to compare QTc with respect to gender, hypertension, diabetes, coronary artery disease (CAD) and left ventricular ejection fraction (LVEF).

Methods: A large consecutive series of pts undergoing myocardial perfusion SPECT (MPS) for CAD evaluation was assessed. DP and NDP were compared with respect to electronically measured QTc duration in the resting ECG. MPS were evaluated using a 5 point scale calculating a summed stress score (SSS) and gated measurements for assessment of LVEF. A LVEF of less than 50% was considered abnormal. An SSS greater than 4 was considered to be consistent with CAD. Variables independently correlated with QTc were identified.

Results: The pt population consisted of 664 pts, 491 male (74%), age 63 ± 10 y, 151 DP (23%), no evidence of CAD 318 (48%). Overall results are summarized in table below. NDP with versus without evidence of CAD had similar QTc, QTc 421 ± 25 and 424 ± 25 ms, respectively; $p=0.23$. In contrast, DP with evidence of CAD had significantly longer QTc than DP without CAD, QTc 430 ± 25 and 422 ± 22 ms, respectively; $p=0.041$. Looking at LVEF, NDP and DP without CAD had similar LVEF, LVEF 63 ± 9 and $62 \pm 10\%$, respectively; $p=0.22$. In contrast, DP with CAD had significantly worse LVEF than NDP with CAD, LVEF 47 ± 12 and $53 \pm 10\%$; $p=0.001$. Female gender (0.231/1f yes; $p<0.001$), age (0.13/per year; $p=0.001$), hypertension (0.12/1f yes; $p=0.003$) and LVEF (-0.124/per 1%; $p=0.003$) correlated significantly and independently with longer QTc. Diabetes per se did not. Of note, betablocker therapy was not correlated with QTc.

QTc in the overall population

	<u>" hei</u>		<u>p</u>
male/female	420±25	431±24	<0.001
Hypertension yes/no	426±26	418±21	<0.001
Diabetes yes/no	426±24	422±25	0.14
CAD yes/no	423±24	423±26	0.81
LVEF normal/abnormal	422±24	427±25	0.032

Conclusions: Our data suggest that QTc prolongation in DP with CAD is rather linked to more advanced myocardial disease than to diabetes per se. If so, prolonged QTc might identify DP at particularly high risk of CAD.

P1711 Head-to-head comparison between SPECT myocardial perfusion imaging and non-invasive angiography with multi-slice CT in asymptomatic diabetics



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Purpose: MSCT detects atherosclerosis, whereas MPI detects ischemia; how these 2 techniques compare in asymptomatic patients with DM 2 is unknown. A head-to-head comparison between multi-slice computed tomography (MSCT) and SPECT myocardial perfusion imaging (MPI) in asymptomatic patient with diabetes mellitus (DM) type 2 was performed.

Methods: 30 asymptomatic patients with DM 2 underwent both MSCT and MPI. MSCT studies were classified as having no coronary artery disease (CAD), non-obstructive (< 50% luminal narrowing) CAD or obstructive CAD. MPI examinations were classified as showing normal or abnormal (reversible and/or fixed defects).

Results: Based on the MSCT data, 15 (50%) were classified as having no CAD 13 (87%) patients had normal MPI, whereas 2 (13%) patients had abnormal MPI. A total of 11 (37%) patients showed non-obstructive CAD, whereas at least 1 significant ($\geq 50\%$ luminal narrowing) was observed in the remaining 4 (13%) patients. 10 (67%) patients with abnormal MSCT had abnormal MPI; all patients with obstructive CAD had abnormal MPI (100%). However, only 4 of 11 (37%) patients with non-obstructive CAD had abnormal MPI.

Conclusions: MSCT and MPI provide different and complementary information on CAD in patients with DM 2 (atherosclerosis versus ischemia); only one third of patients with non-obstructive CAD on MSCT have ischemia.

P1712 Value of pharmacological stress perfusion scintigraphy in late restenosis in single vessel stented patients



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Purpose: Exercise myocardial perfusion scintigraphy (MPS) is a useful method for the detection of restenosis in patients with multivessel disease. In patients unable to exercise, pharmacological MPS may represent a feasible alternative. A decrease in specificity has been observed when MPS is performed within two months of percutaneous coronary intervention. The aim of this study was to assess the diagnostic performance of pharmacological stress MPS for detecting late restenosis in single vessel stented patients.

Methods: We studied 335 patients (241 males, 94 females) aged 69 ± 11 years, at the average interval 138.8 ± 51.2 days after successful stent implantation with dipyridamole/adenosine stress test, in conjunction with $99mTc$ -hexakis-2-methoxyisobutyl isonitrite SPECT. Before coronary intervention, myocardial perfusion abnormalities were showed in all patients. Quantitative coronary angiography was performed in all patients following myocardial perfusion imaging. Scintigraphic restenosis was defined as a stress-induced perfusion defect with reversibility at rest within the stented vascular territory. Angiographic restenosis was examined using 2 definitions: total area narrowing $\geq 50\%$ or $\geq 70\%$ of the stent site or stent artery.

Results: Restenosis rate (in-stent plus stent related coronary artery stenoses) and asymptomatic restenosis following coronary artery stenting were 37% (125/335) and 44% (55/125) respectively. Scintigraphic and angiographic findings were concordant in 105 of 125 vessels using the 50% definition of restenosis and in 85 of 89 vessels using the 70% definition. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of pharmacological stress MPS in predicting late restenosis ($\geq 50\%$) were 84%, 91%, 85%, 91% and 89% respectively. These values were higher in patients without previous myocardial infarction.

Conclusions: Pharmacological stress MPS can accurately identify late restenosis in single stented patients. Decisions to perform repeat coronary angiography in this patient group should primarily be based on scintigraphic results.

P1713 Detection of silent myocardial ischemia. Impact of myocardial perfusion scintigraphy and stress ECG findings



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Purpose: In many patients with coronary artery disease, reversible perfusion abnormalities may occur during stress without symptoms. There is a controversy in the literature regarding the extent of ischemic burden in silent versus symptomatic ischemia during exercise myocardial perfusion imaging, with some reports indicating similar extent and others indicating less severe ischemia in patients without angina. The aim of this study is to compare scintigraphic and exercise ECG variables between silent and painful ischemia in patients with angiographically documented coronary artery disease (CAD).

Methods: 50 patients diagnosed as CAD by angiography were undergoing symptom-limited exercise $Tc-99m$ MIBI SPECT (Rest-Stress Protocol). 34 pa-

tients (group I) complained of exercise induced chest pain, 16 patients (group II) did not develop chest pain.

Results: Patients with silent ischemia were found to be younger with greater prevalence of positive family history and diabetes as risk factors and previous infarction. They had history of chest pain in only 12.5% compared to 35.3% of patients with painful ischemia. During exercise, they showed longer exercise duration, higher maximum systolic pressure and rate pressure product. They ended exercise due to Shortness of breath in 62.5% versus 35.3% in the angina group with $P < 0.05$. Also silent ischemia showed less ST depression 37.5% compared to 64.7% in angina group. In Myocardial perfusion images, there was more than 13 myocardial perfusion defects in angina group, than in group of silent ischemia (82.4% vs 66.7% respectively). The Reversibility score (Summed difference score) which was considered representative of the severity of myocardial ischemia was significantly higher in angina group, with a higher prevalence of cases with more than two reversible myocardial perfusion defects. Concerning each coronary territory: it has been found that 3 reversible segments or more must be found in LAD and RCA territory to produce significant ST depression in its ECG territory, and to have significant changes could in LCX territory at least two segments should have reversible ischemia in its territory.

Conclusion: Ischemic parameters on scintigraphy and exercise ECG seemed to be more severe in patients with chest pain. More than 4 reversible segments are necessary to produce significant ST depression in silent ischemia group.

P1714 Does heart rate recovery predict coronary artery disease in diabetes?



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Background: Heart rate recovery (HRR) has been shown to be generally impaired in patients (pts) with diabetes. Abnormal HRR is also an independent predictor of all-cause and cardiovascular mortality. However, little is known regarding the interrelation of HRR and coronary artery disease (CAD) in diabetic versus non-diabetic pts. The aim of this study was to evaluate HRR patterns with respect to the presence of CAD and diabetic status.

Methods: A large consecutive series of pts who underwent symptom limited bicycle exercise testing for myocardial perfusion SPECT (MPS) were evaluated. An abnormal value for HRR was defined as reduction of 12 beats per minute or less (based on the prognostic literature) 1 minute after exercise termination. MPS was assessed using a 20 segment model with a 5 point scale to calculate a summed stress score (SSS). An SSS < 4 was considered normal (no CAD). Pts with versus without diabetes and CAD were then compared. Moreover, variables independently associated with HRR were identified by linear regression.

Results: The pt population consisted of 666 pts, mean age 63 ± 11 years, 174 (26%) pts were female, 153 (23%) pts had diabetes. The mean work load achieved was 139 ± 49 Watt, peak heart rate 147 ± 16 /min, 350 (52%) had evidence of CAD on MPS and 147 (22%) pts an abnormal HRR. There was no statistically significant difference between HRR in gender ($p=0.8$). Diabetics had a lower HRR than non-diabetics, 18 ± 10 and 22 ± 12 , respectively ($p=0.001$), irrespective of CAD status. Pts without CAD had similar HRR compared to patients with evidence of CAD, 21 ± 11 and 20 ± 12 , respectively ($p=0.4$). In a linear regression model, peak heart rate (0.18/per beat, $p<0.001$) and diabetes (-3.1 , if yes, $p=0.003$) were the only variables significantly correlating with HRR. Of note, left ventricular function and betablocker therapy did not correlate with HRR. A multiple logistic regression model revealed HRR not to be a predictor of CAD ($p=0.3$).

Conclusion: HRR was independently and inversely associated with peak heart rate and significantly associated with diabetes, irrespective of CAD status and gender. Furthermore, HRR did not provide any incremental value in predicting CAD during stress testing.

P1715 The effect of verapamil on the restoration of myocardial perfusion and functional recovery in patients with angiographic no-reflow after primary percutaneous coronary intervention



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Objective Angiographic Thrombolysis in Myocardial Infarction (TIMI) flow grade ≤ 2 after primary percutaneous coronary intervention (PCI), defined as angiographic no-reflow, predicts poor functional recovery in patients with acute myocardial infarction (MI). We investigated the effect of verapamil on the restoration of myocardial perfusion and functional recovery in patients with angiographic no-reflow after PCI.

Methods Technetium-99m ($99mTc$) tetrofosmin single-photon emission computed tomographic (SPECT) imaging was performed (before, immediately after and 1 month after PCI) in 101 consecutive patients with acute MI. The defect score was calculated as the sum of perfusion defect in a 13-segment model (scores of 3, complete defect to 0, normal perfusion). The asynergic score, de-

defined as the number of asynergic segments, was assessed by echocardiography before and 1 month later. Multiple logistic regression analysis was performed to elucidate the effect of verapamil administration.

Results Of 101 patients, 32 patients (31%) had angiographic no-reflow and were divided into 2 groups: 18 patients with verapamil (Group 1) and 14 patients without verapamil (Group 2). Sixty-nine patients had TIMI grade 3 reflow after PCI (Group 3). The change in the defect score 1 month after PCI in Group 1 was significantly larger than that in Group 2 ($p=0.003$). The asynergic score improved more at 1 month in Group 1 compared to that in Group 2 ($p=0.007$). Moreover, logistic regression analysis revealed that TIMI flow grade ≤ 2 after PCI ($P=0.04$, $OR=5.51$), the defect score before PCI ($P=0.03$, $OR=1.15$), the asynergic score before PCI ($P=0.01$, $OR=0.64$) and the administration of verapamil ($P=0.002$, $OR=22.4$) were independently associated with successful myocardial reperfusion immediately after PCI.

Conclusions: Intracoronary verapamil restored myocardial perfusion in patients with angiographic no-reflow after PCI and lead to better functional recovery after acute MI.

P1716 Diagnostic performance of 64-slice CT in symptomatic patients with previous coronary bypass surgery evaluation of grafts and coronary arteries



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Objectives: Evaluation of the performance of 64-slice CT angiography in patients that previously underwent coronary artery bypass surgery (CABG), for detection of graft obstruction and native coronary artery stenosis.

Background: CT accurately detects coronary graft occlusion. Assessment of graft stenosis and coronary artery disease in post-CABG patients is more challenging and has not been described using 64-slice CT.

Methods: 64-slice CT angiography (Siemens Sensation 64, Germany) was performed in 52 symptomatic patients, 10.3 ± 5.1 years after CABG. Scan parameters: rotation time 330ms, detector width 0.6mm. Two independent, blinded observers assessed all grafts and coronary arteries for significant ($>50\%$) luminal narrowing. Using conventional quantitative angiography as reference, descriptive statistics were performed. Confidence of assessment was classified as high, moderate or low. The accuracy of CT on patients basis analysis is showed in the table.

Results: A total of 109 grafts, including 182 graft segments, 123 distal coronary run-offs and 116 non-bypassed coronary branches (288 segments) were analyzed. Per-segment detection of graft disease by CT yielded a sensitivity and specificity of 99% (71/72) and 96% (106/110). Nearly all obstructed run-offs were identified (8/9, sensitivity 89%), although overestimations frequently occurred. In non-grafted coronary branches, CT detected significant stenosis (per segment) with a sensitivity and specificity of 97% (62/64) and 86% (192/224). Overestimation occurred more often in calcified segments (positive predictive value of 66% (62/94)). Assessment confidence, inter-observer agreement and diagnostic performance was better in grafts compared to distal run-offs and non-grafted coronary branches.

Diagnostic performance of CT per-patient

	TP	TN	FP	FN	Accuracy
Any graft disease	36	15	1	0	98.1%
Any distal run-off disease	7	37	6	1	86.3%
Any non-grafted coronary artery disease	28	11	8	0	83.0%
Any obstructive coronary/graft disease	50	1	1	0	98.1%

True positive (TP); true negative (TN); false positive (FP); false negative (FN). Accuracy: $[TP+TN]/[TP+TN+FP+FN]$.

Conclusion: 64-slice CT allows complete angiographic evaluation after bypass surgery, although overestimation of coronary stenosis frequently occurred due to extensive vessel wall calcification.

P1717 Non invasive assessment of coronary artery disease by multislice computed tomography in patients with acute chest pain



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Screening for coronary calcium allows the exclusion of coronary artery disease (CAD) with a high negative predictive value of up to 98%. However diagnostic accuracy is limited by a reduced specificity in the range of 60%. In the following study we examined the possibility to improve the diagnostic accuracy by combining coronary calcium screening with non invasive coronary angiography using 64 slice computed tomography (CTA).

We examined 199 patients (82 female, 117 male, age 61.3 ± 12.6 years), who attended the emergency department with acute chest pain. We excluded patients showing signs of acute myocardial ischemia in ECG or laboratory testing. We determined the extent of coronary calcifications using a 64 slice scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany). For quantification we calculated the Volume score. In patients with exclusion of coronary calcifications we refrained from an additional CTA. The exclusion of CAD was assumed. Also in

patients with scores above 400 we refrained from an additional CTA as a limited evaluation because of extended calcifications had to be expected. In these patients the existence of CAD was assumed. In patients with scores from 1-400 we performed an additional CTA to assess possible coronary stenoses. Afterwards all patients underwent conventional coronary angiography.

In 41 patients coronary calcifications could be excluded and CAD was ruled out in conventional angiography. 68 patients of those 83 patients with scores above 400 (547 ± 382) showed significant CAD in conventional angiography. In the group of 75 patients with scores from 1-400 who underwent CTA, 49 patients showed a significant CAD in conventional angiography. In 45 of these 49 patients also the CTA had revealed a significant CAD. In 24 of 26 patients without CAD in conventional angiography also CTA ruled out CAD. In 3 patients evaluation was not possible, the results were considered as false negative resp. false positive. Over all we calculated a sensitivity of 97% at a specificity of 79%. The negative predictive value was 95%, the positive predictive value 80.9%.

An additional CTA in patients with moderate coronary calcifications increases the reduced specificity of coronary screening in the assessment of CAD up to 79% at an overall diagnostic accuracy of 91%.

P1718 Accuracy of 64-slice CT to detect noncalcified coronary plaques



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Objectives: We evaluated the accuracy of a new 64-slice CT-scanner to visualize atherosclerosis in the proximal coronary system compared to intravascular ultrasound (IVUS).

Background: Noninvasive determination of plaque composition and plaque burden may be important to improve risk stratification.

Methods: In 20 patients a 64-slice CT-scan (Sensation 64, Siemens Medical Solutions, Forchheim, Germany) and an IVUS-investigation of vessels without stenosis $>50\%$ was performed. Diagnostic image quality with 64-slice CT was obtained in 36 vessels in 19 patients.

Results: In these vessels that were divided in 3 mm sections, 64-slice CT enabled a correct detection of plaque in 54/65 (83%) sections containing noncalcified plaques, 50/53 (97%) sections containing mixed plaques and 41/43 (95%) sections containing calcified plaques. In 192/204 (94%) sections atherosclerotic lesions were correctly excluded. In addition 64-slice CT enabled the visualisation of 7/10 (70%) sections revealing a lipidpool and could identify a spotty calcification pattern in 27 of 30 (90%) sections. The correlation coefficient to determine plaque volumes per vessel was $r=0.69$ ($p<0.001$) with an underestimation of mixed and noncalcified plaque volumes ($p<0.03$) and a trend to overestimate calcified plaque volumes by 64-slice CT. The interobserver variability to determine plaque volumes was 37%. Interobserver agreement to identify atherosclerotic sections was good (Cohens Kappa coefficient= 0.75).

Conclusion: 64-slice CT reveals encouraging results to detect different types of coronary plaques located in the proximal coronary system noninvasively. The ability to determine plaque burden is currently hampered mainly due to an insufficient reproducibility.

P1719 Influence of a lipid lowering therapy on coronary atherosclerosis assessed by multi-slice computed tomography



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Purpose: Treatment of elevated lipid levels has shown to reduce plaque burden and mortality in patient with coronary artery disease (CAD) and multi-slice computed tomography is a non-invasive modality to detect and classify coronary plaques non-invasively. The aim of the present study was to detect coronary lesions in male persons without established CAD but with an increased risk for disease and to assess the effect of a lipid lowering therapy (LLT) with 20 mg atorvastatin on plaque burden.

Methods: 46 male patients (pts) (61 ± 10 years, PROCAM score > 3 . percentile and/or atypical chest pain) without lipid lowering therapy were included. After a native scan to assess calcium burden, contrast-enhanced scans were performed in all pts. 27/46 pts received a follow-up scan (2. scan after 488 ± 138 days, LLT in 20/27 pts). Coronary plaque burden was assessed on coronary cross sectional slices volumetrically.

Results: Patients with LLT ($n=20$): Total cholesterol and LDL-cholesterol levels decreased significantly under LLT (225 ± 41 mg/dl vs. 162 ± 37 mg/dl, $p<0.05$). Calcium scoring remained unchanged (261 ± 301 vs. 282 ± 360) but total plaque burden decreased significantly from 0.149 ± 0.108 vs. 0.128 ± 0.075 ml ($p<0.001$).

Patients without LLT ($n=7$): Total cholesterol remained unchanged (214 ± 64 mg/dl vs. 230 ± 62 mg/dl). In 5/7 patients a LLT was recommended due to the presence of atherosclerotic lesions. In these patients, calcium burden increased from 873 ± 1101 vs. 1017 ± 1268 ($p>0.05$) without a significant change in total plaque burden (0.647 ± 0.607 vs. 0.628 ± 0.523 , $p=0.81$).

Conclusions: For the first time the influence of a lipid lowering therapy on coronary plaque burden could be assessed non-invasively by MSCT. A lipid lowering therapy with 20 mg atorvastatin/die lead to a significant reduction of coronary plaque burden which was not reflected in calcium scoring. Thus, contrast application to visualize non-calcified coronary plaques is mandatory to assess these changes. MSCT has the potential to monitor medical treatment in patients with coronary atherosclerosis.

P1720 64-multislice CT provides a novel non-invasive diagnostic approach in patients with aortic stenosis: evaluation of left ventricular function and planimetry of the aortic valve area



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Purpose: to evaluate (1) planimetry of the aortic valve area (AVA) and (2) left ventricular function with 64-multislice computed tomography (64-MSCT) in patients with aortic stenosis.

Methods: 21 patients were examined with 64-MSCT (Sensation 64™, Siemens) (64x0.6 mm; 0.33 rot.; 120 kV; 700-900 mAs; 100 ml Iodixanol (Visipaque 320™) at 5 ml/s). (1) Planimetry of the AVA: Image reconstruction during maximal aortic valve opening using retrospective ECG-gating (12% of RR-interval)(eff.sl. 0.75 mm, inc.0.4, B25f+). (2) Assessment of left ventricular function: Image reconstruction at every 10% of RR-interval (eff.sl.1.5 mm;inc.1.2;B30f). LV-EF, LV-EDV and LV-ESV were calculated using Circulation™, Siemens. All patients underwent transthoracic echocardiography (TTE) including measurement of AVA with Continuity Equation (Doppler VTI-integral) and LV-EF, LV-EDV, LV-ESV (Simpon's rule).

Results: (1) Planimetry of the AVA by 64-MSCT ($1.07\text{cm}^2 \pm 0.38$) was significantly ($r=0.82$; $p=0.0003$) correlated with TTE ($1.02\text{cm}^2 \pm 0.37$). (2) LV-EF, LV-ESV and LV-EDV by 64-MSCT were correlated with TTE ($p=0.004$; $p=0.002$; $p<0.001$). LV-EF was slightly overestimated (+0.7%) and LV-EDV and LV-ESV were slightly underestimated (-3.9; -3.3ml) with 64-MSCT (Bland-Altman-plot). Mean LV-EF;-ESV;-EDV were $60.1\% \pm 8.9$; $38\text{ml} \pm 14$; $95\text{ml} \pm 29$ by 64-MSCT, respectively. Intraobserver variability was 2.6% (LV-EF); 4.1% (LV-ESV); 3.6% (LV-EDV) suggesting a good reproducibility.

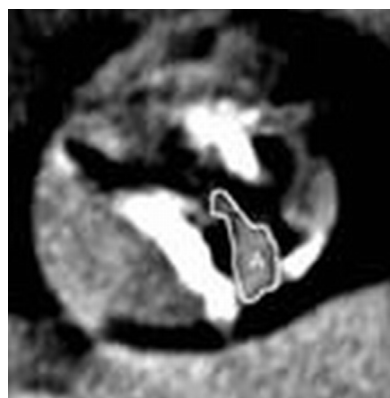


Fig. 1. Aortic valve area (A).

Conclusion: 64-MSCT provides a non-invasive diagnostic approach in patients with aortic stenosis. 64-MSCT allows an accurate planimetry of the AVA and assessment of left ventricular function. In patients with aortic stenosis in whom concomitant CAD is suspected, 64-MSCT could be the imaging modality of choice because the simultaneous evaluation of CAD and aortic stenosis is feasible.

P1721 Effective radiation dose in angiography of coronary artery bypass grafts using multislice computed tomography



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Purpose Multislice Computed Tomography (MSCT) angiography is increasingly considered a valid modality to image coronary artery anatomy in appropriately selected patients. Recent estimates of effective dose for native coronary scans are as much as 3 times that of conventional diagnostic coronary angiography. However, effective dose will increase with scanned length. Hence, doses would be significantly increased for a scan involving free grafts proximally anastomosed to the ascending aorta and further still if internal mammary artery (IMA) grafts are imaged to their origin. Values quantifying this have yet to be published. We aimed to prospectively evaluate the effective doses in 113 patients with bypass grafts followed up as part of the Beating Heart Against Cardioplegic Arrest Study (BHACAS). We compared these values to estimated doses for conventional coronary angiography and MSCT coronary angiography of native arteries previously published by authors from this institute.

Methods A Siemens Sensation 16 scanner was used to perform a topogram, calcium scoring scan (which included any vein grafts), test bolus and coronary angiogram with ECG gating. The manufacturer's standard protocols were used in each case. Effective dose was estimated using the ImPACT Dosimetry Calculator and Monte Carlo data published by the Radiation Protection Division of the UK Health Protection Agency.

Results For our graft study, data from 113 patients were used. Median age was 68.3 years [61.3 - 74.8 years]. The following values are the mean $\pm$ the standard deviation: Estimated effective dose for the calcium scoring scan was $3.1\text{mSv} \pm 0.4$ and for MSCT coronary angiography $21.1\text{mSv} \pm 1.0$. This compares with previous data looking at native artery scans: Calcium scoring scan ($n=63$) $2.6\text{mSv} \pm 0.3$, MSCT coronary angiography ($n=63$) $15.1\text{mSv} \pm 2.1$ and as part of the same study, conventional coronary angiography ($n=91$) $5.6\text{mSv} \pm 3.6$.

Conclusions: MSCT of coronary artery bypass grafts exposes the patient to a significant dose of radiation. In cases involving IMA grafts this can be up to 4 times that involved in a conventional diagnostic coronary angiogram. In practice every effort should be made to keep exposure to a minimum.