UNIVERSIDADE ESTADUAL PAULISTA
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Cristina Schmitt Gregolin

Efeito dos Exercícios Aeróbio e de Força sobre a Remodelação Cardíaca Induzida por Dieta Rica em Açúcar e Gordura

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutora em Patologia.

Orientadora: Profa. Dra. Camila Renata Corrêa Camacho
Coorientador: Prof. Dr. Antonio Carlos Cicogna

Botucatu
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UNIVERSIDADE ESTADUAL PAULISTA

Câmpus de Botucatu

ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE CRISTINA SCHMITT GREGOLIN, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM PATOLOGIA, DA FACULDADE DE MEDICINA - CÂMPUS DE BOTUCATU.

Aos 21 dias do mês de junho do ano de 2024, às 09:00 horas, no(a) Sala de Bioinformática - Unipex - FM/Botucatu - Unesp, realizou-se a defesa de TESE DE DOUTORADO de CRISTINA SCHMITT GREGOLIN, intitulada **Efeito dos Exercícios Aeróbio e de Força sobre a Remodelação Cardíaca Induzida por Dieta Rica em Açúcar e Gordura**. A Comissão Examinadora foi constituída pelos seguintes membros: Profa Dra CAMILA RENATA CORREA CAMACHO (Orientador(a) - Participação Presencial) do(a) Unidade de Pesquisa Experimental (UNIPEX) - FM/Botucatu - Unesp, Prof. Dr. ANDRÉ FERREIRA DO NASCIMENTO (Participação Virtual) do(a) Universidade Federal de Mato Grosso (UFMT), Profa. Dra. FRANCIS LOPES PACAGNELLI (Participação Presencial) do(a) Universidade do Oeste Paulista (Unoeste). Após a exposição pela doutoranda e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, a discente recebeu o conceito final: APROVADA. Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.

Profa Dra CAMILA RENATA CORREA CAMACHO

Camila Renata Correa Camacho

Impacto potencial desta pesquisa

O mundo globalizado tem se direcionado ao consumo de uma dieta comum, a dieta ocidental. A dieta ocidental é caracterizada por conter alimentos de alta densidade calórica e baixa qualidade nutricional. O consumo desse tipo de dieta, em associação ao sedentarismo, é considerado um dos principais fatores de risco para o desenvolvimento das doenças cardiovasculares. As doenças cardiovasculares são as principais causas de morte no mundo, representando um importante problema de saúde pública e econômico. As doenças que afetam o coração possuem o processo de remodelação cardíaca (RC) como base fisiopatológica comum. Nesse sentido, é importante uma melhor compreensão de estratégias terapêuticas que possam atuar sobre o processo de remodelação cardíaca.

Já é bem estabelecido que a prática de exercício físico possui efeitos cardioprotetores capazes de prevenir, reverter ou atenuar as doenças cardíacas. Os efeitos benéficos do exercício físico parecem estar associados ao fato de que sua prática contrapõe os estímulos estressores que levam à remodelação cardíaca patológica. No entanto, ainda existem incertezas sobre como os diferentes tipos de exercício, aeróbio e de força, exercem seus efeitos sobre o processo de RC e se esses efeitos são semelhantes. Essa lacuna é ainda maior quando consideramos um cenário de RC induzida pelo consumo de dieta rica em açúcar e gordura. Somado a isso, a baixa aderência ou incapacidade de realização da prática de atividade física por parte dos indivíduos dificulta seu uso como ferramenta terapêutica.

Portanto, esse estudo irá ajudar a sanar as lacunas sobre como o exercício aeróbio e de força atuam sobre a RC induzida por dieta e auxiliar no entendimento dos mecanismos que conferem o efeito cardioprotetor de diferentes tipos de exercício no coração agredido, assim, guiando a realização de estudos mais aprofundados e possibilitando a descoberta de alvos terapêuticos, facilitando assim o tratamento da RC.

Potential impact of this research

The globalized world has been moving towards the consumption of a common diet, the Western diet. The Western diet is characterized by high-calorie, low-nutrient foods. The consumption of this type of diet, combined with a sedentary lifestyle, is considered one of the main risk factors for the development of cardiovascular diseases. Cardiovascular diseases are the leading causes of death worldwide, representing a significant public health and economic problem. Diseases affecting the heart have cardiac remodeling (CR) as a common pathophysiological basis. Therefore, it is important to better understand therapeutic strategies that can target the cardiac remodeling process.

It is well established that physical exercise has cardioprotective effects capable of preventing, reversing, or attenuating heart diseases. The beneficial effects of physical exercise seem to be associated with the fact that its practice counteracts the stress stimuli that lead to pathological cardiac remodeling. However, there are still uncertainties about how different types of exercise, aerobic and strength training, exert their effects on the CR process and whether these effects are similar. This gap is even greater when considering a scenario of CR induced by the consumption of a diet rich in sugar and fat. Additionally, the low adherence to or inability to perform physical activity by individuals complicates its use as a therapeutic tool.

Therefore, this study will help fill the gaps regarding how aerobic and strength exercise act on diet-induced CR and aid in understanding the mechanisms that confer the cardioprotective effect of different types of exercise on the affected heart. This will guide the conduct of more in-depth studies and enable the discovery of therapeutic targets, thus facilitating the treatment of CR.

Dedicatória

Ao longo da minha jornada acadêmica, a qual foi moldada pelo apoio e colaboração de homens e mulheres, reconheço que não trilhei este caminho sozinha e, por isso, torna-se extremamente desafiador eleger a quem dedicar esse trabalho. No entanto, sempre que reflito sobre meu percurso dentro da academia, uma temática se destaca em minha mente: a experiência de ser mulher e os desafios que essa identidade carrega consigo. Reconheço que fazer ciência no Brasil é uma tarefa desafiadora para qualquer pessoa, dadas as inúmeras barreiras que enfrentamos, como por exemplo, financeiras, estruturais, culturais, educacionais e humanas. Porém, para nós mulheres, esses desafios são amplificados pelo machismo, uma barreira adicional que muitas vezes se mostra mais difícil de superar do que todas as outras combinadas.

Sendo assim, é com imensa admiração que, em nome da minha mãe, Neli Arseila Schmitt Gregolin - mulher de extrema força, determinação e resiliência -, dedico este trabalho a todas as mulheres, cientistas ou não, que, como ela e eu, enfrentam diariamente as adversidades impostas por uma sociedade patriarcal e ainda assim não desistimos e seguimos em busca de nossos sonhos. Que possamos continuar a abrir caminhos e inspirar futuras gerações de mulheres a perseguir seus sonhos, desafiando os limites impostos pela sociedade.

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Epígrafe

“A ciência se origina em e se dedica a uma investigação livre: a ideia é que qualquer hipótese, não importa quão estranha seja, merece ser considerada em seus méritos. A supressão de ideias que sejam desconfortáveis pode ser comum na religião e na política, mas não é um caminho para o conhecimento; não tem lugar no empreendimento científico. Não sabemos com antecedência quem irá ter novos insights fundamentais.”

- Carl Sagan

Resumo

Introdução: Dieta rica em açúcar e gordura, aliada ao sedentarismo, aumenta o risco para doenças cardiovasculares (DCVs), as quais estão entre as principais causas de morte no mundo. A remodelação cardíaca (RC) é uma resposta adaptativa às agressões ao coração, observada nas doenças que atingem o coração, exigindo compreensão de possíveis estratégias terapêuticas. Apesar do efeito benéfico do exercício físico nas DCVs, estudos são necessários para entender como os tipos de exercício podem influenciar a RC. **Objetivo:** Avaliar os efeitos dos exercícios aeróbio e de força sobre os parâmetros ecocardiográficos de ratos com remodelação cardíaca induzida por dieta. **Material e métodos:** Ratos *Wistars* (n=60, 30/grupo) receberam dieta controle (C) ou dieta rica em açúcar e gordura (HSF) por 20 semanas. Após a confirmação da RC por análise ecocardiográfica, os ratos foram redistribuídos em: não treinados (C e HSF) e treinados (C + exercício de força [C+EF]; C + exercício aeróbio [C+EA]; HSF + exercício de força [HSF+EF]; HSF + exercício aeróbio [HSF+EA]). Exercício aeróbio (EA): corrida em esteira (1h/dia) alternando 8 min a 80% e 2 min a 20% da capacidade máxima (CM). Exercício de força (EF): subidas em escada com cargas crescentes, 50%, 75%, 90% e 100% da CM, 1 min de descanso entre as subidas. Os protocolos foram realizados 5x/sem. durante 8 semanas. Na 28ª semana, os grupos foram reavaliados por análise ecocardiográfica. Estatística: MANOVA e Bonferroni ($p<0,05$). **Resultados:** Na 20ª semana os grupos HSF apresentaram remodelação cardíaca concêntrica, e disfunção diastólica e sistólica, bem como aumento da pressão arterial sistólica (PAS), hiperglicemia e hipertrigliceridemia. Após os protocolos foi observado melhora da capacidade física avaliada pelo teste de esforço aeróbio ou de força nos grupos treinados. Com relação aos parâmetros metabólicos os EA e EF preveniram o ganho de peso ao longo do tempo e reduziram a PAS. Na análise ecocardiográfica, os EA e EF reduziram a ERVE e ainda que o EF normalizou o tamanho do átrio esquerdo (AE) e a relação AE/aorta. Em relação a função sistólica, ambos os exercícios aumentaram o volume sistólico ejetado, mantiveram a fração de ejeção e a % de encurtamento endo e mesocárdico, bem como reverteram o decréscimo da VEPP nos animais HSF. Quanto à função diastólica, apenas o EF normalizou os tempos de relaxamento isovolumétrico e desaceleração da onda E, e relação E'/A' nos animais HSF, divergindo do EA. O índice de performance miocárdica manteve-se alterado apenas em HSF+EA. **Conclusão:** Ambos os exercícios melhoraram os parâmetros ecocardiográficos associados a estrutura e função sistólica de ratos com RC induzida por dieta HSF de forma semelhante, entretanto a modulação dos parâmetros de função diastólica é distinta.

Palavras-chave: disfunção cardíaca, obesidade, dieta hipercalórica.

Abstract

Introduction: A diet rich in sugar and fat, combined with sedentary lifestyle, increases the risk for cardiovascular diseases (CVDs), which are among the leading causes of death worldwide. Cardiac remodeling (CR) is an adaptive response to heart insults observed in heart diseases, requiring understanding of potential therapeutic strategies. Despite the beneficial effect of physical exercise on CVDs, studies are needed to understand how types of exercise may influence CR. **Objective:** To evaluate the effects of aerobic and strength exercises on echocardiographic parameters of rats with diet-induced cardiac remodeling. **Materials and methods:** Wistar rats (n=60, 30/group) received control diet (C) or high-sugar-fat diet (HSF) for 20 weeks. After confirmation of CR by echocardiographic analysis, rats were redistributed into: untrained (C and HSF) and trained (C + strength exercise [C+SE]; C + aerobic exercise [C+AE]; HSF + strength exercise [HSF+SE]; HSF + aerobic exercise [HSF+AE]). Aerobic exercise (AE): treadmill running (1h/day) alternating 8 min at 80% and 2 min at 20% of maximum capacity (MC). Strength exercise (SE): stair climbing with increasing loads, 50%, 75%, 90%, and 100% of MC, 1 min rest between climbs. Protocols were conducted 5x/week for 8 weeks. In the 28th week, groups were reevaluated by echocardiographic analysis. Statistics: MANOVA and Bonferroni ($p<0.05$). **Results:** At the 20th week, HSF groups showed concentric cardiac remodeling and diastolic and systolic dysfunction, as well as increased systolic blood pressure (SBP), hyperglycemia, and hypertriglyceridemia. After the protocols, improvement in physical capacity was observed as evaluated by aerobic or strength test in trained groups. Regarding metabolic parameters, AE and SE prevented weight gain over time and reduced SBP. In echocardiographic analysis, AE and SE reduced left ventricular relative wall thickness (RWT), and SE normalized left atrium (LA) size and LA/aorta ratio. Regarding systolic function, both exercises increased ejection volume, maintained ejection fraction (EF) and endo- and mesocardial fractional shortening, and reversed the decrease in posterior wall shortening velocity (PWSV) in HSF animals. Regarding diastolic function, only SE normalized isovolumetric relaxation time (IVRT) and E-wave deceleration time (EDT), and E'/A' ratio in HSF animals, diverging from AE. Myocardial performance index remained altered only in HSF+AE. **Conclusion:** Both exercises improved echocardiographic parameters associated with structure and systolic function in rats with HSF diet-induced CR similarly, however, modulation of diastolic function parameters is distinct.

Key words: cardiac dysfunction, obesity, hypercaloric diet.

Sumário

Sumário

Capítulo I

Revisão de Literatura

1.1. Doenças cardiovasculares e remodelação cardíaca

O coração juntamente com os vasos sanguíneos, compõem o sistema cardiovascular; as injurias que atingem esse sistema são denominadas de doenças cardiovasculares (DCVs). As DCVs são consideradas a principal causa de morte no mundo[1]. Segundo a Organização Mundial da Saúde (OMS), 17,9 milhões de pessoas morrem anualmente em decorrência das DCVs, o que corresponde a 32% das mortes globais. Dentre os óbitos por DCVs, 85% são decorrentes de infarto do miocárdio e acidente vascular encefálico[1]. No Brasil, as DCVs correspondem a 30% das mortes atribuídas as doenças crônicas não transmissíveis e, no ano de 2017, a taxa de incidência padronizada por idade foi de 687,5 casos por 100 mil habitantes[2]. Além de serem o grupo de doenças que mais mata no Brasil e no mundo, as DCVs são às que mais impactam nos gastos diretos com hospitalização e indiretos por redução da produtividade devido à ausência ao trabalho[2]. As DCVs e suas complicações resultaram em um gasto de US$ 4,18 bilhões na economia brasileira entre 2006 e 2015[2]. Assim sendo, as doenças cardiovasculares representam um significativo desafio tanto em termos de saúde pública quanto econômico.

O coração é um órgão que pode ser visto como “bomba”, uma vez que sua função é “bombear” o sangue através do sistema vascular de forma a manter a perfusão dos tecidos periféricos atendendo às demandas bioquímicas corporais. Para que isso ocorra, o coração deve manter os gradientes pressóricos entre as câmaras cardíacas (átrios e ventrículos direitos e esquerdos) em níveis ideais, a fim de permitir seu enchimento adequado, durante o período da diástole, e gerar estresse sistólico parietal, durante a sístole, que energiza o sangue intraventricular com capacidade de superar a impedância do sistema arterial e acarretar a ejeção do sangue para a aorta e demais artérias. Nesse sentido, a força deformante (capacidade contrátil) deve superar a força antideformante intrínseca (matriz extracelular) e extrínseca (pressão diastólica aórtica). Posto isso, existem quatro fatores que regulam a função cardíaca: 1) Frequência cardíaca, 2) capacidade intrínseca miocárdica, 3) pré-carga e 4) pós-carga. Quando ocorre alteração de qualquer um desses fatores regulatórios cardíacos, o coração deve se adaptar para atender a essa

nova exigência e manter a função cardíaca adequada. A esse processo adaptativo é dado o nome de remodelação cardíaca (RC).

A RC é definida como a mudança na expressão genômica resultando em alterações moleculares, celulares e intersticiais e manifestada clinicamente como alterações no tamanho, forma e função do coração[3]. Considerando que a RC é um mecanismo adaptativo, ela pode ter caráter 1) fisiológico, pois condições saudáveis como gravidez ou prática de exercício físico geram estresse capaz de alterar os fatores que regulam a função cardíaca; ou 2) patológico, uma vez que injurias sustentadas também geram estresse capaz causar desequilíbrio dos fatores que regulam e mantem a função cardíaca, como exemplo temos, a hipertensão arterial (aumentando a pós carga), infarto agudo do miocárdio (afetando a capacidade intrínseca miocárdica) e o desbalanço imunológico, metabólico e redox associado à obesidade e ao consumo de dieta desequilibrada[3-5].

Embora ambas as formas de RC sejam processos adaptativos e possam compartilhar características semelhantes, elas são decorrentes de estímulos desencadeadores distintos que possuem tempos de duração distintos. Nesse sentido, os eventos moleculares que precedem a RC variam de acordo com o tipo de estímulo estressor, o que, por conseguinte, resulta em desfechos diversos.[3,6]. O padrão hipertrófico fisiológico é marcado pela integridade e equilíbrio entre os diferentes constituintes do tecido miocárdico (moleculares, celulares, intersticiais e vasculares), normalidade da relação entre a espessura da parede e o diâmetro das cavidades atrial e ventricular, preservação ou melhoria do quadro bioenergético, funcional e dos sistemas antioxidantes, bem como, regeneração. A adequação do sistema cardiovascular, na remodelação cardíaca fisiológica, apresenta branda hipertrofia do cardiomiócito (10-20%), com ausência de fibrose e morte celular, o que a torna reversível e não representa um risco potencial para a falência cardíaca[6]. Por outro lado, a hipertrofia patológica é geralmente acompanhada por fibrose intersticial e perivascular e morte de cardiomiócito com aumento dos níveis de colágeno tipo I, bem como ativação de miofibroblastos fazendo com que a harmonia tecidual, geométrica, energética e antioxidante seja rompida, comprometendo a performance cardíaca[3,4,6].

A RC patológica possui etiologia diversa, no entanto, é importante reforçar, que independente da etiologia, os desajuste que que fazem a RC mudar de um processo adaptativo a mal adaptativo podem ser categorizados em 1) ventriculares: dilatação, adelgaçamento da parede, aumento da esfericidade e incompetência da valva mitral; 2) miocárdicos: perda de cardiomiócitos por necrose, apoptose e autofagia, degradação da matriz extracelular e fibrose, e rarefação da microvasculatura, e 3) miocitários: reexpressão de genes fetais, desarranjo mitocondrial, perda de miofilamentos, hipertrofia, alteração nas proteínas contráteis e no citoesqueleto, miocitólise, dessensibilização adrenérgica, prejuízos no acoplamento excitação/contração/relaxamento, distúrbio metabólico-energético, alta expressão de citocinas inflamatórias e estresse oxidativo[7].

A RC pode ser considerada a base fisiopatológica comum nas doenças cardíacas, e embora inicia-se como uma medida compensatória ao aumento da demanda cardíaca, sucumbe a natureza nociva e persistente do estímulo, acarretando deterioração da função, progressão para insuficiência cardíaca e aumento do risco de morte súbita[6,8]. Desta forma, a condução de estudos destinados a esclarecer sua fisiopatologia e fornecer *insights* acerca de potenciais alvos terapêuticos se torna imperativo.

1.2. Dieta ocidental e potencias mecanismos fisiopatológicos associados a remodelação cardíaca

Os processos de industrialização, urbanização e globalização desencadearam transformações significativas nos aspectos sociais, econômicos e culturais, resultando em modificações nos hábitos de vida da população, incluindo a mudança dos padrões alimentares. Esse fenômeno, particularmente evidente nas regiões ocidentais, é em grande parte impulsionado pela indústria alimentícia, que contribuiu para que o perfil alimentar passasse a ser representado pelo consumo da chamada “Dieta Ocidental” (DO)[9]. Zimmet[10] usou o termo “Coca-colonização”, para fazer referência à presença onipresente da Coca-Cola, Pepsi e McDonald’s, descrevendo um mundo que está se movendo em direção à uma dieta comum, a Dieta Ocidental. A DO é caracterizada pela presença de alimentos, ricos em açúcares refinados, sal, farinha branca, carnes

processadas, gorduras animais purificadas e aditivos alimentares, e que, possuem baixas quantidades de fibras, vitaminas, minerais e outras moléculas derivadas de plantas, como antioxidantes[11].

Nas últimas décadas, o número de estudos que associam o consumo da DO ao desenvolvimento das doenças cardiovasculares vem crescendo[12,13], no entanto, ainda há muito a ser compreendido. Iqbal, et al[12], em estudo de caso controle padronizado, chamado INTERHEART, o qual incluiu 5.761 casos e 10.646 indivíduos controle, envolvendo participantes de 52 países, mostrou que a ingestão da dieta ocidental (alta carga em alimentos fritos, alto teor de sódio e ingestão de carne), avaliada por um escore de risco dietético, aumenta em 30% o risco de infarto agudo do miocárdio (IAM). Srour et al.[14] em um estudo de coorte prospectivo (NutriNet-Santé), com 105.159 participantes, verificaram que o alto consumo de alimentos ultraprocessados foi associado a maiores riscos de doenças cardiovasculares, coronarianas e cerebrovasculares. Neste mesmo sentido, Juul et al.[15] no “Framingham Offspring Study”, verificaram que o consumo de cada porção diária adicional de alimentos ultraprocessados foi associada a 7%, 9%, 5% e 9% do aumento no risco de doença cardiovascular grave, doença arterial coronariana grave, doenças cardiovasculares (DCV) em geral e mortalidade por DCV respectivamente. Estes estudos sustentam que o maior consumo de alimentos ultraprocessados e com alto teor se açúcar e gordura está associado ao aumento do risco de incidência e mortalidade por DCV.

Posto isso, quais são os mecanismos fisiopatológicos que conectam o consumo da dieta ocidental ao desenvolvimento das doenças cardíacas? O consumo da dieta ocidental é caracterizado por criar desequilíbrio energético e nutricional, juntamente com a ativação, seja direta ou indireta, do sistema imunológico. Nesse contexto Christ. A., Lauterbach, M. e Latz, E.[11] sugerem que o consumo da DO está intimamente ligado à perda da homeostase imuno-metabólica. Portanto, a desregulação imuno-metabólica emerge como pilar fisiopatológico para o desenvolvimento das doenças crônicas associadas ao consumo da dieta ocidental, entre as quais as doenças cardíacas.

Como mencionado anteriormente, dentre as principais características da dieta ocidental, está a presença de alimentos com alta densidade calórica.

Assim, o consumo crônico da DO favorece o desequilíbrio energético entre as calorias consumidas e as calorias gastas direcionando para o desenvolvimento da obesidade - é importante ressaltar que além do desbalanço entre o consumo e gasto calórico, fatores genéticos, epigenéticos, fisiológicos, comportamentais, socioculturais e ambientais também contribuem para a manifestação da obesidade[16]. A obesidade é uma doença caracterizada pelo acúmulo excessivo de gordura corporal, sendo assim, o tecido adiposo pode ser considerado o órgão inicialmente prejudicado.

A função primordial do tecido adiposo (TA) é estocar, em forma de triglicerídeos, o excesso de energia consumida e mobilizá-la quando necessário. Em adição, o TA também atua como órgão endócrino por secretar diversas substâncias denominadas adipocinas, como por exemplo hormônios, citocinas e fatores de crescimento[17,18]. Essas moléculas estão envolvidas em diversos processos metabólicos, entre os quais podemos citar, a regulação da sinalização da insulina, uso da glicose e oxidação de ácidos graxos[18]. Em condições de obesidade, a sobrecarga energética, nos adipócitos, atua como gatilho estressor inicial, para a instauração de um processo inflamatório, o qual tem por intuito promover o remodelamento do TA para se ajustar a demanda aumentada. O processo de remodelamento do tecido adiposo é caracterizado por hiperplasia (aumento do número de células) e hipertrofia (aumento do tamanho das células) dos adipócitos, infiltração de células imunes e remodelação da matriz extracelular (MEC)[16]. Esses processos adaptativos promovem, primeiramente, a expansão saudável do TA que ocorre simultaneamente a redução do estoque de triglicerídeos. Esse processo inicial de adaptação do TA, ocorre a custas da perda da homeostase corpórea, levando ao aumento dos níveis circulantes de substâncias como triglicerídeos e glicose. Em uma tentativa de estabelecer a homeostase corpórea, os sistemas atuam para atingir um novo ponto de equilíbrio, caracterizado elevação de peso, níveis circulantes de glicose e lipídeos sanguíneos, tônus simpático e níveis hormonais. A longo prazo, a permanência da sobrecarga energética e da inflamação acarretam desregulação dos mecanismos adaptativos e levam a disfunção do tecido adiposo, sendo caracterizada pela secreção desregulada de adipocinas, com aumento da secreção de citocinas pró-inflamatórias, armazenamento excessivo de lipídios e

adipogênese, bem como angiogênese prejudicada, hipóxia local e fibrose. Essas alterações metabólicas associadas a limitação na expansibilidade do tecido adiposo afetam homeostase metabólica global e também leva ao acúmulo de gordura ectópica com consequências lipotóxicas[19].

Além do desequilíbrio energético associado ao desenvolvimento da obesidade, a DO também acarreta desequilíbrio nutricional, por ser pobre em fibras, vitaminas, minerais e compostos bioativos que se comportam como antioxidantes. Essas características da DO à associam a deterioração da barreira intestinal devido ao desequilíbrio dos microorganismos que povoam o intestino[20]. A preservação da integridade da barreira intestinal é de extrema importância para a manutenção da saúde, uma vez que ela desempenha um papel crucial na proteção do organismo contra micróbios intestinais, antígenos alimentares e toxinas[21]. A diminuição dos microrganismos comensais que normalmente habitam a mucosa intestinal, sendo substituídos por patógenos é denominada de disbiose[21]. A dieta ocidental é pobre em fibras, o que favorece o desaparecimento gradual de cepas bacterianas que normalmente se alimentam de fibras, reduzindo a produção de ácidos graxos de cadeia curta, que possuem efeitos regulatórios benéficos sobre a barreira intestinal. Juntamente com a redução de microrganismos específicos, a baixa ingestão de fibras faz com que outros microrganismos comensais alterem seu metabolismo e passem a degradar o muco glicanos que protegem o intestino. A DO também é rica em alimentos contendo emulsificantes, frutose, sal e adoçantes artificiais, os quais são capazes de induzir disbiose. Por consequência, a disbiose leva a redução da produção de muco, proteínas antimicrobianas, células T regulatórias, bem como alteração da estrutura das “tight junstion” e por fim, aumento da permeabilidade intestinal. Essas alterações acarretam a produção aumentada de padrões moleculares associado a micróbios (MAMPs) que, devido ao aumento da permeabilidade da barreira intestinal, são translocados para a parede intestinal ou corrente sanguínea, podendo então acarretar endotoxemia bem como a instauração de uma inflamação crônica de baixo grau e distúrbios metabólicos[22], os quais tem sido associado ao desenvolvimento de doenças cardiovasculares[23].

Um outro importante fator estressor envolvendo consumo da DO é o

estabelecimento de estresse oxidativo (EO). Fato associado tanto ao desequilíbrio energético quanto a escassez de antioxidantes presente nesse tipo de dieta. Os radicais livres – espécies reativas de oxigênio (EROS) e nitrogênio (ERN) - são espécies instáveis e altamente reativas geradas acidentalmente em nosso corpo, principalmente como subproduto do metabolismo ou durante o processo de fagocitose[24,25]. Os radicais livres possuem papel dubio no organismo, podendo atuar como sinalizadores moleculares ou, quando em excesso, como promotores de danos a proteínas, lipídeos e DNA. Portanto, equilíbrio entre pró-oxidantes e antioxidantes celulares é essencial para manutenção da função celular e qualquer desvio neste sistema onde a geração de ERO exceda a capacidade antioxidante da célula resulta em estresse oxidativo e disfunção celular[24,26]. Uma vez que os radicais lives são um subproduto do metabolismo, a principal fonte de produção de EROS no organismo é a mitocôndria. Os macronutriente - carboidratos, lipídeos e proteínas - provenientes da dieta são degradados a glicose, ácidos graxos e aminoácidos, sendo a glicose e os ácidos graxos usados como principal fonte energética do organismo para síntese de ATP. A glicose e os ácidos graxos serão convertidos a Acetil Coenzima A (Acetil-CoA) que através do Ciclo de Krebs dará origem aos agentes redutores FADH2 e NADH, que irão fornecer elétrons para a cadeia transportadora de elétrons mitocondrial, que possui como produto final a formação de ATP; no entanto, alguns dos elétrons transferidos ao longo da cadeia de transporte de elétrons escapam, e a redução sequencial de oxigênio através da adição de elétrons leva à formação de uma série de EROS. Portanto, produção de EROS é um subproduto inevitável da atividade da cadeia respiratória mitocondrial[24,25,27]. Em condições de normalidade há um equilíbrio entre a produção de espécies reativas de oxigênio e sua neutralização pelos mecanismos antioxidantes corporais. Porém, em um cenário de sobrecarga energética, o fornecimento excessivo de elétrons para a cadeia transportadora mitocondrial supera a demanda por ATP (oferta energética maior que os gastos energéticos), acarretando aumento de potencial de membrana mitocondrial, e como consequência, ocorre uma produção crescentes de EROS, que ultrapassa a capacidade antioxidante do organismo[24].

Além da mitocôndria, o excesso de nutrientes – hiperglicemia,

hipertrigliceridemia, ácidos graxos livres, também podem levar a formação de EROS e ERN de inúmeras outras formas, entre as quais podemos citar o aumento da atividade da xantina oxidase (XO), NADPH oxidase (NOX), via do poliol, via da hexosamina, atividade da proteína quinase C (PKC) e aumento da síntese de produtos finais de glicação (AGEs) e lipoxidação (ALEs) avançada. A produção excessiva de EROS e ERN e a consequente instauração do estresse oxidativo, desempenha um papel em várias doenças, incluindo doenças neurodegenerativas, inflamatórias e cardiovasculares[24,25].

Nesse contexto, é possível compreender que a dieta ocidental atua como uma fonte de desequilíbrio tanto energético quanto nutricional. Esse desequilíbrio, por sua vez, acarreta a perda da homeostase imuno-metabólica nos diversos tecidos corporais. A perda da homeostase metabólica e imunológica associa-se ao estabelecimento crônico de baixo grau de inflamação e estresse oxidativo. O desequilíbrio imuno-metabólico pode ser caracterizado, entre outras alterações, pela instauração da obesidade e disbiose intestinal. Os quais estão intimamente associados ao surgimento de outros distúrbios metabólicos e hormonais como resistência à insulina, lipotoxicidade e disfunções no sistema renina-angiotensina-aldosterona e simpático, assim como perturbações hemodinâmicas e mecânicas, como aumento do volume plasmático e hipertensão arterial. Essas alterações, de forma direta ou indireta, impactam os mecanismos regulatórios do coração e, consequentemente, desencadeiam o processo de remodelação cardíaca patológica. Além disso, é fundamental destacar que a instauração crônica de baixo grau da inflamação e estresse oxidativo somado ao processo de senescência aumentam substancialmente o risco de desenvolvimento de doenças cardíacas.

Diante do exposto torna-se crucial a realização de pesquisas de estratégias, tanto farmacológicas quanto não farmacológicas, capazes de interferir nos mecanismos fisiológicos subjacentes ao desenvolvimento da remodelação cardíaca. E por conseguinte, barrar sua progressão ou até mesmo reverter o processo de remodelamento cardíaco, contribuindo assim para a redução do impacto das doenças cardíacas no bem-estar da população e na economia.

1.3. Exercício físico e o coração

O exercício ou treinamento físico pode ser definido como um subconjunto da atividade física, caracterizado pela realização repetida de movimentos corporais, executados de forma planejada e estruturada, que envolve a melhora ou manutenção de um ou mais componentes da aptidão física ou saúde[28]. O exercício físico é geralmente separado em dois tipos o aeróbio e de força. O exercício aeróbio envolve exercícios realizados por longos períodos (por exemplo, 10 a 40 minutos), de forma contínua, com grande atividade muscular envolvendo centenas de repetições consecutivas que desafiam a entrega de oxigênio para os músculos ativos. Por outro lado, os programas de exercícios de força envolvem treinamento com pesos e/ou uso de máquinas de alta resistência com exercício limitado a algumas repetições (geralmente menos de 20) de forma intermitente[29].

Para melhor entender como os exercícios aeróbio e de força promovem as adaptações cardíacas é importante voltar nosso olhar para as respostas cardiovasculares associadas a cada modalidade. Durante a prática de exercício físico a demanda energética se eleva em relação aos níveis de repouso, desafiando os fatores regulatórios cardíacos. Predominantemente, a oferta energética ocorre a partir do uso de oxigênio, portanto, para atender à demanda aumentada de oxigênio, os sistemas cardiovascular e respiratório devem se ajustar a fim de suprir adequadamente os músculos em atividade[30]. É importante ressaltar que a magnitude das adaptações cardiovasculares é dependente da modalidade, duração, intensidade e padrão da atividade executada. Posto isso, a execução de exercício aeróbio requer maior aporte energético, do que a prática de exercício de força estático ou dinâmico e consequentemente, mais oxigênio (daí o uso do termo aeróbio, com oxigênio)[31]. Esse fato está associado ao seu caráter contínuo que envolve repetições consecutivas de movimentos musculares. Outra importante característica do exercício aeróbio é o estabelecimento de um estado estável/platô, definido com momento em que a energia ofertada se equilibra ao gasto energético demandado para a realização do exercício e os fatores responsáveis pelo fornecimento dessa energia atingem níveis elevados (acima do repouso) de equilíbrio. De modo geral, durante a execução de exercício aeróbio ocorre rápido aumento do volume sistólico

ejetado até que o estado estável seja atingido. O aumento do volume de ejeção ocorre devido ao aumento do retorno venoso – promovido pelo aumento da constrição venosa em decorrência da contração da musculatura esquelética - que irá aumentar o volume diastólico no final do ventrículo esquerdo – pré-carga. O aumento da pré-carga gera maior estiramento do miocárdio e maior força de contração em decorrência do mecanismo de Frank-Starling. O sistema nervoso simpático, ativado pela execução do exercício físico, também possui papel fundamental no aumento da força de contração cardíaca. Assim o aumento do volume diastólico final do ventrículo esquerdo associado a diminuição do volume sistólico final do ventrículo esquerdo, gera o aumento do volume ejetado. Em atividades de longa duração e alta intensidade, pode ocorrer uma diminuição do volume sistólico ejetado após atingido o platô, devido à regulação térmica que diminui o retorno venoso, causada pela vasodilatação aumentada, redistribuição sanguínea e perda de volume plasmático[31,32]. A frequência cardíaca (FC) também se eleva rapidamente até que o estado estável seja atingido, e ao contrário do volume de ejeção, pode se acentuar após atingir esse limiar de estabilidade durante a prática de exercido aeróbio intenso e de longa duração devido a diminuição do volume de ejeção sistólico. Inicialmente o aumento da FC ocorre em decorrência a diminuição da atividade parassimpática e a *posteriori* por ativação do sistema nervoso simpático. Uma vez que o débito cardíaco (DC) é dependente da variação do volume sistólico ejetado e da frequência cardíaca (DC = FC X volume sistólico) ele também se eleva, até que seja atingido o estado estável. Com relação aos níveis pressóricos, há aumento rápido da pressão arterial sistólica (PAS) até que o platô seja alcançado, efeito associado ao aumento do volume de ejeção sistólico. Já a pressão diastólica parece não se alterar ou se elevar suavemente em decorrência do aumento da vasodilatação periférica. Desde que há aumento da pressão sistólica e manutenção da pressão arterial diastólica a pressão arterial média se eleva acompanhando a modificação da pressão arterial sistólica. A resistência periférica total (RVPT) diminui rapidamente até que seja atingido o platô, esse fato contribui para que a PAS não atinja valores ainda mais acentuados bem como o aumento do aporte sanguíneo para o músculo em trabalho. A diminuição da RVPT, ocorre devido aumento do metabolismo na musculatura esquelética

associada ao aumento da vasodilatação periférica[31,32].

A modalidade de exercício físico de força, envolve uma combinação de movimentos estáticos e dinâmicos. Inicialmente, há uma contração estática até que a força muscular ultrapasse a carga a ser levantada, desencadeando o movimento subsequente, que pode ser uma contração dinâmica concêntrica (encurtamento) ou excêntrica (alongamento). Além disso, existe o componente estático associado à manutenção da carga. Durante a execução do exercício de força dinâmico há uma dissociação entre a demanda energética e o sistema cardiorrespiratório. Parte dessa dissociação se deve ao fato de que grande parte da energia utilizada nessa modalidade de exercício é proveniente de fontes anaeróbias (sem oxigênio), contrastando com os exercícios aeróbios. Somado a isso, durante a execução do exercício de força ocorre constrição mecânica do fluxo sanguíneo para a musculatura, devido à natureza estática da contração, que irá afetar a atividade do sistema cardiovascular. Posto isso, as adaptações cardiovasculares em decorrência do exercício de força dinâmico possuem características das atividades aeróbias e isométricas/estáticas[32]. A resposta cardiovascular durante a execução do exercício de força é extremamente dependente da carga/intensidade e número de repetições, desta forma, quanto mais alta a carga e número de repetições maior será a resposta do sistema cardiovascular. Em um contexto geral o exercício de força está associado a leve aumento ou redução do volume ejetado. Esse contraste entre o exercício aeróbio e de força em relação ao volume de ejeção está associado ao perfil estático e ao predominante uso de fontes anaeróbias de energia. Durante a execução de exercícios estático de baixa intensidade e alta intensidade ocorre a manutenção ou redução do volume de ejeção sistólico, respectivamente. A redução do volume de ejeção parece estar associada à diminuição da pré-carga, gerada pelo aumento da pressão intratorácica (manobra de Valsalva) que comprime a veia cava e reduz o retorno venoso, e aumento da pós-carga em decorrência do aumento da pressão arterial sistólica. Com relação aos níveis pressóricos, a PAS também se eleva gradualmente em decorrência do aumento das repetições, por outro lado, não há alteração da pressão arterial diastólica (PAD). Em uma condição de exercício estático a pressão arterial sistólica mante-se constantemente elevada assim como a PAD. É importante ressaltar que o

aumento da PAS observada durante a execução do exercício estático é superior à observada na realização da atividade aeróbia. Nesse mesmo sentido, a pressão arterial média também aumenta a níveis mais elevados que na atividade aeróbia. O aumento do trabalho na musculatura esquelética durante a execução de exercício estático, assim como no exercício aeróbio, também aumenta a demanda metabólica, no entanto a tensão intramuscular promove constrição mecânica dos vasos sanguíneos e impede o fluxo sanguíneo. A constrição dos vasos durante a fase estática do exercício de força acarreta acumulo de produto do metabolismo (H^+, ADP e entre outros) levando a estimulação reflexa e elevação da PAS. A resistência periférica total se eleva ligeiramente durante a execução do exercício de força, contribuindo para o aumento da PAS. Porém, no exercício estático pode haver uma redução contudo, essa redução é inferior à observado durante a execução de exercício aeróbio e não se predomina ao aumento da contrição mecânica dos vasos. Assim como a pressão arterial, a frequência cardíaca tende aumentar gradualmente em associação ao aumento da intensidade (carga ou número de repetições) do treinamento[31].

No que diz respeito às adaptações estruturais, o exercício de força, especialmente na forma estática, é reconhecido por impor uma carga pressórica adicional ao miocárdio devido ao aumento da pressão arterial sistólica[31,33]. Esse aumento da PAS exige aumento na força contrátil miocárdica para superar a resistência na aorta, gerando maior estresse parietal. Devido a essas características, o exercício de força de alta intensidade e majoritariamente de natureza estática está associado ao desenvolvimento de hipertrofia concêntrica[33,34]. Por outro lado, o exercício aeróbio é visto como modalidade de exercício que impõe carga de volume sobre o miocárdio, em associação ao aumentando do retorno venoso que leva ao aumento do volume diastólico final do ventrículo esquerdo e de ejeção ventricular. Portanto, devido à sobrecarga de volume observada durante a prática do exercício aeróbio ele é associado ao desenvolvimento de hipertrofia excêntrica[34,35].

Devidos as adaptações cardiovasculares associadas ao exercício físico citadas acima, ele tem sido usado como uma importante ferramenta terapêutica não farmacológica para a prevenção e tratamento de inúmeras doenças, entre elas as doenças cardíacas. Os benéficos do exercício sobre a saúde do

coração, em especial o exercício aeróbio - tipo de exercício mais estudado pela comunidade científica - já são comprovados na literatura e, portanto, propõe-se sua inserção como estratégia terapêutica e preventiva à instalação ou agravamento das cardiopatias[36,37]. Os *Guidelines* de saúde cardiovascular recomendam que os indivíduos acumulem pelo menos 150 minutos/semana de atividade física aeróbia de intensidade moderada ou 75 min/semana de atividade de intensidade vigorosa, ou uma combinação equivalente de ambos, realizada em sessões com duração mínima de 10 minutos. Também se recomenda a pratica de atividade de fortalecimento muscular, de intensidade moderada a alta em pelo menos dois dias por semana[38,39].

Estudos evidenciam uma relação inversa entre a prática de exercícios físicos e o desenvolvimento de doenças cardíacas[40]. Esse antagonismo baseia-se no fato de que os efeitos benéficos do exercício parecem contrapor-se aos estímulos patológicos que induzem a remodelação cardíaca[6,41]. O exercício físico pode influenciar diretamente o coração, afetando as várias células e estruturas que compõem o tecido cardíaco, mas também possui efeitos indiretos, uma vez que a atividade física tem a capacidade de influenciar outros tecidos corporais, além do coração (por exemplo, músculos esqueléticos, vasos sanguíneos, tecido adiposo), que, por sua vez, exercem efeitos benéficos secundários sobre o coração[42-46].

Bernardo et al.[8] em uma elegante revisão de literatura descreveram os mecanismos diretos pelos quais o exercício físico (majoritariamente o aeróbio) leva a cardioproteção. Entre eles estão, 1) adaptações dos miócitos cardíacos, que incluem hipertrofia e proliferação, 2) adaptações vasculares, 3) efeitos sobre a atividade elétrica e processo de excitação-contração (E-C) acoplamento, 4) adaptações mitocondriais (metabolismo energético e *status redox*), 5) respostas de estresse celular (sobrevivência e morte), 6) manutenção da matriz extracelular (MEC), e 7) comunicação com outros.

Os efeitos indiretos do exercício físico estão associados a ação do exercício físico sobre outros tecidos além do cardíaco e, portanto, com a modulação os fatores agressores indiretos e fatores de risco associados as doenças cardíacas. Entre esses estes fatores estão a redução dos níveis pressóricos e lipídeos séricos, melhora no metabolismo da glicose, bem como

perda de peso (redução da massa gorda)[47,48].

Embora tanto o exercício aeróbio quanto o exercício de força influenciem as mesmas variáveis fisiológicas e fisiopatológicas envolvidas no processo de remodelação cardíaca, ambos os exercícios possuem natureza distinta e, portanto, o estresse gerado sobre essas variáveis adaptativas pode diferir. Como consequência, a magnitude das adaptações quem influenciam direta e/ou indiretamente ao coração e, portanto, modulam o processo de remodelação cardíaca também podem ser distintas.

Em um contexto amplo, a literatura tem associado o exercício aeróbio com sendo mais eficaz sobre a melhora da capacidade cardiorrespiratória, redução dos níveis pressóricos de repouso (sistólico e diastólico), diminuição da frequência cardíaca de repouso e perda de gordura. Por outro lado, o treinamento de força parece ser superior ao exercício aeróbio com relação ao ganho de massa muscular, força, densidade mineral óssea e melhora da taxa metabólica basal. As duas modalidades de exercício parecem exercer efeitos semelhantes com relação ao metabolismo da glicose (resposta insulínica à glicose, níveis basais de glicose e sensibilidade à insulina) e concentração de lipídeos séricos (HDL e LDL)[47,49].

Contudo, estudos comparando os efeitos de diferentes tipos de exercício sobre a remodelação cardíaca em um cenário de dieta ocidental ainda são escassos. Estudos em humanos que confrontam efeitos de diferentes modalidades de exercício aeróbio e de força são divergentes, mas sugerem que ambas as modalidades possuem efeitos distintos e ainda enfatizam a importância de estudar com mais afinco o efeito do exercício de força, uma vez que o estudo dessa modalidade tem sido negligenciado pela comunidade científica. Lekavich et al. em um estudo prospectivo randomizado e controlado, estudaram os efeitos de 6 meses de treinamento aeróbio versus treinamento de força em homens e mulheres com sobrepeso, dislipidêmicos e sedentários; no momento pós-treinamento foi verificado que o VO_2 relativo, pulso de O_2 e pico de volume de fluxo sanguíneo hiperêmico foram maiores no grupo treinamento aeróbio, mas o volume diastólico final do VE e acoplamento ventrículo-arterial foram maiores no treinamento de força, evidenciando os efeitos diferenciais do treinamento aeróbio e de força na população estudada[50]. Em ensaio clínico

randomizado conduzido por Christensen R.H. et al., 39 participantes sedentários com obesidade abdominal foram alocados aleatoriamente em três grupos: treinamento intervalado de alta intensidade (realizado 3 vezes por semana durante 45 minutos), treinamento de força (realizado 3 vezes por semana durante 45 minutos) ou nenhum exercício (grupo controle). Os resultados indicaram que tanto o exercício aeróbio quanto o de força reduziram o tecido adiposo epicárdico em 32% e 24%, respectivamente, em comparação com o grupo controle. Enquanto o treinamento aeróbio não apresentou redução no tecido adiposo pericárdico, o exercício de força resultou em uma redução de 31% em comparação com o grupo controle. Além disso, ambos os tipos de exercício levaram a um aumento na massa do ventrículo esquerdo. Estes dados destacam a potencial importância preventiva de diferentes modalidades de exercício como forma de reduzir a gordura cardíaca em indivíduos com obesidade abdominal[51]. Em um estudo de meta-análise comparando diferentes modalidades de exercício na insuficiência cardíaca[52], entre as quais modalidades aeróbias e de força, concluiu que o treinamento intervalado é mais eficaz para melhorar a fração de ejeção do ventrículo esquerdo (LVEF - left ventricular ejection fraction) e o diâmetro diastólico final do ventrículo (LVEDD - left ventricular end-diastolic diameter), sugerindo que o treinamento aeróbio é melhor que o de força em um cenário de insuficiência cardíaca.

Assim como os estudos em humanos, estudos em animais comparando os efeitos de diferentes modalidades de exercício em um cenário de remodelação cardíaca induzido por dieta também são escassos. Gomes, M. J. et al. compararam os efeitos do exercício aeróbio e de força no remodelamento cardíaco de ratos infartados que apresentavam hipertrofia do ventrículo esquerdo e disfunção sistólica, e verificaram que o grupo com infarto do miocárdio submetido ao treinamento de força apresentou menor espessura relativa da parede do ventrículo esquerdo do que o grupo com infarto do miocárdio associado ao treinamento aeróbio[53]. Hugo, Q. et al. avaliaram os efeitos do treinamento físico aeróbio ou do treinamento de força em parâmetros morfométricos, funcionais e de estresse oxidativo cardíaco em ratas com privação de hormônio ovariano e diabetes e verificaram que o treinamento físico aeróbio bem como o treinamento de força promovem atenuação da disfunção

morfométrica cardíaca (massa do ventrículo esquerdo, diâmetro da cavidade do ventrículo esquerdo na diástole e espessura relativa do ventrículo) associada à redução do estresse oxidativo. Entretanto, somente o treinamento físico aeróbio dinâmico foi capaz de atenuar a disfunção sistólica e diastólica nesta condição[54].

Diante do exposto e das lacunas existentes na literatura com relação a estudos comparando os efeitos de diferentes modalidades de exercício sobre o processo de remodelação cardíaca em um cenário de dieta rica em açúcar e gordura, faz-se necessário a realização de estudos experimentas para verificar se os exercício aeróbio e de força são capazes de modular a remodelação cardíaca induzida por dieta rica em açúcar e gordura, bem como verificar se o efeito de ambas as modalidades de exercício são distintos ou equivalentes.

A Figura 1 sumariza as informações descritas nas seções acima, sobre como a dieta ocidental pode levar a remodelação cardíaca e como o exercício pode atuar para atenuar esse processo.

1.4. Modelo de estudo

Estudos experimentais *in vivo,* são uma importante ferramenta de pesquisa, pois permitem a aplicação de metodologias invasivas não possíveis em humanos, esse fato, amplia drasticamente a possibilidade de análise e conhecimento sobre a questão de interesse. No entanto, um desafio para os pesquisadores é a escolha de uma modelo animal de doença que reproduza com eficiência o cenário de doença observado nos humanos e seja translacional. Nesse sentido, diversos tipos de dietas foram formulados com o intuito de mimetizar as doenças crônicas de humanos associadas ao consumo da dieta ocidental (obesidade, diabetes tipo 2, doença hepática gordurosa não alcoólica, câncer colorretal e cardiovasculares)[55]. Apesar de ainda conterem fragilidades, esses modelos vêm se mostrando eficazes e essenciais para a realização de estudos pré-clínicos[55].

O nosso grupo de estudo desenvolveu um modelo animal de doenças de humano induzido por dieta que vem se mostrando eficaz para o estudo das doenças crônicas associadas ao consumo da dieta ocidental. Ao longo dos decorrentes estudos, o grupo verificou que ratos tratados dieta rica em açúcares

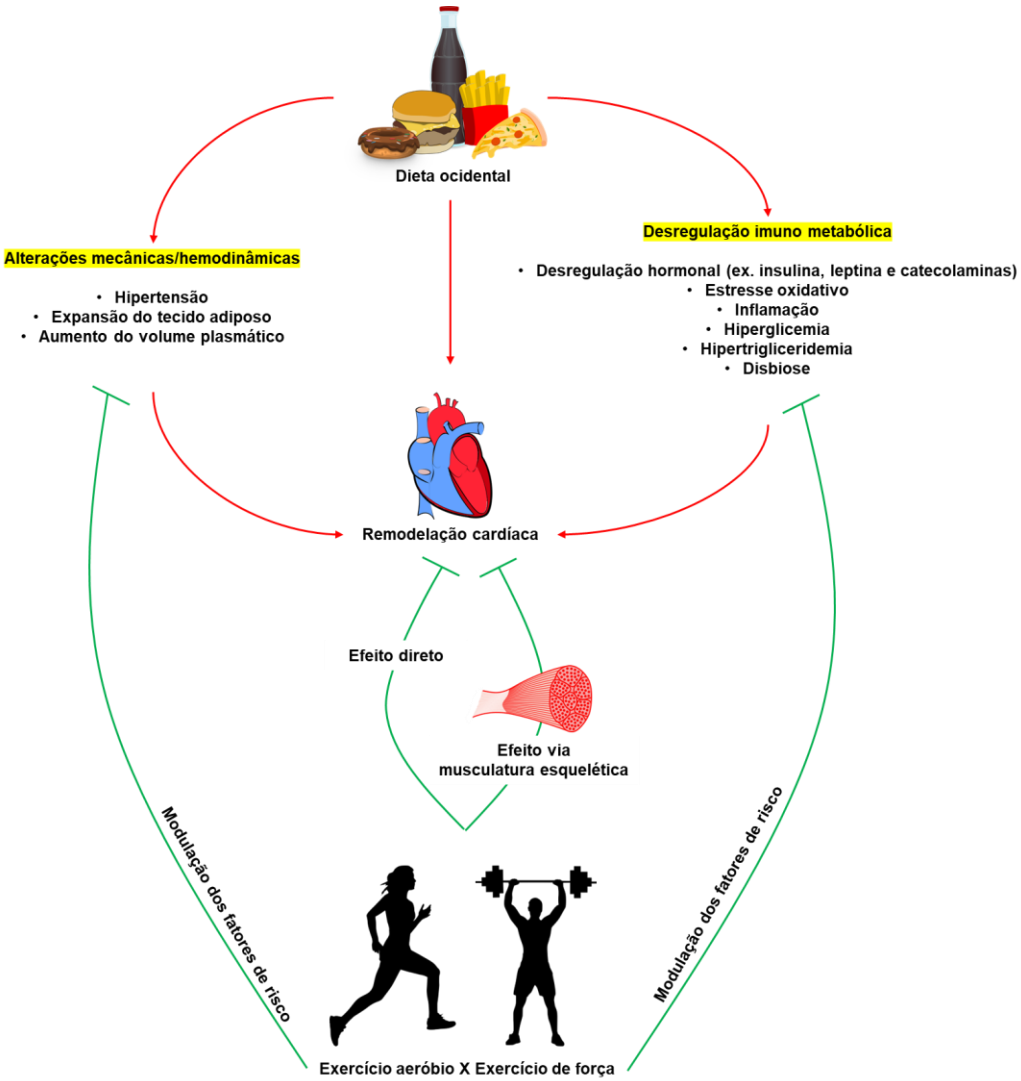

Figura 1 - Síntese dos possíveis caminhos pelos quais a dieta ocidental pode levar ao processo de remodelação cardíaca e possíveis meios pelos quais o exercício físico (aeróbio ou de força) pode atenuar os efeitos da dieta e mitigar o processo de remodelação cardíaca. As setas vermelhas indicam os possíveis meios pelo qual a dieta pode lavar a remodelação cardíaca, os quais podem ser diretos sobre o coração ou indiretos via desregulação imuno-metabólica ou por alterações mecânicas/hemodinâmicas. As setas em verde mostram os possíveis meios pelos quais os diferentes tipos de exercício podem antagonizar/barrar os efeitos da dieta, os quais podem ser por ação direta no coração, através da modulação dos fatores de risco imuno-metabólicos ou mecânicos/hemodinâmicos ou ainda via ação em outros órgãos, tendo como principal a musculatura esquelética.

e gordura (high-sugar-fat-diet, HSF) por 30[56] ou 20[57] semanas desenvolvem disfunção cardíaca, bem como aumento do peso e do índice de adiposidade, hiperglicemia, hipertrigliceridemias, hipertensão e resistência à insulina (HOMA-IR). Outros estudos realizados pelo grupo mostraram ainda que, a mesma dieta é capaz de acarretar, disfunção renal[58-60] e hepática[61-63]. O modelo de dieta

utilizado pelo grupo também promove aumento de marcadores inflamatórios e de estresse oxidativo em diversos tecidos, entre os quais o tecido adiposo[56,64], fígado[62] e coração[56,65].

Segundo a Organização Mundial de saúde (OMS), os principais fatores de risco modificáveis associados ao desenvolvimento das doenças cardíacas e acidente vascular encefálico (AVE) são o consumo de dieta não saudável, juntamente com o sedentarismo, uso de tabaco e uso nocivo de álcool. A presença desses fatores de risco primários, por sua vez, leva ao desenvolvimento de "fatores de risco intermediários" e, entre eles, estão o sobrepeso e a obesidade, hipertensão arterial, hiperglicemia e hiperlipidemias. Levando em conta que o padrão alimentar atual nas sociedades do ocidente tem sido representado pelo consumo da dieta ocidental e que os modelos animais de indução de doenças cardíaca por meio de dietas, em sua grande maioria, também acarretam o desenvolvimento dos fatores de risco intermediários[66,67], espelhando assim o cenário de doença cardíaca observado em humanos, o modelo desenvolvido por nosso grupo se torna um bom modelo para se estudar as doenças cardíacas, por outro lado, a presença de diversas agressões simultâneas, e a ausência de todos os componentes da dieta ocidental (como conservantes) dificulta o estudo isolado dos efeitos da dieta sobre o coração e a reprodução exata da ambiente alimentar que o humano está inserido.

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2. Hipótese

Os exercícios físicos aeróbio e de força agem sobre a remodelação cardíaca, induzida por dieta rica em açúcar e gordura, através da modulação de parâmetros ecocardiográficos distintos.

3. Objetivos

3.1. Objetivo geral

Avaliar os efeitos dos exercícios aeróbio e de força sobre os parâmetros ecocardiográficos de ratos com remodelação cardíaca induzida por dieta.

3.2. Objetivos específicos

- Avaliar os fatores de risco cardiometabólicos induzidos pelo consumo de dieta rica em açúcar e gordura e os efeitos dos diferentes tipos de exercício sobre estes parâmetros;
- Mensurar no tecido cardíaco citocinas inflamatórias e marcadores de estresse oxidativo.

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Capítulo II

Artigo Científico

Effect of Aerobic and Strength Exercises on Cardiac Remodeling Induced by High-Sugar-Fat Diet

Introduction

The processes of urbanization, industrialization and globalization have triggered significant transformations in social, economic and cultural aspects, resulting in changes in the population's lifestyle habits, including changes in eating patterns [1][2].This phenomenon, particularly evident in western regions, is largely driven by the food industry, which contributed to the dietary profile becoming represented by the consumption of the so-called "Western Diet" (WD)[2][3]. The WD is characterized by the presence of foods rich in refined sugars, salt, white flour, processed meats, purified animal fats and food additives, and which have low amounts of fiber, vitamins, minerals and other molecules derived from plants, such as antioxidants[3][4].

The World Health Organization states that unhealthy diet together with the physical inactivity, tobacco use and harmful use of alcohol are the most important behavioural risk factors of heart disease and stroke[1]. In this direction the changes in the eating patterns towards the western diet is contributing to the increase of the cardiovascular diseases (CVDs)[3][5][6]. The CVDs are the leading cause of death globally and they also generate a great impact on direct hospitalization costs and indirect costs due to reduced productivity due to absence from work. So, the CVDs are not only a health problem but also an economic problem[1][3].

The CVDs are a group of disorders the affect blood vessels and the heart. The heart diseases have as a common pathological process the cardiac remodeling (CR). CR is defined as changes in genome expression resulting in molecular, cellular and interstitial changes and manifested clinically as changes in size, shape and function of the heart as a result from cardiac load or injury [7][8][9]. CR is influenced by hemodynamic load, neurohormonal activation and other factors still under investigation. In this direction the consumption of a western diet can affect the heart directly through local activation of the immune system, oxidative stress and metabolic dysregulation, among others; or indirectly, via development of the cardiometabolic risk factors as obesity, low HDL levels, hypertriglyceridemia, hyperglycemia, insulin resistance and hypertension[10][11][12][13].

In this context is very important to investigate therapeutic strategies that could prevent, stop or reverse the CR. Exercise training is considered an important non pharmacological therapeutic strategy since it's well known cardioprotection [14][15][16][17]. Several studies show that it has an inverse relationship with the development of heart disease[18]. This statement is associated with the fact that the beneficial effects of exercise seem to antagonize the direct or indirect pathological stimuli that promotes the cardiac remodeling[14].

Exercise training is generally separated into two types: aerobic and strength exercises. Aerobic exercise involves exercise performed for long periods (e.g., 10 to 40 minutes), continuously, with high muscular activity involving

hundreds of consecutive repetitions that challenge oxygen delivery to active muscles. Strength exercise programs involve weight training and/or use of high-resistance machines with exercise limited to a few repetitions (usually less than 20), intermittently, before exhaustion[19]. Since the different types of exercise have distinct stimuli to the cardiovascular system doe to its different nature, the cardiac adaptation to the heart could also distinct. Whoever is still not well elucidate how different types of exercise could influence the cardiac remodeling induced by a high sugar-fat diet.

Therefore, studying different types of exercise in the context of cardiac remodeling induced by high sugar-fat diet in animal model is essential for better understanding the underlying mechanisms, developing effective interventions, and improving human health outcomes. Also, it could provide insights into the role of exercise as a potential strategy for mitigating the adverse effects of an unhealthy diet on cardiac diseases. Thus, the objective of this study was to evaluate the effects of aerobic and strength exercises on echocardiographic parameters in rats with diet-induced cardiac remodeling.

Materials and Methods

Animals and Experimental Model

Male Wistar rats (21 days, ± 50g) were supplied by São Paulo State University Animal Center-UNESP, Botucatu/SP, and kept in individual polypropylene cages with environment enrichment in a controlled temperature (24˚C ± 2˚C) and relative humidity (55% ± 5%) environment and on a reverse 12h light-dark cycle. The animals (n= 60) were initially randomly divided into two groups (pre-exercise moment): Control (C, n=30) and High Sugar-Fat (HSF, n=30). Over twenty weeks, group C received the Control Diet (CD) contained soybean meal, sorghum, soybean peel, dextrin, soy oil, vitamins, and minerals, and the HSF group received the High Sugar-Fat Diet (HSFD) contained soybean meal, sorghum, soybean peel, dextrin, sucrose, fructose, lard, vitamins, and minerals, plus 25% sucrose in the drinking water. Both diets are described on Table 1 and were adapted from Francisqueti *et al*.[20]. The water and food intake were offered *ad libitum*. At the 20th week both groups underwent to echocardiographic assessment; this evaluation had the objective to verify the presence of cardiac remodeling on the HSF group[21]; it was characterized by the increase of the relative wall thickness (RWT), decrease of the posterior wall shortening velocity (PWSV) and increase of ratio between early diastolic mitral inflow and tissue doppler imaging of early diastolic velocity of mitral annulus (E/TDI E'). After the confirmation of the cardiac remodeling, the animals of the group C were divided in three groups (post-exercise moment): non trained (C, n=10) and trained (C + Aerobic Exercise [C+AE, n=10] and C + Strength Exercise [C+SE, n=10]; and the HSF group was also divided in three groups: non trained (HSF, n=10) and trained (HSF + Aerobic Exercise [HSF+AE], n=10) and HSF + Strength Exercise [HSF+SE], n=10). The experimental design is shown in Figure 1. At the end of the experimental protocol, 24h after the last exercise

section, the rats were fasted for 8h, anesthetized with sodium pentobarbital (40 mg/kg/i.p.), and euthanized by decapitation.

All the experiments and procedures were approved by the Animal Ethics Committee from Botucatu Medical School (1333/2019) and performed in accordance with the National Institute of Health's Guide for the Care and Use of Laboratory Animals[22].

Table 1 – Diets compositions

	Chow	
Components	**Control**	**High-Sugar-Fat ***
Soybean meal (g/kg)	360	345
Sorghum (g/kg)	279	75
Soy hulls (g/kg)	151	113
Maize starch (g/kg)	157	20
Sucrose (g/kg)	-	80
Fructose (g/kg)	-	180
Soybean oil (g/kg)	24	-
Lard (g/kg)	-	154
Minerals (g/kg)	25	25
Salt (g/kg)	4	8
Nutritional values		
Protein (%)	21.12	18.14
Carbohydrate (%)	60.46	53.2
Fat (%)	4.20	16.49
% Energy of protein	23.20	16.74
% Energy from carbohydrate	66.42	49.02
% Energy from fat	10.38	34.25
Energy (kcal/g)	3.64	4.33

*Animals that received the high-sugar-fat diet were given 25% sucrose in their drinking water. The values in the table do not consider sucrose contained in drinking water.

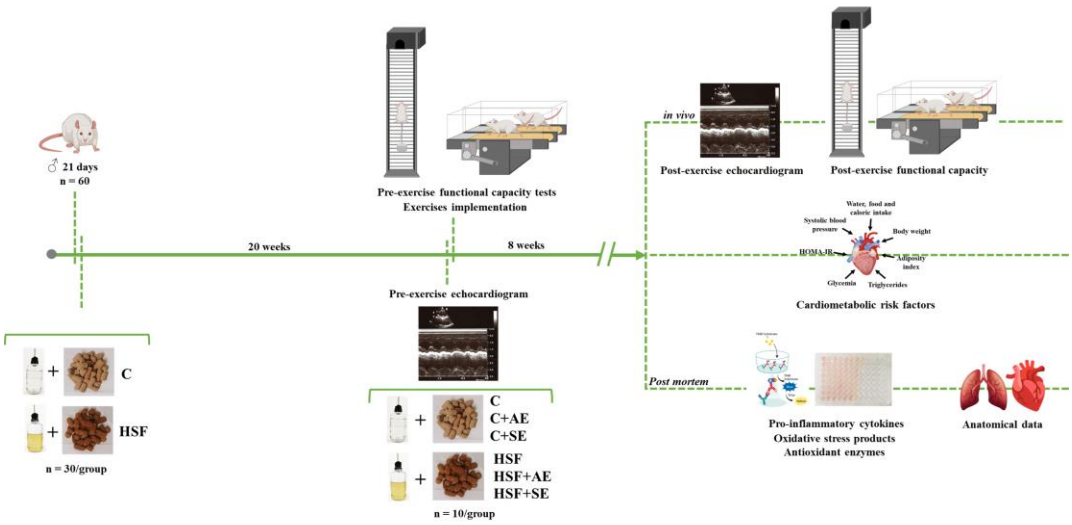

Figure 1 – Experimental design. CD, control diet; HSFD, high-sugar-fat diet; C, control group; C+AE, control + aerobic exercise group; C+RE, control + strength exercise group; HSF, high sugar-fat; HSF+AE, high sugar-fat + aerobic exercise group; HSF+RE, high sugar-fat + strength exercise group.

Maximum carrying load test

Maximum carrying load test (MCLT) was performed on a vertical ladder (1.00 m; 0.20 m, 0.5-cm grid, 80° incline), that required the animals to make 8-12 repetitions per climb. The test was evaluated for each rat by performing ladder climbs with progressively heavier loads. At the first attempt, rats climbed the ladder carrying a load equivalent to 75% of their bodyweight. After completing the first climb, the load was increased by 15% bodyweight until a load was reached where the rats could not climb the entire ladder. The heaviest load that the rat successfully carried the entire length of the ladder was considered the maximum carrying load. Failure was determined when the rat could not progress up the ladder after three successive stimuli to the tail[23][24]. The maximum carrying load test was conducted before and at the end of the strength training protocol for all groups and at the end of the 2^{ed}, 4th, 6th week for groups C+ST and HSF+ST to adjust the training load. The animals were submitted to an acclimatation to the training environment prior the test (Table 2).

Strength exercise protocol

The strength exercise protocol used in this study was adapted from Gomes *et al*.[24] and Leite *et al*.[23]. The trained groups (C+SE and HSF+SE) were submitted to strength training regimens consisting of four climbing sessions. These sessions entailed progressively increasing loads of 50%, 75%, 90%, and 100% of each animal's maximal carrying capacity. A one-minute rest period was implemented between each climb, which took place within the housing chamber

situated at the top of the ladder. This training protocol was administered over an 8-week period, five days per week—Monday through Friday (Table 2).

Table 2 – Acclimatation period and strength exercise protocol

Acclimatation period		
Days	**Load**	**# Climbing**
1st	-	3
2nd	-	3
3rd	-	3
4th	Carrying load apparatus	4
Strength exercise protocol		
Weeks	**Load (g)**	**# Climbing**
	Initial maximum carrying load test	
1st	1x 50%, 1x 75%, 1x 90% e 1x 100%	4
2nd	1x 50%, 1x 75%, 1x 90% e 1x 100%	4
	Maximum carrying load test – Intensity adjustment	
3rd	1x 50%, 1x 75%, 1x 90% e 1x 100%	4
4th	1x 50%, 1x 75%, 1x 90% e 1x 100%	4
	Maximum carrying load test – Intensity adjustment	
5th	1x 50%, 1x 75%, 1x 90% e 1x 100%	4
6th	1x 50%, 1x 75%, 1x 90% e 1x 100%	4
	Maximum carrying load test – Intensity adjustment	
7th	1x 50%, 1x 75%, 1x 90% e 1x 100%	4
8th	1x 50%, 1x 75%, 1x 90% e 1x 100%	4
	Final maximum carrying load test	

Treadmill exercise test

Exercise tolerance was assessed using the exhaustion speed, evaluated by a treadmill exercise test (TET) as previously described[25]. The TET was conducted on a motorized treadmill for rats (AVS Projects – São Carlos, SP, Brazil) following three days of adaptation to a treadmill environment at low speed (5 m/min, 5 to 15 min/day), Table 3. In summary, the TET commenced at 6 m/min and increased by 3 m/min every 3 minutes until exhaustion. Exhaustion was defined by an inability to maintain the proposed speed. Additionally, TETs

were performed at the beginning and end of the exercise protocol for groups C, C+AE, HSF, and HSF+AE to evaluate exercise tolerance. Moreover, TETs were conducted after the 3rd and 5th weeks for groups C+AE and HSF+AE to adjust the training intensity (Table 3).

Aerobic exercise protocol

The aerobic exercise consisted of an aerobic interval training protocol based on the study by Neves *et al*.[26]. The trained groups (C+AE and HSF+AE) were subjected to treadmill training, comprising 30, 40, and 50 minutes in the 1st, 2nd, and 3rd weeks, respectively, and 60 minutes from the 4th to the 8th week. The running sessions were divided into two intensities: 8 minutes at a speed corresponding to 80% of the exhaustion speed and 2 minutes at a speed corresponding to 20% of the exhaustion speed. This training regimen was implemented 5 days per week over 8 weeks (Table 3).

Table 3 – Acclimatation period and aerobic exercise protocol

Acclimatation period		
Days	**Velocity (m/min)**	**Duration (min)**
1st	5	5
2nd	5	10
3rd	5	15
Aerobic exercise protocol		
Weeks	**Velocity (m/min)**	**Duration (min)**
Initial Treadmill exercise test		
1st	80% 8’ e 20% 2’	30
2nd	80% 8’ e 20% 2’	40
3rd	80% 8’ e 20% 2’	50
Treadmill exercise test – Intensity adjustment		
4th	80% 8’ e 20% 2’	60
5th	80% 8’ e 20% 2’	60
Treadmill exercise test – Intensity adjustment		
6th	80% 8’ e 20% 2’	60
7th	80% 8’ e 20% 2’	60
8th	80% 8’ e 20% 2’	60
Final treadmill exercise test		

Nutritional profile

The nutritional profile was characterized by body weight, chow, water, and caloric intake, which were evaluated at the pre- and post-exercise moments. Body weight was measured weekly, while food and water intake were calculated daily. Caloric intake was determined by multiplying the energy value (Kcal) of the chow (g) and water (mL) by the daily consumption of each[27] using the following formulas:

a. For control diet: caloric intake (kcal/day) = chow intake (g) x energy value of the diet (3.64 kcal/g);

b. For the hypercaloric diet; caloric intake (kcal/day) = [chow intake (g) x energy value of diet (4.33 kcal/g)] + [water intake (mL) x 0.25 x 4 kcal per gram of carbohydrate].

Cardiometabolic risk factor

The cardiometabolic risk factors evaluated were adiposity index (AI), systolic blood pressure (SBP), homeostatic model assessment of insulin resistance (HOMA-IR), and plasma glucose, insulin, and triglycerides.

The deposits of retroperitoneal, visceral, and epididymal fat were dissected and weighed, and the AI was calculated by summing the weight of the deposits divided by body weight and multiplied by 100[27]. The SBP in conscious rats was measured using the noninvasive tail-cuff method with an electro-sphygmomanometer, Narco Bio-System (International Biomedical, Austin, TX, USA). The arterial pulsations were recorded in a computerized data acquisition system (AcqKnowledge® MP100, Biopac Systems Inc., Santa Barbara, CA, USA), and the average of three readings was recorded for each measurement[28]. Fasting glucose was determined in blood samples collected from the tail tip using a portable glucometer (Accu-Chek Performa; Roche Diagnostics, Indianapolis, IN, USA). The HOMA-IR was calculated according to the formula: HOMA-IR = [fasting glucose (mmol/L) × fasting insulin (μU/mL)]/22.5. Insulin hormone levels were measured using the enzyme-linked immunosorbent assay (ELISA) method (Elabscience® Rat INS(Insulin) ELISA Kit, USA, REF: E-EL-R2466) following the manufacturer's instructions. Triacylglycerol concentrations were determined using specific kits (BIOCLIN®, Belo Horizonte, MG, Brazil) and analyzed by an automated colorimetric enzymatic method (Chemistry Analyzer BS-200, Mindray Medical International Limited, Shenzhen, China).

Body weight, SBP, glucose, and triglycerides were evaluated at the pre- and post-exercise moments, while HOMA-IR and AI were assessed only at the post-exercise moment.

Pro-inflammatory cytokines in left ventricular tissue

The concentrations of pro-inflammatory cytokines were measured in cardiac tissue homogenate (1:10 in PBS, pH 7.4) using a beater homogenizer

(Bullet Blender, Next Advance, Inc., NY, USA) followed by centrifugation at 3500 rpm at 4°C for 10 min. The supernatant was used for the analysis of the tumoral necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) using the enzyme-linked immunosorbent assay method (ELISA), following the manufacturer's instructions (DuoSet® ELISA Development Systems. R&D System, Minneapolis, MN, USA; REF: DY510-05; DY506-05). The results are expressed in pg/g of protein. The pro-inflammatory cytokines in cardiac tissue were evaluated at the post-exercise moment.

Evaluation oxidative stress products and antioxidant enzymes on cardiac tissue

The oxidative stress products evaluated were malondialdehyde (MDA) and protein carbonylation and the antioxidant enzymes were superoxide dismutase (SOD), Catalase and Glutathione peroxidase (GPx).

Oxidative stress products:

MDA concentrations was measured to estimate lipid peroxidation levels in cardiac tissue homogenate (1:10 in PBS, pH 7.4; centrifugation at 3500 rpm, 4 °C for 10 min). Briefly, 500μL of buffer (0.67% TBA, 15% trichloroacetic acid, and 0.25 N HCL) was added to 200μL sample, and the mixture was centrifuged at 10000 rpm for 10 min. The supernatant was collected and heated in a boiling water bath (100 °C) for 45 min After cooling, the absorbance readings were acquired using microplate reader (Spectra Max 190, Molecular Devices, Sunnyvale, CA, USA). The MDA concentration was obtained through the molar extinction coefficient (1.56 ×105 M−1 cm−1) and sample absorbance. The final result was expressed in nmol/mg of protein.

The protein carbonylation was measured by the adapted method of Mesquita *et al*.[29]. The cardiac tissue homogenate (1:10 in PBS, pH 7.4; centrifugation at 3500 rpm, 4 °C for 10 min) was diluted 1:10 in PBS buffer. In 100μL of the sample were added 100 μL of 2,4-dinitrophenylhydrazine (10 mM DNPH in 2M HCl), and then incubated for 10 min at room temperature. Subsequently, 50μL of 6M sodium hydroxide (NaOH) were added in the sample and incubated again for 10 min at room temperature. Absorbance was recorded at 450 nm using a microplate reader (Spectra Max 190, Molecular Devices, Sunnyvale, CA, USA). The carbonylated protein content was achieved by absorbance measures and the molar extinction coefficient (22,000 M^{-1} cm^{-1}) and expressed as nmol mg^{-1} protein.

Measurement of antioxidant enzymes:

Superoxide dismutase (SOD) activity was determined by the technique of Crouch *et al*.[30]. The activity was measured based on the inhibition of superoxide radical reaction with pyrogallol by spectrophotometry at 420 nm. One unity of SOD activity (U) is defined as the quantify of the enzyme that inhibited 50% of pyrogallol autoxidation, and the results were expressed in U/mg protein/minute.

Catalase (CAT) activity was evaluated by the decrease in hydrogen peroxide (H_2O_2) levels. The breakdown of H_2O_2 in the reaction mixture was measured spectrophotometrically at 240 nm, and the results were expressed as pmol/mg protein/minute, as described by Aebi H.[31].

Glutathione peroxidase (GPx) activity was assessed spectrophotometrically at 340 nm by following β-nicotinamide adenine dinucleotide phosphate (NADPH) oxidation as described by Flohé and Günzler[32]. The enzymatic activity was expressed as μmol/mg protein/minute.

Determination of total protein

The total protein was measured in the supernatant by a colorimetric-enzymatic method and analyzed in automatic enzymatic analyzer system (Chemistry Analyzer BS-200, MindrayMedical International Limited, Shenzhen, China), following the manufacturer's instructions (Total protein monoreagent, BioClin, Quibasa Química Básica Ltda., Belo Horizonte, Minas Gerais, Brazil; K031).

***In vivo* cardiac remodeling evaluation by echocardiogram with tissue Doppler imaging**

Cardiac structure and function were assessed by echocardiography (Vivid S6, General Electric Medical Systems, Tirat Carmel, Israel), using a 5.0 ± 11.5 MHz multi-frequency transducer, in according to previous studies[33][34][35]. Briefly, rats were anesthetized by intraperitoneal injection of a mixture of ketamine (50 mg/kg) and xylazine (0.5 mg/kg). A two-dimensional parasternal short-axis view of the left ventricle (LV) was obtained at the level of the papillary muscles[36] M-mode tracings were obtained from short-axis views of the LV at or just below the tip of the mitral valve leaflets, and at the level of the aortic valve and the left atrium. M-mode images of the LV were printed on a black-and-white thermal printer (Sony UP890MD) at a sweep speed of 100 mm/s. All LV structures were measured by the same observer according to the leading-edge method of the American Society of Echocardiography[37]. Measurements reported are the average of at least five cardiac cycles from the M-mode tracings.

***Post mortem* cardiac morphological analysis**

The presence of ventricular and atrial hypertrophy was determined by analyzing tibia length (TB), and the ratio between left ventricle (LV), right ventricle (RV), atrium (AT), and total heart (TH) per TB [38].

Statistical Analysis

All data were expressed as mean ± standard deviation. The normality test used was the Henze-Zirkler multivariate normality test [39]. For the comparison between groups regarding aerobic and strength functional capacity, baseline and

exhaustion blood lactate concentration, nutritional profile, systolic blood pressure, triglycerides, glycemia and echocardiographic assessment, a multivariate analysis of variance technique (MANOVA) for a repeated measures model in the two-factor scheme was employed; when significant differences were found ($P<0.05$), the post hoc Bonferroni multiple comparisons test was performed[40].

To compare between groups the variables insulin, HOMA-IR, epididymal, retroperitoneal, and visceral adipose tissue, adiposity index, cardiac anatomical data, pro-inflammatory cytokines, oxidative stress products, and antioxidant enzymes, the Analysis of Variance Technique (ANOVA) for the completely randomized experiment in the 2x3 factorial scheme (two diets and three deferment situations for the exercise factor) was used, when significant differences were found ($P<0.05$), the Tukey's multiple comparisons test was performed.

All discussions of the results were conducted considering the 5% significance level. Analyses were performed using RStudio and graphics were generated using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA).

Results

Aerobic and Strength Functional Capacity

The aerobic and strength functional capacity were evaluated by the treadmill exercise test and maximum carrying load test, respectively, and the results are show on Figure 2. The high-sugar-fat diet (HSFD) reduced the aerobic functional capacity (group HSF vs C), characterized by the reduction of the exhaustion velocity, at the pre- and post- exercise moments (Figure 2a), effect not observed for the maximum carrying load test (Figure 2b). The homogeneity between the groups HSF and HSF+AE were compromised at the pre-exercise moment.

The aerobic and strength exercises protocols improved the functional capacity in both diets' scenario, effect showed by comparing the trained groups at pre- versus post-exercise moments and the trained versus non-trained groups at the post-exercise moment (Figure 2a for the aerobic exercise and Figure 2b for the strength exercise).

Therefore, the HSFD reduces the functional capacity when associated with the aerobic exercise test; and both aerobic and strength exercises improves the functional capacity in both diet's scenario.

Nutritional profile

The nutritional profile is presented in Table 4. At the pre-exercise moment the HSFD reduced the chow intake and increased the water and caloric intake. At the post- exercise moment, the chow and water intake were still decreased and increased respectively by the HSFD despite the presence of the exercises. The caloric intake was increased by the HSFD in the pre-exercise moment, and this

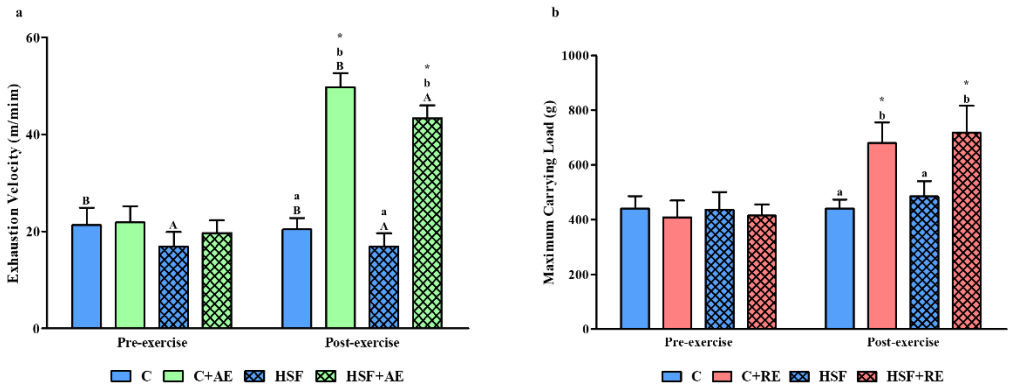

Figure 2 - Aerobic and strength functional capacity. Exhaustion velocity evaluated by treadmill exercise test (a) and maximum caring load evaluated by maximum carrying load test (b) at the pre- and post-exercise moments. C, control group; C+AE, control + aerobic exercise group; C+SE, control + strength exercise group; HSF, high sugar-fat; HSF+AE, high sugar-fat + aerobic exercise group; HSF+SE, high sugar-fat + strength exercise group. n = 7-10 per group. Data presented as mean ± standard deviation; Multivariate analysis of variance (MANOVA) for repeated measures and Bonferroni. Two means followed by distinct lowercase letter (a/b) differ ($p<0.05$) regarding of the exercise, fixed the diet and the moment of evaluation. Two means followed by distinct capital letters (A/B) differ ($p<0.05$) regarding the diets, fixed the types of exercise and the moment of evaluation. *Indicates statistic difference ($p<0.05$) regarding the evaluation moments, fixed the diet and the types of exercise.

result was still observed on the HSF and HSF+SE groups but not on the HSF+AE at the post-exercise moment. The HSFD did not change the body weight (BW) in both moments of evaluation.

The time *per se* reduced the chow intake in both types of diets and exercises protocols. The water intake was reduced over the time in the C+SE group and increased on the HSF and HSF+SE groups, effect not observed on the HSF+AE. The aerobic and strength exercises reduced the caloric intake in both diets scenario when comparing the pre- *versus* post-exercise moments. The BW decreased in the C and C+SE groups over the time. Interestingly, there was an increase of the BW along the time on the HSF group but not in the HSF+AE and HSF+SE groups.

Briefly, the HSFD increases the water and caloric intake and decreases the chow intake, independent of the moment of evaluation. The aerobic exercise prevented the increase of the water intake, differing from the SE, and both exercises prevented the increase of the caloric intake and body weight gain on those animals treated with HSFD.

Cardiometabolic Risk Factors

The cardiometabolic risk factors systolic blood pressure (SBP), triglycerides (TG) and glycemia were evaluated at the pre- and post-exercise moments and the hormone insulin; HOMA-IR, weight of the fat deposits and adiposity index (AI) were evaluated at the post exercise moment, as presented in Figure 4. The HSFD increases the SBP, TG and glycemia at the pre-exercise moment, but the homogeneity for the TG was not observed. The SBP and TG

Table 4 – Nutritional profile

Variables	Groups	Moments	
		Pre-exercise	Post-exercise
Chow intake (g/day)	C	25.0 ±2.19^{B}	23.8 ± 1.90^{B}*
	C+AE	24.5± 1.74^{B}	22.5 ± 1.81^{B}*
	C+SE	24.8± 3.22^{B}	21.2 ± 3.40^{B}*
	HSF	11.8± 1.97^{A}	10.9 ± 2.55^{A}*
	HSF+AE	12.0± 1.72^{A}	8.34 ± 2.12^{A}*
	HSF+SE	11.5 ± 1.71^{A}	7.81 ± 0.95^{A}*
Water intake (ml/day)	C	40.7± 6.24^{A}	39.6 ± 4.62^{A}
	C+AE	39.7 ± 6.24^{A}	41.3 ± 2.92^{A}
	C+SE	43.1 ± 8.56^{A}	37.1 ± 3.36^{A}*
	HSF	55.0 ± 8.84^{B}	59.9 ± 6.58^{B}*
	HSF+AE	52.1 ± 7.67^{B}	53.6 ± 8.86^{B}
	HSF+SE	54.8 ± 6.25^{B}	58.7 ± 6.42^{B}*
Caloric intake (kcal/day)	C	91.0 ± 7.97^{A}	86.6 ± 6.93^{A}
	C+AE	89.3 ± 6.32^{A}	81.8 ± 6.60^{A}*
	C+SE	90.4 ± 11.7^{A}	77.2 ± 12.4^{A}*
	HSF	104 ± 8.28^{B}	107 ± 14.7^{B}
	HSF+AE	104 ± 7.36^{B}	90.3 ± 11.5*
	HSF+SE	106 ± 3.30^{B}	92.5 ± 6.28^{B}*
Body weight (g)	C	508 ± 39.4	486 ± 41.1*
	C+AE	494 ± 22.7	486 ± 41.1
	C+SE	498 ± 61.1	485 ± 66.5*
	HSF	569 ± 83.7	610 ± 89.2*
	HSF+AE	561 ± 56.0	539 ± 68.8
	HSF+SE	544 ± 66.6	549 ± 51.1

C, control group; C+AE, control + aerobic exercise group; C+SE, control + strength exercise group; HSF, high sugar-fat; HSF+AE, high sugar-fat + aerobic exercise group; HSF+SE, high sugar-fat + strength exercise group. n = 7-10 per group. Data presented as mean ± standard deviation; Multivariate analysis of variance (MANOVA) for repeated measures and Bonferroni. Two means followed by distinct lowercase letter (a/b) differ ($p<0.05$) regarding of the exercise, fixed the diet and the moment of evaluation. Two means followed by distinct capital letters (A/B) differ ($p<0.05$) regarding the diets, fixed the types of exercise and the moment of evaluation. *Indicates statistic difference ($p<0.05$) regarding the evaluation moments, fixed the diet and the types of exercise.

levels were still increased at the post-exercise moment by the HSFD while, the glycemia levels on the HSF group reduced to the same level of the control groups. By the time, both exercises reduced the SBP on the HSF groups, on the other side,

just the AE reduce the TG levels. Interestingly the C, C+AE and C+SE groups showed a lover TG concentration over the time. Regarding the glycemia, there was a reduction of its level along the time on the HSF and HSF+AE groups, but not on the HSF+SE.

The plasmatic concentration of insulin, HOMA-IR, epididymal, retroperitoneal and visceral fat deposits and the AI were increased on the HSF group *versus* C group. The aerobic and strength exercises did not change the insulin, HOMA-IR and weight of the epididymal and visceral adipose tissues. Nevertheless, the AE reduced the weight of retroperitoneal adipose tissue and the AI when comparing the HSF+AE *versus* HSF group, this effect was not obtained by the strength exercise (HSF+SE vs HSF).

Therefore, the HSFD increases the SBP, TG, glycemia (at the pre-exercise moment) and AI. The aerobic exercise reduces the TG and AI, effects not observed for the strength exercise. However, both aerobic and strength exercises reduce the levels of SBP over the time.

Effect of aerobic and strength exercises on echocardiographic data

Table 5 shows the echocardiographic data at the pre- and post-exercise moments. The pre-exercise echocardiography analysis shows the effect of 20 weeks of high-sugar-fat diet (HSFD) treatment on the cardiac structural and functional parameters and the homogeneity between the groups. At the post-exercise moment, the echocardiography analysis presents the effect of eight-weeks of aerobic and strength exercises training upon the cardiac remodeling induced by HSFD and the effect of the both exercises protocols along the time. Furthermore, it allows the comparison between the types of exercises.

At the pre-exercise moment the HSFD induced concentric cardiac remodeling characterized by reduced left ventricular diastolic diameter (LVDD), increased posterior wall diastolic thickness (PWDT), interventricular septal diastolic thickness (IVSDT) and relative wall thickness (RWT), accompanied by left atrium (LA) enlargement. The HSFD also induced systolic dysfunction shown by reduction of the posterior wall shortening velocity (PWSV) and tissue Doppler image (TDI) of the systolic velocity of mitral annulus (TDI S) and Tei Index. The diastolic function was also impaired by the HSFD, described by increased isovolumetric relaxation time (IVRT), E wave deceleration time (EDT), TDI of early diastolic velocity of mitral annulus (TDI E'), ratio between mitral E wave and TDI E' (E/TDI E') and ratio between TDI E' and TDI A' (TDI E'/TDI A'). The homogeneity between the HSF groups was not observed for the variables LVDD and TDI S. At the post-exercise moment, the concentric remodeling induced by the HSFD was still observed, characterized by increased PWDT, IVDST and RWT. The effect of the diet on the LVDD was lost.

Regarding the effect of the exercises, only the aerobic exercise increased the LVDD on the HSF+AE group along the time. However, both aerobic and strength exercises reduced the RWT, effect not observe on the HSF group over the time. The LA enlargement induce by the HSFD was reduce by the time in all HSF groups independent of the presence of the exercises. However, on the

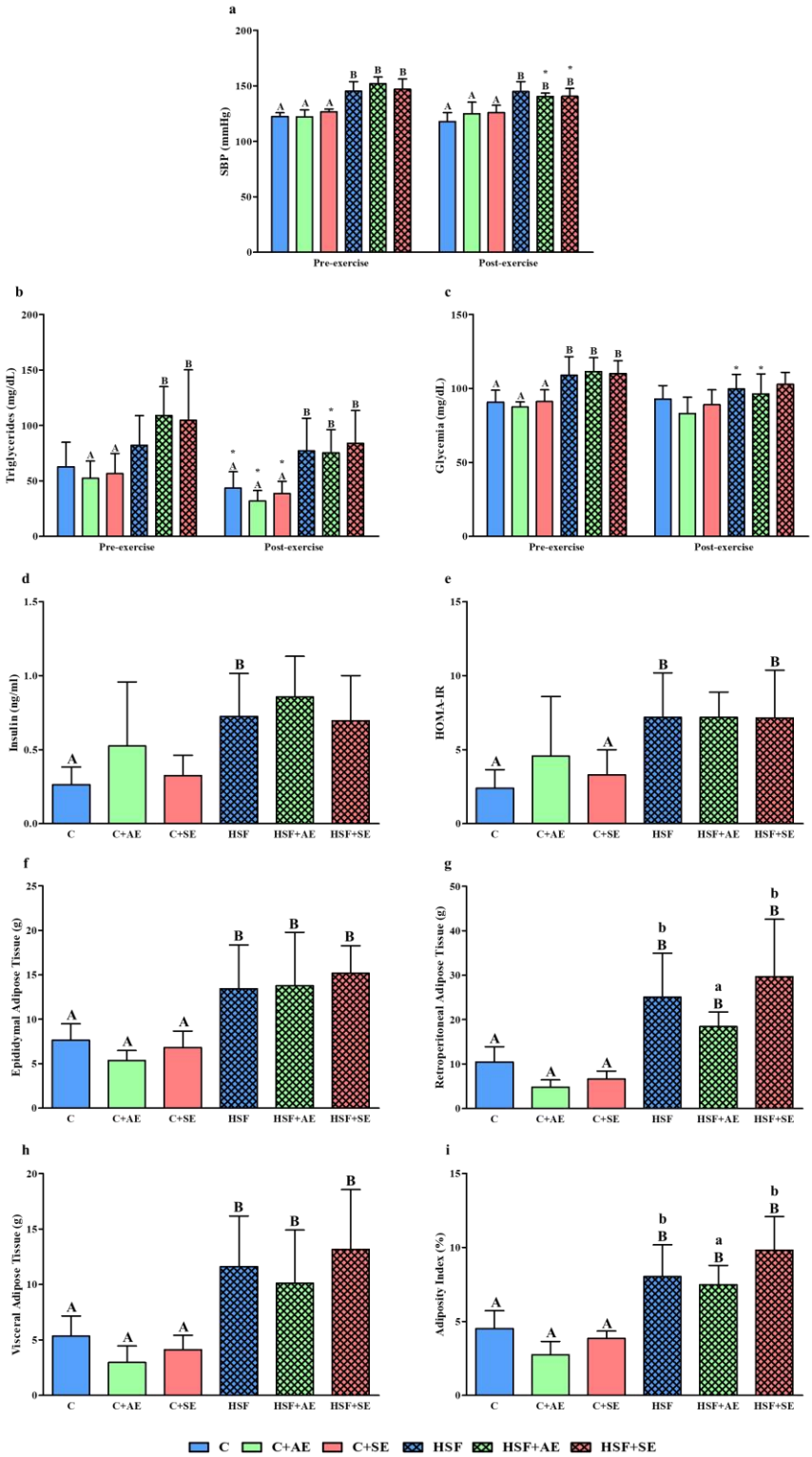

Figure 4 - Cardiometabolic risk factors. Systolic blood pressure (SBP, a), triglycerides (b) and glycemia (c) evaluated at the pre and post exercises moments. Insulin (d), homeostatic model assessment of insulin resistance (HOMA-IR, c), epididimal (f), retroperitoneal (g) and visceral (h) adipose tissues and adiposity index evaluated at the post-exercise moments. Control group; C, control group; C+AE, control + aerobic exercise group; C+SE, control + strength exercise group;

HSF, high sugar-fat; HSF+AE, high sugar-fat + aerobic exercise group; HSF+SE, high sugar-fat + strength exercise group. n = 7-10 per group. Data presented as mean ± standard deviation; Multivariate analysis of variance (MANOVA) for repeated measures and Bonferroni or Two-Way Analysis of Variance (ANOVA) and Tukey's. Two means followed by distinct lowercase letter (a/b) differ ($p<0.05$) regarding of the exercise, fixed the diet and the moment of evaluation. Two means followed by distinct capital letters (A/B) differ ($p<0.05$) regarding the diets, fixed the types of exercise and the moment of evaluation. *Indicates statistic difference ($p<0.05$) regarding the evaluation moments, fixed the diet and the types of exercise.

HSF+SE group the HSFD effect upon the atrium enlargement (LA and LA/AO) was nulled.

Looking at the systolic function at the post-exercise moment, the reduction of the PWSV and TDI S was still observed and, the HSFD also reduced the ejection fraction (EF), endocardial fraction shortening (EFS) and mesocardial fraction shortening (MFS) on the HSF group. The TDI S was also changed on the HSF+AE. Both aerobic and strength exercises prevented the decrease of the EF, EFS and MFS, for the last one, just the SE increase it along the time. Add to that, both AE and SE increased the PWSV along the time. The time per se reduced the Tei Index, effect not observed no the HSF+AE group.

The diastolic parameters IVRT, EDT, TDI E', and TDI E'/TDI A' were kept impaired on the HSF and HSF+AE groups but not on the HSF+SE group. Along the time the IVRT and EDT decreased and the mitral E wave, TDI E' and TDI E'/TDI A' were increased on the HSF+RE group. For the animals treated with the control diet (CD) there was an increase of the EDT along the time independent of the presence of the exercises.

The heart rate value was not altered by the treatments in any moment of evaluation.

Briefly the HSFD induces concentric cardiac remodeling, systolic and diastolic dysfunction, independent of the time of evaluation. Both aerobic and strength exercises reduce concentric remodeling and prevent the decrease and/or improve the systolic function changed by the HSFD. However, just the strength exercise improved the decrease of the diastolic function associated with the HSFD.

Table 5 - Echocardiographic data. *(to be continued)*

Variables	Groups	Moments	
		Pre-exercise	Post-exercise
HR (bpm)	C	246 ± 38.0	220 ± 26.1
	C+AE	255 ± 52.8	250 ± 41.8
	C+SE	255 ± 43.9	260 ± 61.9
	HSF	254 ± 22.4	249 ± 43.8
	HSF+AE	250 ± 33.9	273 ± 57.8
	HSF+SE	257 ± 18.1	244 ± 48.7

Table 5 - Echocardiographic data. *(to be continued)*

Variables	Groups	Moments	
		Pre-exercise	**Post-exercise**
LVDD (mm)	C	7.38 ± 0.30[B]	7.22 ± 0.47
	C+AE	7.26 ± 0.49	7.44 ± 0.31
	C+SE	7.35 ± 0.38	7.33 ± 0.25
	HSF	6.71 ± 0.47[A]	6.96 ± 0.57
	HSF+AE	6.95 ± 0.40	7.36 ± 0.43*
	HSF+SE	6.82 ± 0.60	7.21 ± 0.21
PWDT (mm)	C	1.50 ± 0.06[A]	1.49 ± 0.05[A]
	C+AE	1.51 ± 0.05[A]	1.50 ± 0.04[A]
	C+SE	1.52 ± 0.04[A]	1.50 ± 0.05[A]
	HSF	1.92 ± 0.06[B]	1.79 ± 0.18[B]*
	HSF+AE	1.91 ± 0.11[B]	1.79 ± 0.17[B]*
	HSF+SE	1.88 ± 0.08[B]	1.69 ± 0.18[B]*
IVSDT (mm)	C	1.52 ± 0.06[A]	1.56 ± 0.08[A]
	C+AE	1.51 ± 0.03[A]	1.53 ± 0.05[A]
	C+SE	1.53 ± 0.03[A]	1.52 ± 0.04[A]
	HSF	1.99 ± 0.11[B]	1.92 ± 0.22[B]
	HSF+AE	2.05 ± 0.21[B]	1.98 ± 0.23[B]
	HSF+SE	1.98 ± 0.11[B]	1.90 ± 0.37[B]
RWT	C	0.41 ± 0.03[A]	0.42 ± 0.03[A]
	C+AE	0.42 ± 0.03[A]	0.40 ± 0.01[A]
	C+SE	0.41 ± 0.03[A]	0.41 ± 0.01[A]
	HSF	0.58 ± 0.03[B]	0.52 ± 0.07[B]
	HSF+AE	0.55 ± 0.05[B]	0.48 ± 0.06[B]*
	HSF+SE	0.56 ± 0.07[B]	0.47 ± 0.05[B]*
LA (mm)	C	4.60 ± 0.23[A]	4.75 ± 0.13[A]
	C+AE	4.66 ± 0.18[A]	4.61 ± 0.04[A]
	C+SE	4.75 ± 0.17[A]	4.73 ± 0.21
	HSF	6.05 ± 0.25[B]	5.29 ± 0.39[B]*
	HSF+AE	5.97 ± 0.28[B]	5.37 ± 0.35[B]*
	HSF+SE	5.97 ± 0.24[B]	5.02 ± 0.37*
LA/AO	C	1.20 ± 0.08[A]	1.21 ± 0.04[A]
	C+AE	1.21 ± 0.06[A]	1.18 ± 0.05[A]
	C+SE	1.22 ± 0.05[A]	1.18 ± 0.05
	HSF	1.52 ± 0.10[B]	1.30 ± 0.06[B]*
	HSF+AE	1.51 ± 0.14[B]	1.31 ± 0.08[B]*
	HSF+SE	1.47 ± 0.10[B]	1.24 ± 0.07*

Table 5 - Echocardiographic data. *(to be continued)*

Variables	Groups	Moments	
		Pre-exercise	**Post-exercise**
EF (%)	C	0.93 ± 0.02	0.94 ± 0.01[B]
	C+AE	0.93 ± 0.03	0.94 ± 0.02
	C+SE	0.94 ± 0.01	0.93 ± 0.01
	HSF	0.92 ± 0.02	0.91 ± 0.02[A]
	HSF+AE	0.93 ± 0.03	0.93 ± 0.03
	HSF+SE	0.91 ± 0.05	0.93 ± 0.02
EFS (%)	C	59.7 ± 4.39	62.0 ± 2.01[B]
	C+AE	59.7 ± 5.46	59.7 ± 2.61
	C+SE	60.5 ± 1.82	59.6 ± 2.77
	HSF	56.8 ± 2.83	55.1 ± 3.80[A]
	HSF+AE	58.8 ± 4.99	58.0 ± 4.61
	HSF+SE	55.5 ± 6.72	59.2 ± 2.54
MFS (%)	C	27.1 ± 3.48	28.1 ± 3.15[B]
	C+AE	27.8 ± 6.11	26.4 ± 3.22
	C+SE	25.3 ± 2.75	25.4 ± 2.22
	HSF	22.3 ± 0.63	23.4 ± 4.17[A]
	HSF+AE	24.6 ± 4.18	27.5 ± 3.07
	HSF+SE	22.7 ± 4.81	26.8 ± 2.79*
PWSV (mm/s)	C	79.0 ± 5.29[B]	78.6 ± 6.88[B]
	C+AE	78.9 ± 5.24[B]	76.7 ± 6.45
	C+SE	77.9 ± 6.35[B]	78.9 ± 5.54
	HSF	66.9 ± 3.68[A]	66.8 ± 8.99[A]
	HSF+AE	63.4 ± 5.64[A]	72.0 ± 9.21*
	HSF+SE	66.0 ± 6.18[A]	72.5 ± 8.36*
TDI S (average, cm/s)	C	5.93 ± 0.33[B]	5.79 ± 0.20[B]
	C+AE	5.78 ± 0.37	5.91 ± 0.33[B]
	C+SE	5.90 ± 0.20[B]	5.76 ± 0.31
	HSF	5.30 ± 0.49[A]	5.12 ± 0.45[A]
	HSF+AE	5.26 ± 0.34	5.35 ± 0.56[A]
	HSF+SE	5.29 ± 0.33[A]	5.38 ± 0.25
Tei Index	C	0.26 ± 0.09[A]	0.24 ± 0.09
	C+AE	0.30 ± 0.09[A]	0.22 ± 0.10[A]
	C+SE	0.30 ± 0.11[A]	0.24 ± 0.09
	HSF	0.53 ± 0.16[B]	0.33 ± 0.11*
	HSF+AE	0.46 ± 0.10[B]	0.41 ± 0.15[B]
	HSF+SE	0.50 ± 0.15[B]	0.31 ± 0.08*

Table 5 - Echocardiographic data. *(to be continued)*

Variables	Groups	Moments	
		Pre-exercise	**Post-exercise**
IVRT (ms)	C	22.6 ± 1.27^{A}	22.6 ± 0.97^{A}
	C+AE	22.0 ± 0.58^{A}	22.0 ± 0.58^{A}
	C+SE	21.4 ± 2.74^{A}	23.3 ± 1.32
	HSF	30.5 ± 6.44^{B}	29.5 ± 5.18^{B}
	HSF+AE	33.7 ± 3.32^{B}	29.3 ± 4.50^{B}
	HSF+SE	32.4 ± 3.20^{B}	27.4 ± 5.87*
IVRTn (ms)	C	45.7 ± 4.59^{A}	43.1 ± 2.31^{A}
	C+AE	45.0 ± 3.51^{A}	44.8 ± 3.67^{A}
	C+SE	43.9 ± 5.92^{A}	48.3 ± 6.54
	HSF	62.3 ± 11.0^{B}	60.0 ± 13.0^{B}
	HSF+AE	68.7 ± 8.78^{B}	62.7 ± 14.4^{B}
	HSF+SE	67.0 ± 7.00^{B}	54.4 ± 10.1*
EDT (ms)	C	44.7 ± 1.34^{A}	49.1 ± 2.89^{A}*
	C+AE	42.0 ± 2.24^{A}	47.1 ± 2.73^{A}*
	C+SE	44.8 ± 1.23^{A}	48.2 ± 3.63*
	HSF	61.6 ± 10.9^{B}	59.1 ± 11.9^{B}
	HSF+AE	59.3 ± 3.84^{B}	59.8 ± 7.35^{B}
	HSF+SE	61.9 ± 7.22^{B}	51.2 ± 6.88*
Mitral E (cm/s)	C	75.8 ± 7.41	79.0 ± 5.79
	C+AE	79.5 ± 6.69	80.8 ± 10.4
	C+SE	75.8 ± 5.55	81.8 ± 7.16
	HSF	79.2 ± 8.10	76.8 ± 5.63
	HSF+AE	78.6 ± 8.17	80.6 ± 6.06
	HSF+SE	79.1 ± 7.70	83.2 ± 7.48*
Mitral A (cm/s)	C	42.2 ± 7.39	44.1 ± 6.32
	C+AE	45.6 ± 11.3	45.3 ± 8.82
	C+SE	43.7 ± 6.02	47.7 ± 10.2
	HSF	44.1 ± 9.60	46.6 ±18.3
	HSF+AE	45.1 ± 12.6	51.0 ± 16.8
	HSF+SE	45.4 ± 9.29	44.2 ± 5.80
E/A	C	1.82 ± 0.18	1.81 ± 0.19
	C+AE	1.81 ± 0.37	1.82 ± 0.30
	C+SE	1.76 ± 0.26	1.77 ± 0.33
	HSF	1.85 ± 0.34	1.84 ± 0.61
	HSF+AE	1.81 ± 0.32	1.69 ± 0.38
	HSF+SE	1.81 ± 0.52	1.92 ± 0.36

Table 5 - Echocardiographic data. *(conclusion)*

Variables	Groups	Moments	
		Pre-execise	Post-exercise
TDI E' (average, cm/s)	C	5.26 ± 0.25^{B}	5.19 ± 0.19^{B}
	C+AE	5.34 ± 0.35^{B}	5.40 ± 0.60^{B}
	C+SE	5.37 ± 0.21^{B}	5.63 ± 0.60
	HSF	3.58 ± 0.38^{A}	3.83 ± 0.80^{A}
	HSF+AE	3.69 ± 0.81^{A}	4.25 ± 1.27^{A}
	HSF+SE	3.69 ± 0.56^{A}	4.66 ± 0.90*
Mitral E/TDI E' (cm/s)	C	14.4 ± 1.36^{A}	15.2 ± 1.31
	C+AE	14.9 ± 1.00^{A}	15.1 ± 2.18
	C+SE	14.1 ± 1.23^{A}	14.6 ± 1.02
	HSF	22.4 ± 3.34^{B}	21.0 ± 5.31
	HSF+AE	22.1 ± 4.53^{B}	20.4 ± 5.71
	HSF+SE	21.4 ± 2.08^{B}	18.7 ± 4.97
TDI E'/ TDI A' (cm/s)	C	1.52 ± 0.12^{B}	1.54 ± 0.15^{B}
	C+AE	1.55 ± 0.08^{B}	1.51 ± 0.07^{B}
	C+SE	1.52 ± 0.06^{B}	1.55 ± 0.19
	HSF	0.78 ± 0.10^{A}	0.91 ± 0.36^{A}
	HSF+AE	0.80 ± 0.25^{A}	0.99 ± 0.47^{A}
	HSF+SE	0.76 ± 0.20^{A}	1.17 ± 0.32*

HR, heart rate; LVDD, left ventricular diastolic diameter; PWDT, posterior wall diastolic thickness; IVSDT, interventricular septal diastolic thickness; RWT, relative wall thickness; LA, left atrium; LA/AO, LA normalized by AO; EF, ejection fraction; EFS, endocardial fractional shortening; MFS, mesocardial fractional shortening; PWSV, posterior wall shortening velocity; TDI S, tissue doppler imaging (TDI) of systolic velocity of the mitral annulus; Tei Index, myocardial performance index; IVRT, isovolumetric relaxion; IVRTn, isovolumetric relaxion time normalized by HR; EDT, E-wave deceleration time; E/A, ratio between early (E) to late (A) diastolic mitral inflow; TDI E', TDI of early diastolic velocity of mitral annulus; E/ TDI E', ratio between E and TDI E'; TDI E'/TDI A', ratio between TDI E' and TDI A'; C, control group; C+AE, control + aerobic exercise group; C+SE, control + strength exercise group; HSF, high sugar-fat; HSF+AE, high sugar-fat + aerobic exercise group; HSF+SE, high sugar-fat + strength exercise group. n = 7-10 per group Data presented as mean ± standard deviation; Multivariate analysis of variance (MANOVA) for repeated measures and Bonferroni. Two means followed by distinct lowercase letter (a/b) differ ($p<0.05$) regarding of the exercise, fixed the diet and the moment of evaluation. Two means followed by distinct capital letters (A/B) differ ($p<0.05$) regarding the diets, fixed the types of exercise and the moment of evaluation. *Indicates statistic difference ($p<0.05$) regarding the evaluation moments, fixed the diet and the types of exercise.

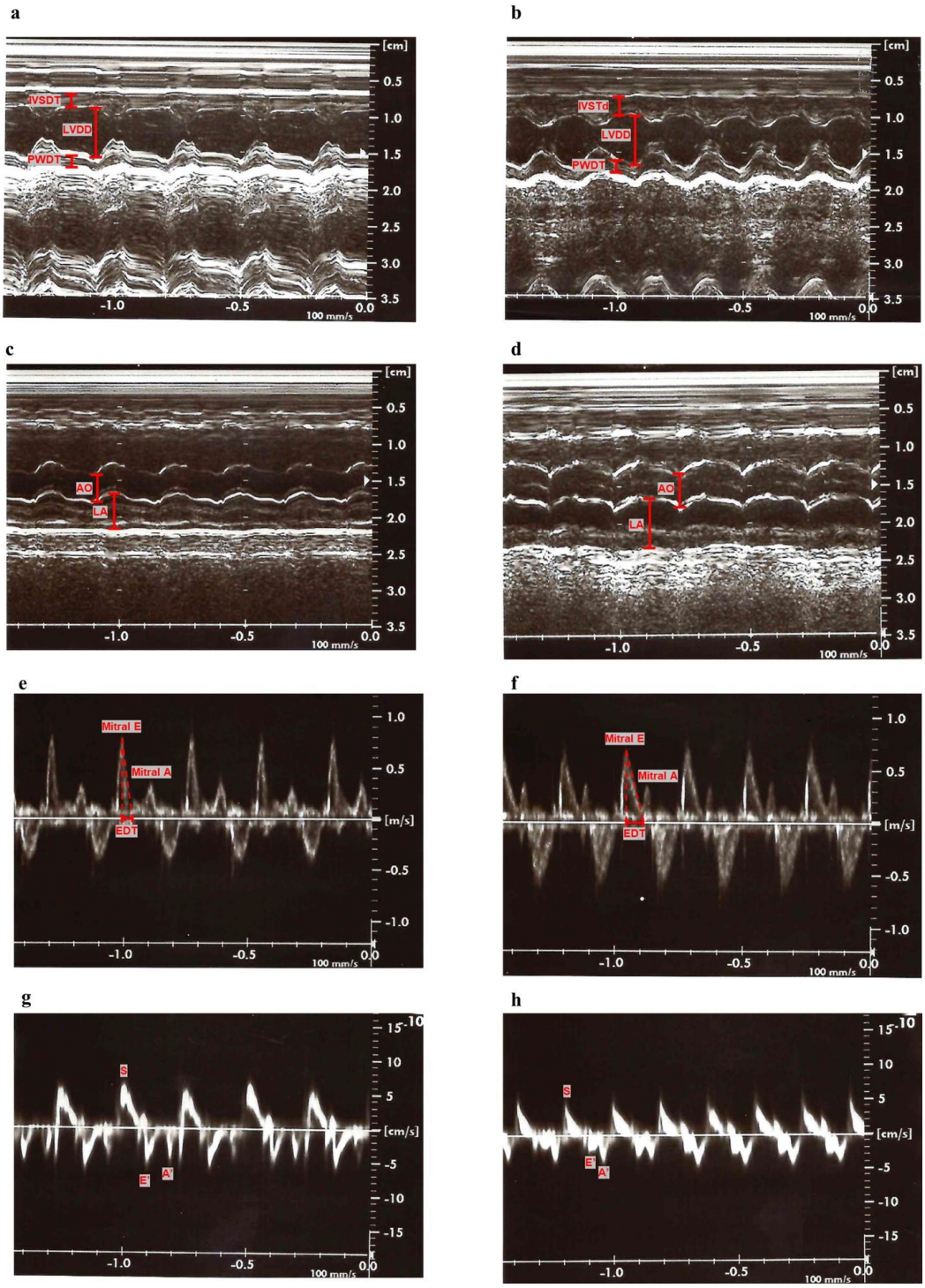

Figure 5 - Echocardiographic images of the findings observed at the pre-exercise moment and presented in Table 5. Figures a, c, e and g are pictures of an animal from the control group (C) and Figures b, d, f, h are pictures of an animal from the high sugar-fat group (HSF). Figures a and b shows the left ventricle (LV) structure where we can visualize the interventricular septal diastolic thickness (IVSDT), LV diastolic diameter (LVDD) and posterior wall diastolic thickness (PWDT). Figures c and d shows the structure of the left atrium (LA) and aorta (AO). Figures e and

f shows the E-wave deceleration time (EDT) and early (E) to late (A) diastolic mitral inflow. Figures g and h shows the tissue doppler imaging (TDI) of early diastolic velocity of mitral annulus (E'), TDI of late diastolic velocity of mitral annulus (A') and the TDI of systolic velocity of the mitral annulus (S).

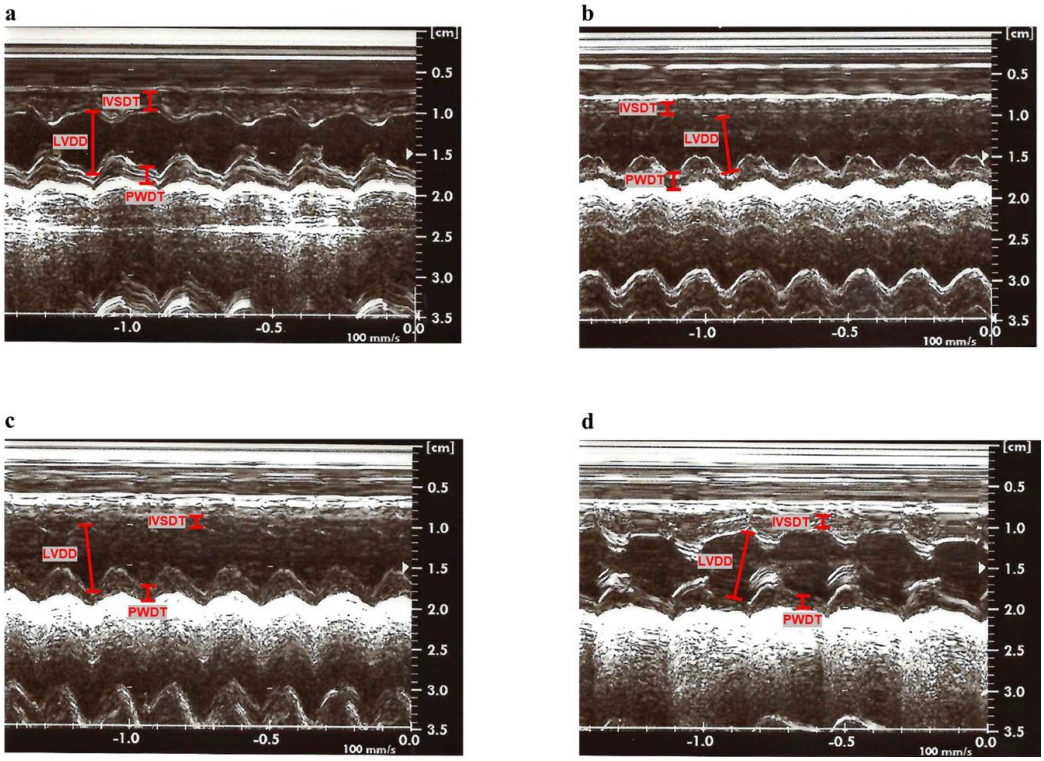

Figure 6 - Echocardiographic images of the findings observed at the post-exercise moment and presented in Table 5. Figures a, b, c and d shows the left ventricle (LV) structure where we can visualize the interventricular septal diastolic thickness (IVSDT), LV diastolic diameter (LVDD) and posterior wall diastolic thickness (PWDT) for control group (C), high sugar-fat group (HSF), high sugar-fat + aerobic exercise group (HSF+AE) and high sugar-fat + strength exercise group (HSF+SE) respectively.

Effect of aerobic and strength exercises on cardiac anatomical data

Cardiac anatomical data are presented in Table 6. The high-sugar-fat diet elevated the left ventricle weight (LV) normalized by tibia on the HSF group, effect not observed on the HSF+AE and HSF+RE groups. There is no alteration for the length of the tibia and for the weight of the heart, LV, right ventricle (RV) in absolute and normalized to the tibia values.

Thus, both types of exercises prevented the increase of LV weight (LV) normalized by tibia induced by the HSFD.

Table 6 - Cardiac anatomical data.

Variable	Groups					
	C	C+AE	C+RE	HSF	HSF+AE	HSF+RE
Tibia (cm)	4.47 ± 0.10	4.74 ± 0.08	4.38 ± 0.23	4.36 ± 0.09	4.41 ± 0.15	4.45 ± 0.12
Heart (g)	1.26 ± 0.17	1.28 ± 0.13	1.23 ± 0.20	1.41± 0.17	1.37 ± 0.14	1.29 ± 0.13
LV (g)	0.88 ± 0.10	0.91 ± 0.09	0.86 ± 0.14	0.99 ± 0.11	0.98 ± 0.09	0.91 ± 0.10
RV (g)	0.29 ± 0.06	0.28 ± 0.05	0.27 ± 0.07	0.31 ± 0.07	0.30 ± 0.06	0.28 ± 0.03
Atria (g)	0.094 ± 0.021	0.096 ± 0.014	0.096 ± 0.019	0.106 ± 0.025	0.098 ± 0.007	0.094 ± 0.026
Heart/Tibia	0.28 ± 0.03	0.29 ± 0.03	0.28 ± 0.04	0.33 ± 0.04	0.31 ± 0.04	0.29 ± 0.03
LV/Tibia	0.20 ± 0.02	0.20 ± 0.02	0.20 ± 0.03	0.23 ± 0.02^{B}	0.22 ± 0.02	0.20 ± 0.02
RV/Tibia	0.064 ± 0.013	0.063 ± 0.010	0.062 ± 0.014	0.072 ± 0.017	0.067 ± 0.015	0.063 ± 0.007
Atria/Tibia	0.021 ± 0.003	0.021 ± 0.004	0.021 ± 0.006	0.025 ± 0.005	0.021 ± 0.003	0.020 ± 0.005

LV, left ventricle; RV, right ventricle; C, control group; C+AE, control + aerobic exercise group; C+SE, control + strength exercise group; HSF, high sugar-fat; HSF+AE, high sugar-fat + aerobic exercise group; HSF+SE, high sugar-fat + strength exercise group. n = 7-10 per group. Data presented as mean ± standard deviation; Two-Way Analysis of Variance (ANOVA) and Tukey's. Two means followed by distinct lowercase letter (a/b) differ ($p<0.05$) regarding of the exercise, fixed the diet and the moment of evaluation. Two means followed by distinct capital letters (A/B) differ ($p<0.05$) regarding the diets, fixed the types of exercise and the moment of evaluation.

Pro-inflammatory cytokines, oxidative stress products and antioxidant enzymes on left ventricular tissue

Pro-inflammatory cytokines, oxidative stress products and antioxidant enzymes on left ventricular tissue are shown in Table 7. The HSFD did not change significatively the left ventricular concentrations of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α) and interleucine-6 (IL-6), as well as the stress oxidative markers, malondialdehyde (MDA) and protein carbonylation, and activity of the antioxidant enzymes, glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase.

Since the HSFD did not change the pro-inflammatory cytokines, oxidative stress products and antioxidant enzymes profile on this study, we were not able to evaluate the effect of aerobic and strength exercises upon these variables.

Table 7 – Pro-inflammatory cytokines, oxidative stress products and antioxidant enzymes activity on left ventricular tissue. *(to be continued)*

Variables	Groups					
	C	C+AE	C+SE	HSF	HSF+AE	HSF+SE
Pro-inflammatory cytokines						
TNF-α (pg/mg of prot)	64.2±25.8	70.8±18.3	60.4±33.7	36.4±16.8	46.0±19.2	50.2±29.7
IL-6 (pg/mg of prot)	481±233	599±319	406±186	294±123	361±162	306±127
Oxidative stress products						
MDA (nm/mg of prot)	33.8±9.67	39.2±20,0	38.9±9.93	54.7±25.8	52.4±18.6	35.4±11.2
Prot. Carbonylation (nm/mg of prot)	117±26.0	118±24.7	114±27.4	122±20.1	142±42.0	103±32.2

Table 7 – Pro-inflammatory cytokines, oxidative stress products and antioxidant enzymes activity on left ventricular tissue. *(conclusion)*

Variables	Groups					
	C	C+AE	C+SE	HSF	HSF+AE	HSF+SE
Antioxidant enzymes activity						
SOD (pmol/mg of prot/min)	0.93±0.24	0.89±0.16	0.85±0.20	0.96±0.15	0.97±0.13	0.83±0.24
Catalase (Umol/mg of prot/min)	2.79±0.55	2.79±0.64	2.44±0.61	3.30±1.24	3.31±0.96	2.86±1.49
GPx (μmol/ mg of prot/min)	3.88±1.5	3.69±1.16	4.02±1.49	4.65±0.42	3.98±0.82	3.59±1.53

TNF-α, Tumor necrosis factor-alpha; IL-6, interleucine-6; MDA, malondialdehyde; Prot., Protein; SOD, superoxide dismutase; GPx, Glutathione Peroxidase (qual). C, Control group; C+SE, Control + Strength Exercise group; C+AE, Control + Aerobic Exercise group; HSF, High Sugar-Fat; HSF+SE, High Sugar-Fat + Strength Exercise group; HSF+AE, High Sugar-Fat + Aerobic Exercise group. n = 7-10 per group. Data presented as mean ± standard deviation; Two-Way Analysis of Variance (ANOVA) and Tukey's. Two means followed by the same lowercase letter (a/b) do not differ ($p<0.05$) regarding the types of exercise, fixed the diet and the moment of evaluation. Two means followed by the same capital letter (A/B) do not differ ($p>0.05$) regarding the diets, fixed the types of exercise and the moment of evaluation.

Discussion

Changes in food consumption patterns towards diets rich in sugar and fat, coupled with reduced physical exercise, have contributed to the rapid increase in the incidence of cardiac diseases over the last few decades. Cardiac remodeling (CR) is an adaptive process in response to stressors and is a common feature among diseases that affect the heart. Identifying an ideal therapeutic approach to manage the associated alterations remains a challenge. Non-pharmacological strategies are emerging as effective tools for the prevention and treatment of cardiac diseases. In this study we confirmed[21] that the high-sugar-fat diet (HSFD) elaborated by our group can lead to development of cardiometabolic risk factors – high SBP and AI, hypertriglyceridemia and hyperglycemia - and cardiac remodeling - characterized by concentric remodeling (high RWT) and systolic (reduced PWSV) and diastolic (reduced E/DTI E') dysfunction. We also observed that the aerobic (AE) and strength (SE) exercises were able to modulate some of the cardiometabolic risk factors and mitigate the cardiac remodeling, even in the presence of the stressor (HSFD), emphasizing the idea that exercise training is a good therapeutic strategy. However, this study also shows that the modulation of the cardiac risk factors and the echocardiography parameters of the cardiac remodeling can differ regarding the type of exercise applied.

It is important to notice that the focus of this study was to evaluate the effect of different types of exercise on echocardiography parameters of cardiac remodeling. However, since we used an animal model of cardiac remodeling induced by high-sugar fat diet (HSFD), we can't ignore the cardiometabolic risk factors also developed by the diet, since they can also act as a stressor to heart and it's modulation by the exercise's protocols can indirectly improve the CR.

In this report, both aerobic and strength training protocols improved the functional capacity, highlighting the effectiveness of the chosen protocols, as

demonstrated previously[24][26][41].

Discussing the nutritional profile assessed through water, food, caloric intake, and body weight, both aerobic and strength exercises proved to be effective in reducing caloric intake over time when associated with the HSFD. Despite the overall reduction in caloric intake in both trained groups, food consumption among the HSF, HSF+AE, and HSF+SE groups was similar. Only aerobic exercise successfully prevented an increase in water intake over time. Although there is no statistically significant difference in chow intake between the HSF+SE and HSF groups, there is a noticeable numerical difference, indicating that the HSF+RE group consumed less chow. We believe that, in combination with the slight reduction in water intake, this can explain the overall decrease in caloric intake observed in the HSF+SE group. The reduction in energy intake due to exercise training has been demonstrated in others animal studies[42][43][44][45].

The mechanisms involved in the inhibition of ingestion were not well elucidated. Some studies suggest that the decrease in energy intake results from changes in the appetite control system toward orexigenic or anorexigenic hormones associated with the regulation of acylated ghrelin and the inhibition of neuropeptide Y via an increase in insulin and leptin[46][47][48][49]. However, in our study, both types of exercises, *per se*, were not able to change the levels of insulin (HSF+AE vs HSF and HSF+SE vs HSF) and the HOMA-IR. It is important to consider that the effect of the HSFD on increasing insulin and HOMA-IR was not observed in all groups treated with the HSFD; however, there is high data variability, making it difficult to discuss a protective effect of exercise against the HSFD. On the other side, leptin concentrations were not evaluated in our study. Batacan Jr. *et al*.[50] suggested two other mechanisms that could be involved in the reduction of energy intake associated with exercise: the release of catecholamines and corticotropin-releasing factor[51]. In this direction, we believe that stress could be an important factor involved in the reduction of alimentary consumption in our study.

In line with the reduction of the caloric intake, was observe a prevention of increased body weight in both HSF+AE and HSF+SE groups but not in the HSF without exercise. Similar results were observed in previous studies[50][52][53]. This found could be explained by the reduction of the caloric intake associated with both exercises protocol. We were expecting that the blunted weight gain generated by both types of exercise would be associated with a reduction of the fat deposits; surprisingly, only the aerobic exercise reduced the retroperitoneal fat deposit and the adiposity index, differing from the strength exercise. Despite the fact of both types exercise reduced the caloric intake over the time, only the AE inhibit the elevation of caloric intake promoted by the HSFD, reaching similar levels as the C group. The finding of our study, regarding the effect of the SE, diverges from others where the SE was able to reduce de adiposity[54]. On the other side, Melo *at al*. in a study using a strength training protocol, found similar results to ours regarding the adiposity index. In his study the SE was not able to reduce the AI even reducing the visceral and epididimal adipose tissues[41]. The beneficial effects of physical activity on weight loss and

weight gain control are well documented since the practice of exercise increases energy expenditure and creates a calorie deficit essential for weight loss[55][56][57][58]. On the other hand, the aerobic exercise, is known to have more prominent effect in weight loss than strength exercise[56][57]. The aerobic exercise leads to calorie burn, fat oxidation, and metabolic adaptations[55][59] while, strength training provides stimulus for muscle growth, generating muscle hypertrophy and increasing lean muscle mass, which is associate in higher metabolic rate. In that direction the strength exercise could not enhance short-term weight loss, but it does result in healthy changes in body composition and may play an important role in long-term weight management[58][60]. These different characteristics toward the types of exercises helps to understand the reduction of the AI only on the HSF+AE group but not on the HSF+SE[61].

Together with the intrinsic metabolic differences associated with the type of exercise, some important factors addressed to the exercises protocol should be considered to discuss these results. The exercise session duration between the aerobic and strength protocols are distinct; the strength exercise session duration was shorter than the aerobic exercise. Said that, the exercise volume determines energy expenditure and depends on duration and intensity[58], so the energy expended during the SE exercise was probably lower than the AE. Together this information help understanding the prevention of increasing body weight associate with lower AI observed in the HSF+AE.

However, why the RE had the same effect on the body weight in the presence of the HSFD but the reduction of body weight is not associated with decrease in the AI? The HSFD used in our study has less proteins (18.14%) than the CD (21.12%) and, add to that, the groups treated with the HSFD eat less chow and drink more water with added sucrose (25%) than the groups treated with the CD. Besides that, the HSF+SE as well the HSF group drank more water than the HSF+AE along the time. In this context we speculate the practice of strength exercise, which the main effect in built lean mass, when associate with predominant consumption of sugar and fat could lead to a loss of lean mass. This find emphasize the importance of nutritionally balanced diet[62].

Still talking about the metabolic findings, the HSFD was able to promote hyperglycemia at the pre-exercise moment, however this effect was lost at the pos-exercise moment. Interestingly, the HSF+SE was the only group that did not present a reduction on glycemia levels along the time. In the same direction, the HSFD increase the triglycerides (TG) levels and only the AE was able significantly reduce it along the time. These findings diverge from other studies where the SE was able to reduce the triglycerides and the glycemia. This divergence between the studies could be explained by the difference in the experimental design, since the studies uses the exercise as a preventive agent and not as a treatment[54][63]. On the other hand, substrate utilization as fuel sources during exercise training is highly influenced by the type of exercise. Studies suggest that strength exercise is effective in promoting lipolysis. However, due to rest intervals, fatty acids are not oxidized; rather, they are re-esterified to triacylglycerols. Aerobic interval training is associated with increased fat oxidation, and this may be the mechanism behind the observed triglyceride (TG)

lowering effect. Glucose utilizations occur in a greater extent during high exercise intensity, while fatty acids (FAs) oxidation increases during low to moderate exercise intensity as well as during prolonged exercise. These results align with the nutritional findings, reinforcing that the difference between exercise stimuli and duration is an important factor in determining the final results.

Both types of exercises, in our study, were able to reduce the SPB levels. This finding has been described before in both human[64][65][66][67][68] and animal[23][50][69][70][71] studies. For this reason, the exercise training is already recommended as a therapeutic approach to hypertension. However, the recommended type of exercise is primarily endurance supplemented by strength exercise. This is because the intensive isometric exercise can have a marked pressor effect[72][73]. As reviewed by Gronek *et al*.[74] the mechanisms that exercise reduces the blood pressure is mostly by the change of vascular function and structure. The improvement of vascular function occurs by vasodilatation via increasing endothelial NO synthase an antioxidant capacity, and reducing the vasoconstrictor tone via reduction of endothelin-1 and angiotensin II pathways. The structure changes via changing the diameter of the artery, intima media thickness, artery stiffness and compliance, and baroreflex sensitivity[74].

When analyzing the cardiac remodeling, the high-sugar-fat diet (HSFD) was able to induce concentric cardiac remodeling and systolic and diastolic dysfunction, as observed in previous studies from our group[21]. Now, looking at the effects of aerobic and strength exercises on cardiac remodeling, we observed that both forms of exercise had the ability to mitigate cardiac structural and functional impermeant induced by the HSFD. Intriguingly, strength exercise (SE) appears to be more effective than aerobic exercise (AE), especially in improving the echocardiography variables associated with diastolic dysfunction.

Both AE and SE were able to attenuate the concentric remodeling by reducing RWT over the time. The reduction of the RWT goes together with the cardiac anatomical data, were just the HSF group showed increased LV weight normalize by tibia length, but not the HSF+AE and HSF+SE. This find corroborates with others studies where aerobic and strength exercises were able to mitigate the pathological hypertrophy in both human[75][76][77] and animal models[78][79][80][81][82]. Helping understands this find, our animal model of cardiac remodeling is associated with increased systolic blood pressure (SBP), and as mentioned before, both types of exercise reduced the magnitude of the SBP. Since high level of systolic pressure is associated with concentric remodeling[83] and the reduction of it levels can lead to an improvement of it[84], we hypothesize that the reduction of the SBP levels by both aerobic and strength exercises reflected in a reduction of the magnitude of the concentric remodeling. Interestingly, the variables involved on the attenuation of the RWT seems to be distinct between the AE and SE. The aerobic exercise was associated with an increase in the LVDD over the time, but not the SE. In health condition, the aerobic exercise is associated with eccentric form of non-pathologic cardiac hypertrophy, which is primarily characterized by an increased left ventricular (LV) cavity dimension[85]. The AE training increases the venous return and, consequently, imposes a volume overload (increased pre-load) on the heart; this

overload results in the elevation of the final diastolic pressure in the LV, the parietal stress produces a response in the sarcomeres leading to an increase in the length and width of the cardiomyocyte and overall size of the LV cavity, this occurs with the aim to normalize the diastolic left ventricular final pressure and is characterized as eccentric hypertrophy[86][87]. The same effect is observed in a scenario of aerobic interval exercise[88]. On the other side, the strength exercise is associate with a concentric form of non-pathologic LV hypertrophy characterized by augmented ventricular wall thickness without changes in cavity size[86] doe to the high intraventricular pressure that is needed to open the aortic valve; during the systole, high intraventricular pressure leads to increase myocardial wall stress, which is the major stimulus for cardiac hypertrophy in the pressure-overloaded (post-load). This pressure overload stimulates parallel growth of the sarcomeres and to augmented LV wall thickness that characterizes the concentric hypertrophy[86]. In this direction, since the RWT is a ratio between LVDD and PWDT, the attenuation of the increased RWT when the HSFD is associated with the AE seems to be attributed more to an improvement of the diastolic diameter, differing from the strength exercise, this find could be associated with LV enlargement as observe in a health condition of eccentric hypertrophy induced by the AE; emphasizing the distinct stimulus of each type of exercise.

In diseases conditions, where a pathologic hypertrophy is already established, the exercise seems to impose an antagonist effect upon pathologic stimuli and revert the structure alteration in the heart[14][89] and this antagonistic effect is dependent of type of disease. In a study with spontaneously hypertensive rats, Engel *et al.*[71] observed that the aerobic interval training increases the LVDD corrected by BW, but it was not associated with a decrease in RWT. In a model of myocardial infarction, the aerobic exercise reduced the left ventricular end-diastolic dimension at post-exercise moment increased by the myocardium infarction[78]. In another study witch the aim was to evaluate the impact of modality and intensity of early exercise training on ventricular remodeling after myocardial infarction, Batista *et al.*[90] did not detect any changes on the LVDD. Besides the well-known positive affect of aerobic interval training against cardiac remodeling its effect upon LVDD seems to be dependent of the type of stress (animal model of disease) and more studies are needed to verify if the aerobic interval training mitigates the concentric remodeling by mainly actin increasing the LVDD in a scenario of HSFD and cardiometabolic risk factors.

The high-sugar-fat diet (HSFD) increases the left atrium (LA) diameter and the LA normalized by the aorta (AO). Conversely, time *per se* reduces both variables. Interestingly, the effect of the HSFD was nullified in the presence of strength exercise, for both LA and LA/AO, an effect not observed when aerobic exercise is present. However, the increases in LA diameter observed in echocardiography analysis did not correlate with a significant increase in LA weight in post-mortem anatomical data analysis. Although our study did not detect a statistically significant difference in body weight when comparing groups that received the HSFD versus those that received the control diet (CD), the adiposity index increased, characterizing the development of obesity in the HSF,

HSF+AE, and HSF+SE groups.

Obesity is associated with LA enlargement, as observed in our study. LA enlargement is usually induced by pressure and/or volume overload, diastolic dysfunction - which, even in the absence of obesity, has been linked to LA enlargement -[91] and reduced compliance of the left ventricle (LV). Additionally, an increase in LA size in the presence of lower ejection fraction and eccentric hypertrophy (not observed in our study) can suggest a role for systolic dysfunction and increased LA pressure. Our model is characterized by concentric remodeling in association with high systolic blood pressure and systolic and diastolic dysfunction. However, we can say that diastolic dysfunction is predominant, since the only systolic variables decreased in the pre-exercise moment are PWSV and TDI S (not homogeneity), while several diastolic parameters were changed, including IVRT, EDT, E/E', and E'/A'.

Based on this information, we can speculate that the observed atrium enlargement in our model is due to increased volume overload, resulting from the increased adiposity (plasma volume) in association with concentric remodeling and diastolic dysfunction. Additionally, strength exercise was the only type of training that mitigated diastolic dysfunction at the post-exercise moment, aligning with the fact that the increased LA diameter due to the diet was nullified in the HSF+SE group. These findings together reinforce the idea that increased LA, in association with diastolic dysfunction, is mitigated by strength exercise but not by aerobic exercise in our study.

The question that remains is why the SE was able to mitigate the diastolic dysfunction but not the AE? Does that mean that the AE is not as effective as SE in a scenario of cardiac remodeling induce by HSFD? During aerobic exercise, circulatory flow increased, and the diastolic period decreases such that the atrioventricular valves are closed for logger than basal conditions. This effect is attenuated by increases in atrial pressure and contractility and enhanced ventricular lusitropy (ability of the ventricle to relax) during exercise. The described physiological alterations due to AE can lead to an LA enlargement over a longer period of training[92]. Even though, both aerobic and strength exercises imposes a volume overload to the heart, this effect tends to be more prominent on aerobic exercise doe to the higher venous return observed in this modality of exercise[85][93]. Said that, in a disease scenario of high adiposity index - which is associated with to imposes a chronic volume overload due to increased plasmatic volume - and presence of diastolic dysfunction, the above-mentioned physiological alteration as a result to aerobic exercise could have added a volume overload to the heart and prevented the improvement of the diastolic function. Together with that, the eight weeks of exercise could have been not enough to permit the heart to adapt to this new stimulus generated by the AE in the presence of the chronic pathologic stimuli of the HSFD, and in consequence of that, we were not able to see the improvement of the diastolic function as observed by the SE. This hypothesis also helps understanding why the HSF+SE group, but not the HSF+AE group showed an improvement of the diastolic function and nulled the increase in LA size.

The finding of the present study is in contrast to several studies that have

shown improvement of the diastolic function after aerobic exercise in different disease conditions[75][82]. However, some studies go along with ours, D'Haese *et al*.[82] evaluated the effect of 12-week moderate- and high-intensity endurance training on a diabetes-induced cardiac dysfunction in rats, despite they affirmed that the HIIT was effective in alleviating diastolic dysfunction by improving the end-diastolic pressure, they did not observed any improvement of the time constant for isovolumetric relaxation, evaluated by hemodynamic measurement. In a human study witch 38 patients, with stable heart failure and reduced ejection fraction, that were split into either aerobic exercise training, strength training, or control groups over a period of 12 weeks training, Lan *et al*. observed that AE was associated with evidence of worsening myocardial diastolic function, whereas this was not apparent after SE[94]; their findings help to support ours. We believe that these conflicts are associated with the different animal model used and different types of exercises protocols.

Regarding systolic function, the high-sugar-fat diet (HSFD) led to a reduction in PWSV and TDI S (not homogeneous). At the post-exercise moment, both aerobic and strength training prevented the HSFD-induced decrease in EF, EFS, and MFS. Additionally, both types of exercise showed improvement over time, reducing PWSV and nullifying the HSFD's effect on this variable. On the other hand, only strength exercise improved MFS over time.

The development of ventricular dysfunction impairments in a model of diet-induced dysfunction is multifactorial and complex, involving alterations in myocardial substrate utilization, calcium handling, as well as oxidative stress, inflammation, mitochondrial dysfunction, and structural remodeling. All these processes are likely to be influenced by exercise training, as reviewed by Bernardo *et al*.[14]. Since our study did not investigate the possible molecular mechanisms involved in the improvement of the structure and function by different types of exercise, we cannot suggest the possible molecular mechanism involved in the prevention and mitigation of cardiac systolic dysfunction.

However, our study reinforces literature data that shows both aerobic and strength exercises are able to improve systolic function in both human[75][95][96] and animals studies[97][88][98]. It is important to note that the data supporting the beneficial effects of strength exercise against cardiac dysfunction are scarcer than those evaluating the effect of aerobic exercise.

In our study the HSFD did not increase the pro-inflammatory cytokines - IL-6 and TNF-α - and the oxidative stress products - malondialdehyde and protein carbonylation - on left ventricular tissue. Also, we did not observe any alterations on the activity of the antioxidant enzymes glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase neither by the HSFD nor by the aerobic and strength exercise. Since the HSFD did not increase the inflammatory and oxidative stress markers in the cardiac tissue, we were not able to verify the effect of the different types of exercise on these variables. In the same direction, the non-changed levels of the oxidative stress products can help understanding the non-changed levels of the antioxidant enzymes. This results conflicts with other were a diet high in sugar and fat induce increase on the IL-6 and TNF as well MDA and protein carbonylation levels[99][100][101]. These conflicting results

could be attributed to the different composition of the diet, experimental design and also to the fact that the inflammation and oxidative stress responses are time dependent. Said that, more studies are need to understand the role of the inflammation and the oxidative stress on the pathophysiological process of the cardiac remodeling induced by HSFD.

Conclusion

The high-sugar-fat diet induced cardiac concentric structural changes and systolic and diastolic dysfunction, coupled with the development of cardiometabolic risk factors. Both aerobic and strength exercises were able to mitigate the echocardiographic parameters of the cardiac remodeling induced by high sugar-fat diet. In our study both aerobic and strength exercise protocols improved echocardiographic parameters of the concentric remodeling and the systolic dysfunction. Notably, the strength exercises had a more prominent effect on mitigating echocardiographic parameters of diastolic dysfunction than the aerobic exercise. Further studies are need to investigate the molecular mechanisms behind the finds observed in our study. We hope that this study could bring insights into the potential of exercise as a strategy for mitigating the adverse effects of an unhealthy diet on cardiac function.

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Conclusão

A dieta rica em açúcar e gordura, elaborada por nosso grupo de estudo, induz à remodelação cardíaca concomitantemente ao desenvolvimento de fatores de risco cardiometabólicos. A remodelação cardíaca é caracterizada por alterações estruturais concêntricas e disfunção sistólica e diastólica leves avaliada por análise ecocardiográfica. Observamos que os exercícios aeróbio e de força foram eficazes em atenuar a remodelação estrutural concêntrica e a disfunção sistólica de forma semelhante. No entanto, o exercício de força demonstrou ser mais efetivo do que o exercício aeróbio na mitigação da disfunção diastólica. Portanto, os resultados do nosso estudo reforçam os efeitos cardioprotetores dos exercícios aeróbio e de força, especialmente em um cenário de remodelação cardíaca induzida por dieta rica em açúcar e gordura. Além disso, destacamos que esses efeitos podem depender da modalidade de exercício empregada. Esperamos que o estudo estimule a realização de estudos futuros, especialmente estudos moleculares, para desvendar os mecanismos associados a esses efeitos.

Anexo

CERTIFICADO Nº 1333/2019 – CEUA

Certificamos que o projeto intitulado: **"Análise Proteômica do Miocárdio de ratos com disfunção cardíaca induzida por dieta rica em açúcar e gordura: Papel dos exercícios aeróbico e resistido"**, conduzido pela Pesquisadora: **Cristina Schmitt Gregolin –** Orientadora: Profa. Dra. Camila Renata Correa Camacho, registrada com o **nº 1333/2019**, que envolve a produção, manutenção ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto humanos), para fins de pesquisa científica – encontra-se de acordo com os preceitos da Lei n. 11.794, de 08 de outubro de 2008, do Decreto n. 6.899, de 15 de julho de 2009, com as normas editadas pelo Conselho Nacional de Controle de Experimentação Animal (CONCEA), e foi APROVADA pela Comissão de Ética no Uso de Animais da Faculdade de Medicina de Botucatu, em reunião ordinária de 27 de novembro de 2019.

Finalidade	( ) Ensino (**X**) Pesquisa Científica
Vigência da autorização	01 de janeiro de 2022
Espécie/Linhagem/Raça	Ratos Wistar
Nº de animais	60
Idade/Peso	21 dias – 50 gramas
Sexo	Machos
Origem	Biotério Central

Sara Rosa Stanley Sampaio
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Faculdade de Medicina de Botucatu/UNESP

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