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EFFECTS OF BILATERAL COMMON CAROTID ARTERIES OCCLUSION ON CARDIAC INOTROPISM IN ANESTHETIZED DOGS. ROLE OF THE AUTONOMIC NERVOUS SYSTEM ON THE REFLEX RESPONSE

Inotropic variations induced by bilateral carotid occlusion (BCO) under different conditions of the autonomic nervous system were studied in dogs anesthetized with morphine and sodium pentobarbital and submitted to cardiac pacing. Maximal velocity of contraction (V_{max}^{TP}) was utilized for evaluation of the myocardial contractile state.

The animals were divided into four groups: eight control dogs, ten dogs submitted to vagal blockade with atropine, ten animals submitted to beta-adrenergic blockade with propranolol and ten dogs with double autonomic blockade. They presented significant elevations of the systolic and the diastolic aortic pressures and left ventricular and diastolic pressure during BCO. Following carotid occlusion, the V_{max}^{TP} rose in control (2.95 ± 0.16 to 3.27 ± 0.23 L/s; $P < 0.01$) and in vagal blocked (3.12 ± 0.15 to 3.61 ± 0.26 L/s; $p < 0.01$) animals. In beta blocked animals, the values of the index decreased during BCO (2.38 ± 0.10 to 2.09 ± 0.11 L/s; $p < 0.001$) and in the dogs submitted to double autonomic block there was no modification of the V_{max}^{TP} (2.59 ± 0.07 to 2.61 ± 0.08 L/s).

It is concluded that the variations of V_{max}^{TP} in control and vagal blocked animals reflect the inotropic improvement due to sympathetic hyperactivity. It was supposed that the impairment of the contractile state found in animals treated with propranolol was caused by myocardial hypoxia secondary to alpha-adrenergic coronary vasoconstriction while the administration of atropine permitted adequate accommodation of the coronary circulation in dogs submitted to double autonomic blockade. Hence, in the last group of animals, there was no variation of the V_{max}^{TP} .

Carotid sinus baroreceptors exert considerable influence on the control of the cardiocirculatory system. It has been found that carotid sinus hypotension that occurs during carotid occlusion, through reflex alterations of autonomic activity, promotes changes of the heart rate¹⁻³, cardiac output^{4,5}, peripheral vascular resistance^{4,5}, arterial pressure^{2,5,6} and cardiac inotropism^{2,3,5,6}.

During bilateral carotid occlusion (BCO), there are important modifications of the left ventricular end diastolic pressure (preload) and the aortic diastolic pressure (afterload). Nevertheless, the indices of myocardial contractility utilized in investigations relating BCO and inotropic state, are influenced by alterations of these variables.

Previous studies indicate that maximal velocity of contraction (V_{max}^{TP}) is insensitive to changes in afterload⁷⁻¹⁰ and is not affected by variations of the preload, when there

are no important changes in myocardial fiber length⁹⁻¹².

Accordingly, the present investigation was conducted in order to evaluate the behavior of the inotropic state during BCO in anesthetized dogs submitted to cardiac pacing. The study was undertaken in dogs with no previous treatment and animals submitted to autonomic blockade using atropine and/or propranolol.

METHODS

Experiments were performed in 28 healthy, male, mongrel dogs, weighing from 10 to 15 kg, anesthetized with intramuscular morphine (2 mg/kg) followed by intravenous sodium pentobarbital (20 mg/kg). The animals were heparinized with 500 i.u/kg. Through a midline incision in the neck, both common carotid arteries were dissected and freed in the mid cervical region. The heart was paced by an atrial electrode inserted through the right

femoral vein, to maintain its rate constant during carotid occlusion.

Lead avF of the electrocardiogram, the arterial pressure, the intraventricular pressure and the first derivation of the ventricular pressure (dp/dt) were registered in a eight-channel photographic recorder (Electronics for Medicine).

Catheterization of the left ventricle was performed by percutaneous insertion of a 8 cm teflon catheter having an internal diameter of 1.4 mm, over a n.º 18 gauge needle, through the apex of the heart. The catheter was attached to a Stathan P23Db pressure transducer with an intervening adaptor, to filter the high frequency artifacts produced by motion of the catheter. The dynamic characteristics of this system was obtained by the method of Fry¹³. The degree of damping was 0.48 and the natural resonant frequency was 57 cycles/sec.

The dp/dt was obtained using a resistance capacitance differentiating circuit (Electronics for Medicine, model RC.1) with a time constant of 0.5 msec, which provided an output linearly proportional to the input frequency, confidence limits of 5%, up to the maximum frequency of 75 cycles./Sec.

Aortic blood pressure was measured in the ascending aorta by means of a 80 cm teflon catheter inserted into the femoral artery and attached to a Statham P23AA pressure transducer.

A teflon catheter was introduced into the left femoral vein for administration of drugs used after anesthesia of the animals.

The zero reference point for pressure measurements was taken as the back of the animals.

V_{\max} TP was evaluated according to Mason's method

⁸ A curve was obtained plotting the instantaneous values of shortening velocity estimated at 5 msec intervals of isovolumic systole, against simultaneous left ventricular pressure. Values of V_{\max} TP were determined by the linear extrapolation of the descending limb of the curve to the velocity axis. Velocity of shortening (V_{ce} TP) was calculated according to the formula:

$$V_{\text{ce}} \text{ TP} = p/dt / KP$$

where K is the constant of the elastic series, considered as having a value of 32 and P is the total intraventricular pressure.

A control measurement was made and the common carotid arteries were occluded. The arterial pressure rose and when it stabilized at a new level, the variables were again registered. A period of 60 to 120 s elapsed between the occlusion of the carotid arteries and the second measurement.

The effects Of BCO were studied: (a) in control animals (8 dogs), (b) after beta adrenergic blockade with 0.5 mg/kg of and propranolol (10 dogs), (c) after vagal blockade with 0.5 mg/kg of atropine blockade (10 dogs). The dose of propranolol was sufficient to block the inotropic effects of 10 g A/g of adrenaline. When more than one carotid occlusion was performed in the same dog, a interval of at least 20 min. was allowed to elapse.

Differences for paired data were compared by the Student "t" test, and a probability of 5% or less was considered significant.

RESULTS

The results of the experiments are summarized in Table I and Figure 1.

Table I: Cardiocirculatory effects of carotid occlusion.

Groups		HR beats/min	SAP mmHg	DAP mmHg	LVEDP mmHg	V_{\max} TP L/S
Control (8)	Before	153 ± 10.7	134 ± 6.3	103 ± 5.2	8.1 ± 0.5	2.95 ± 0.16
	During	153 ± 10.7	187 ± 9.3	147 ± 7.5	9.6 ± 0.6	3.27 ± 0.23
	p	-	< 0.001	< 0.001	< 0.01	< 0.01
Vagal Block (10)	Before	210 ± 7.8	126 ± 3.1	103 ± 4.0	7.0 ± 0.7	3.12 ± 0.15
	During	210 ± 7.8	168 ± 5.5	140 ± 4.5	7.8 ± 0.7	3.61 ± 0.26
	p	-	< 0.001	< 0.001	< 0.05	< 0.01
Beta Block (10)	Before	122 ± 3.8	134 ± 5.0	96 ± 3.2	10.8 ± 0.7	2.38 ± 0.10
	During	122 ± 3.8	178 ± 4.3	133 ± 3.5	14.9 ± 1.3	2.09 ± 0.11
	p	-	< 0.001	< 0.001	< 0.001	< 0.001
Double Block (10)	Before	151 ± 6.0	125 ± 3.8	94 ± 4.3	9.2 ± 0.5	2.59 ± 0.07
	During	151 ± 6.0	177 ± 8.6	137 ± 7.3	12.4 ± 1.0	2.61 ± 0.08
	p	-	< 0.001	< 0.001	< 0.001	ns

HR: heart rate; SAP: systolic aortic pressure; DAP: diastolic aortic pressure, LVEDP: left ventricular end-diastolic pressure; V_{\max} TP: maximal velocity of contraction; BEFORE: mean values obtained before carotid occlusion; DURING: mean values obtained during carotid occlusion; p: values for the highest probability that the observed differences are due to chance; in parentheses: number of dogs.

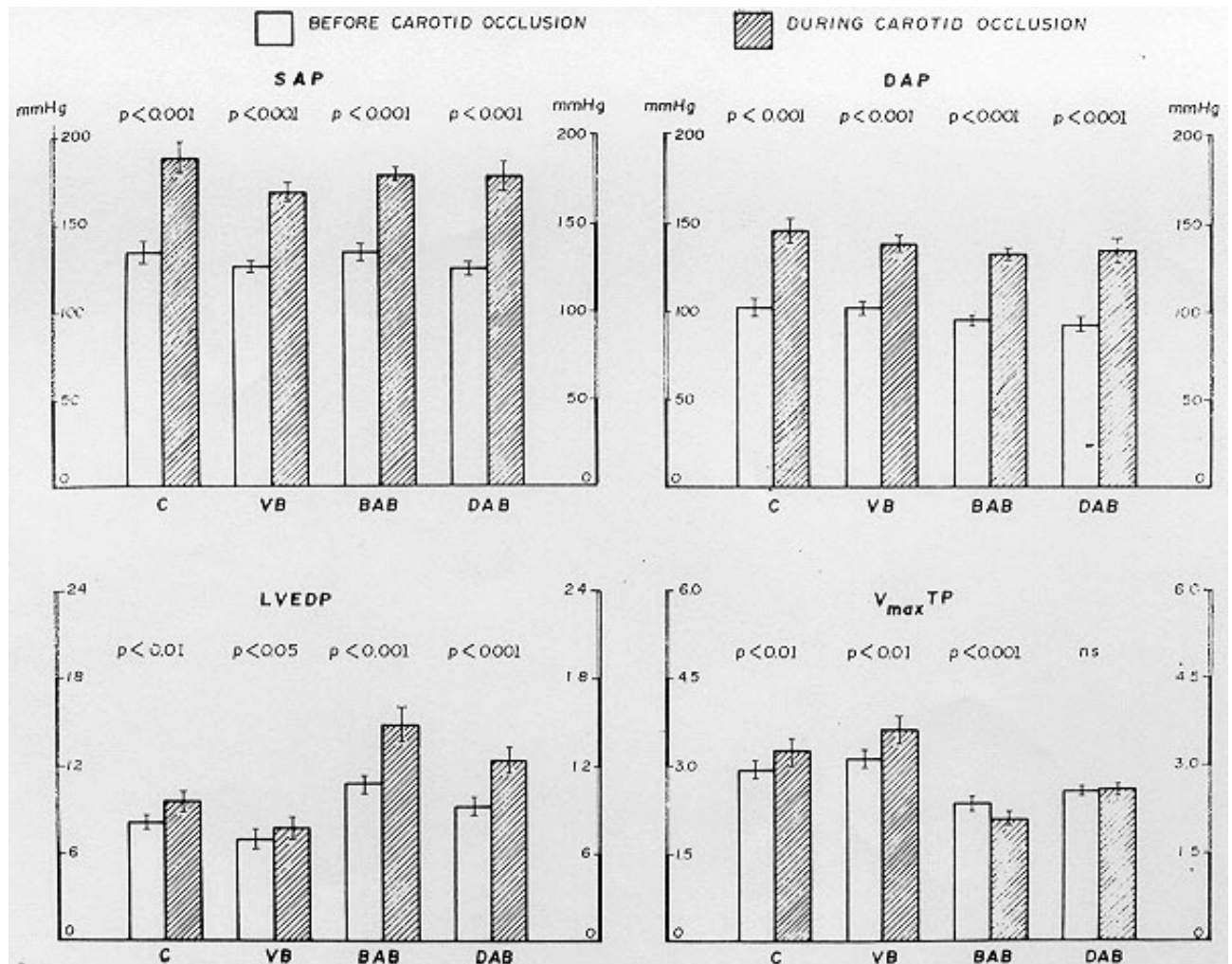


Fig. 1 - Mean values and standard errors of mean (vertical bars) for systolic aortic pressure (SAP), diastolic aortic pressure (DAP) and maximal velocity of contraction ($V_{max} TP$) before and during carotid occlusion in control dogs (C), vagal blockade (VB), beta adrenergic blockade (BAB) and double autonomic blockade (DAB).

A - Control: In the dogs of the control group, studied with a mean heart rate of 153 ± 10.7 beats/min, the systolic aortic pressure (SAP) rose from 134 ± 6.3 to 187 ± 9.3 mmHg ($p < 0.001$) during BCO. The diastolic aortic pressure (DAP) increased from an average of 103 ± 5.2 to 147 ± 7.5 mmHg ($p < 0.001$), while the left ventricular end diastolic pressure (LVEDP) rose from 8.1 ± 0.5 to 9.6 ± 0.6 mmHg ($p < 0.01$). $V_{max} TP$ increased from 2.95 ± 0.16 to 3.27 ± 0.23 L/s ($P < 0.01$) during BCO.

B - Vagal Blockade: In these dogs, studied with a mean heart rate of 210 ± 7.8 beats/min, the BCO produced effects similar to those observed in the control group. SAP increased 42 mmHg from an average value of 126 ± 3.1 mmHg ($p < 0.001$), DAP increased by 37 mmHg from a basal level of 103 ± 4.0 mmHg ($p < 0.001$), while LVEDP increased by 0.8 from the initial level of 7.0 ± 0.7 mmHg ($p < 0.01$). There was elevation of $V_{max} TP$ from 3.12 ± 0.15 to 3.61 ± 0.26 L/s ($p < 0.01$).

C - Beta receptor blockade: With the heart rate maintained in 122 ± 3.8 beats/min, the SAP rose from $135 \pm$

5.0 to 178 ± 4.3 mmHg ($p < 0.001$) and the DAP from 96 ± 3.2 to 133 ± 3.5 mmHg ($p < 0.001$). LVEDP increased from 10.8 ± 0.7 to 14.9 ± 1.3 mmHg ($p < 0.001$), and $V_{max} TP$ decreased from 2.38 ± 0.10 to 2.09 ± 0.11 L/s ($p < 0.001$).

D - Double autonomic blockade: The dogs of this group presented a mean heart rate of 151 ± 6.0 beats/min. the SAP increased from 125 ± 3.8 to 177 ± 8.6 mmHg ($p < 0.001$) and the DAP rose from 94 ± 4.3 to 137 ± 7.3 mmHg ($p < 0.001$). The LVEDP increased from 9.2 ± 0.5 to 12.4 ± 10 mmHg ($p < 0.001$). There were no modifications of $V_{max} TP$ during BCO, the initial values were 2.59 ± 0.07 and passed to 2.61 ± 0.08 L/s during carotid sinus hypotension ($p > 0.05$).

DISCUSSION

Previous studies indicate that $V_{max} TP$ is a sensitive index for reflecting negative inotropic changes^{7,8,12,14,15} and is not influenced by variations of the afterload⁷⁻¹⁰. Some authors

have suggested that the V_{TP}^{max} is preload dependent when there are marked elevations of the LVEDP^{9,16,17}. In the present investigation the increase in LVEDP, although significant, were slight and in this situation it is believed that the myocardial fiber length does not affect the V_{TP}^{max} ⁸⁻¹². These aspects allow us to accept the V_{TP}^{max} as a reliable index of cardiac inotropism in experiments.

Although experiments performed in unanesthetized dogs revealed that BCO does not change cardiac inotropism substantially³, studies conducted in anesthetized dogs indicate that the carotid sinus reflex exerts important role in the regulation of myocardial contractility^{2,5,6,18,19,20}.

General conclusions in most of the investigations undertaken in anesthetized dogs support the classical viewpoint that carotid sinus hypotension promotes vagal inhibition^{4,21,22} and sympathetic hyperactivity^{2,5,6,18}. The increase of adrenergic tonus improves contractile state by means of beta adrenergic myocardial stimulation²²⁻²⁴ and this mechanism can be responsible for V_{TP}^{max} elevation observed in the dogs of the control and vagal blockage groups.

After propranolol infusion, BCO produced impairment of inotropism. Previous works undertaken in dogs with intact vagal activity and submitted to beta-adrenergic blockage by propranolol did not report this kind of results due to bilateral carotid hypotensions^{5,19}. In these studies, the indices utilized to characterize the inotropic state depends on preload and afterload variations. Hence, it is possible that these results may be somewhat compromised.

Obviously, this kind of variation of the contractile state can not be caused by direct sympathetic effect on the myocardium or to vagal inhibition of the heart²⁵.

The negative inotropic effect observed in these animals may be explained by activation of sympathetic innervation of the coronary vascular tree. Adrenergic nerve fibers influence coronary resistance through the stimulation of alpha constrictor and beta dilator receptors²⁶⁻³⁸.

Propranolol, blocking the effects of beta-adrenergic stimuli on coronary vessels,^{29,30,33-35} can unmask alpha-receptor vasoconstriction and limit coronary flow could be a cause of depressed cardiac inotropism.

After administration of atropine and propranolol there was no variation of V_{TP}^{max} during BCO and this is in accordance with investigations carried out in dogs submitted to double autonomic blockade^{2,40}. The mechanisms through which atropine induces alterations of inotropism, in comparison with animals receiving only propranolol is not clear. It is noteworthy, however, that Nayler and cols⁴¹ have found that the combined use of

atropine and propranolol permitted that myocardial demands of blood flow be met during increased left ventricular work in dogs where coronary adjustments had been disarranged by the administration of propranolol only. This finding supports the idea that atropine prevents, in some way, the hazardous effects of propranolol on the coronary blood flow, explaining why BCO produces differing results in beta blocked dogs and in animals with double autonomic block.

RESUMO

Os efeitos da oclusão bilateral das artérias carótidas sobre o inotropismo cardíaco foram estudados em cães anestesiados, com sistema nervoso autônomo íntegro ou bloqueado pela atropina e/ou propranolol. A frequência cardíaca foi mantida constante por meio de marca-passo atrial. Como índice do estado contrátil, utilizou-se a velocidade máxima de contração do ventrículo esquerdo (V_{TP}^{max}).

A oclusão das carótidas provocou nos quatro grupos de animais utilizados (controle, bloqueio vagal, bloqueio betaadrenérgico e duplo bloqueio autonômico), elevação significativa da pressão sistólica e diastólica da aorta e da pressão diastólica final do ventrículo esquerdo. Quando as carótidas foram ocluídas, ocorreu aumento da V_{TP}^{max} nos cães do grupo-controle ($2,95 \pm 0,16$ para $3,27 \pm 0,23$ L/S; $p < 0,01$) e bloqueio vagal ($3,12 \pm 0,15$ para $3,61 \pm 0,26$ L/S; $p < 0,01$). Nos animais submetidos a bloqueio betaadrenérgico ocorreu diminuição no valor do índice ($2,38 \pm 0,10$ para $2,09 \pm 0,11$ L/S; $p < 0,001$);

Conclui-se que as variações da V_{TP}^{max} nos animais dos grupos controle e bloqueio vagal, refletiram a melhora do estado contrátil, conseqüente à hiperatividade simpática.

Supos-se que nos animais tratados com propranolol, a hiperatividade alfaadrenérgica acarretou queda do fluxo coronário, condicionando hipóxia miocárdica e depressão do inotropismo e que a administração de atropina nos animais submetidos a duplo bloqueio autonômico, permitiu adequada acomodação do fluxo coronário em conseqüência do que, não ocorreu depressão do estado contrátil.

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