Laboratory Investigation

Haemodynamic changes and oxygen uptake during crossclamping of the thoracic aorta in dexmedetomidine pretreated dogs

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This study was designed to test the hypothesis that the α_2 adrenergic agonist, dexmedetomidine (DEX), decreases tissue oxygen demand thereby increasing tolerance to hypoxic insult. In 17 anaesthetized dogs, cardiac output was measured with thermodilution, blood flow through the inferior caval vein was determined using an electromagnetic flowmeter, and oxygen consumption was calculated by the Fick principle. The animals were divided into three groups: control group ($n = 5$), D3 and D30 groups ($n = 6$ for each group) treated with two doses of DEX ($3 \mu\text{g} \cdot \text{kg}^{-1}$ and $30 \mu\text{g} \cdot \text{kg}^{-1}$, respectively) prior to aortic crossclamping. Upon crossclamping of the thoracic aorta, the cardiac index decreased in all three groups with the largest decrease in the D30 group, and the smallest decrease in the control group. Blood flow through the inferior vena cava decreased in all three groups of animals while blood flow

through the superior caval vein increased in the control group, did not change in the D3 group, and decreased in the D30 group. Oxygen saturation in mixed venous blood increased in the control group, did not change in the D3 group and decreased in D30 group. Blood flow and oxygen uptake in the lower part of the body decreased in all groups. Oxygen consumption in the upper part of the body decreased equally in all three groups. Arterial lactate concentrations increased almost two-fold in the control group while it increased by only 30% in animals treated with DEX. A lesser increase in lactate concentrations and oxygen extraction in tissues below aortic crossclamping is consistent with the hypothesis that DEX decreases tissue oxygen requirement which might prove particularly useful in clinical situations where tissue hypoxia is expected.

Key words

OXYGEN: consumption;

SURGERY: vascular;

SYMPATHETIC NERVOUS SYSTEM: alpha-adrenergic agonists, dexmedetomidine.

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Cette étude a pour but de déterminer si la dexmédétomidine, un agoniste α_2 adrénergique, diminue la demande tissulaire en oxygène et augmente ainsi la tolérance à l'hypoxie. Dix-sept chiens sous anesthésie régionale sont étudiés. Le débit cardiaque est mesuré par thermodilution. Le débit sanguin de la veine cave inférieure est déterminé à l'aide d'un débitmètre électromagnétique et la consommation en oxygène est calculée à partir du principe de Fick. Les animaux sont divisés en trois groupes : un groupe contrôle ($n = 5$), un groupe D₃ traité avec dexmédétomidine $3 \mu\text{g} \cdot \text{kg}^{-1}$ ($n = 6$) et un groupe D₃₀ traité avec dexmédétomidine $30 \mu\text{g} \cdot \text{kg}^{-1}$ ($n = 6$) administrée avant le clampage aortique. À la suite du clampage de l'aorte thoracique, les trois groupes d'animaux présentent une chute de l'index cardiaque : la plus grande diminution est retrouvée dans le groupe D₃₀ et la plus petite dans le groupe contrôle. Le débit sanguin dans la veine cave inférieure diminue dans les trois groupes, alors que le débit dans la veine cave supérieure augmente dans le groupe contrôle, ne change pas dans le

groupe D_3 et diminue dans le groupe D_{30} . La saturation en oxygène du sang veineux mêlé augmente dans le groupe contrôle, ne change pas dans le groupe D_3 et diminue dans le groupe D_{30} . Le débit sanguin et la consommation en oxygène dans l'hémicorps situés sous le clampage aortique diminuent dans tous les groupes d'animaux. La consommation en oxygène dans l'hémicorps au-dessus du clampage aortique diminue également dans les trois groupes. La concentration artérielle de lactate est presque doublée dans le groupe contrôle alors qu'elle n'augmente que de 30% chez les animaux traités avec dexmédétomidine. Cette plus faible production de lactate accompagnant une moins grande demande tissulaire en oxygène pour les organes sous le clampage aortique chez les animaux traités avec la dexmédétomidine, suggère que ce médicament peut être utile dans les situations cliniques d'hypoxie tissulaire.

The haemodynamic response to crossclamping of the thoracic aorta is complex. Arterial hypertension, the most consistent and prominent response to aortic crossclamping, has classically been attributed to the sudden increase in impedance to aortic flow.¹⁻⁴ Crossclamping of the thoracic aorta is also associated with a decrease in blood flow below the aortic occlusion and a substantial increase in blood flow above the occlusion.⁵⁻⁸ Oxygen consumption below the clamp expectedly decreases reflecting a severe oxygen deprivation in the lower part of the body.^{5,7}

Dexmedetomidine (DEX), the pharmacologically active d-isomer of medetomidine, is a highly specific and selective α_2 adrenergic agonist.⁹ The $\alpha_2:\alpha_1$ selectivity ratio of medetomidine is 1,620:1 compared with 220:1 for that of clonidine.⁹ Dexmedetomidine has sedative properties and causes a dose-dependent decrease in blood pressure and heart rate associated with a decreased concentration of plasma norepinephrine.¹⁰ A detailed description of the pharmacology of DEX is available in a recent excellent review.¹¹

Decreases in lipolysis, and tissue oxygen demand and uptake following administration of α_2 adrenergic agonists have been attributed to an inhibition of adenylate cyclase and a subsequent decrease in intracellular cyclic AMP concentration and a decrease in cellular respiration.^{12,13} Consequently, α_2 adrenergic agonists might increase tissue tolerance to oxygen deprivation by a decrease in tissue oxygen demand.

This study was designed to test the hypothesis that a highly selective α_2 agonist, DEX, decreases tissue oxygen demand thereby increasing tolerance to hypoxic insult in tissues below aortic occlusion.

Methods

The protocol for the study was approved by the Institu-

tional Animal Use Committee. All animals received humane care in compliance with "USDA regulations and the NIH Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 85-23, 1985).

Surgical Preparation

Anaesthesia was induced with methohexitone ($8 \text{ mg} \cdot \text{kg}^{-1}$ iv) in 17 mongrel dogs weighing 17–22 kg. Tracheal intubation was facilitated with metocurine ($0.25 \text{ mg} \cdot \text{kg}^{-1}$ iv); anaesthesia was provided with halothane in oxygen titrated to maintain mean systemic arterial blood pressure between 80–100 mmHg. End-tidal concentrations of halothane were measured using a Datex Anaesthetic Agent Monitor model AM222 and kept constant (0.5%–0.8%) for the duration of the experiments after the surgical preparation was complete. Controlled ventilation was adjusted to maintain arterial carbon dioxide tension between 35–45 mmHg. One carotid and one femoral artery were exposed and catheters were placed into the proximal carotid artery and distal abdominal aorta, respectively. Catheters were also placed into the superior vena cava, 3 cm from the atrium and into the inferior vena cava at the level of diaphragm, via the left external jugular and femoral veins, respectively. The proper positions of these catheters were verified by palpation after sternotomy. A 5 F flow-directed thermodilution catheter (Spectramed Inc., Oxnard CA, model SP5105H) was advanced into the pulmonary artery via the right external jugular vein. Sternotomy was performed, and a snare was placed around the thoracic aorta just above the diaphragm. After initial heparin administration ($300 \text{ u} \cdot \text{kg}^{-1}$), the inferior vena cava was transected above the diaphragm and a cannulating electromagnetic probe of appropriate size (Cliniflow II, model EM701 D, Carolina Medical Electronics, King NC) was inserted. Heparin ($100 \text{ u} \cdot \text{kg}^{-1}$) was administered every hour for the duration of the experiments. Lactated Ringer's solution was infused at a rate of $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ throughout the experiment. During the surgical preparation, sodium bicarbonate 8.4% (25–50 ml) and hetastarch 6% in saline (Hespan®, 50–100 ml) were administered as needed to maintain an arterial pH above 7.34 and a pulmonary artery wedge pressure between 5–10 mmHg, respectively. There were no differences in the amount of infused fluid among the groups. Hetastarch or sodium bicarbonate was not administered after baseline measurements. Animal body temperature, measured by a thermistor at the tip of the pulmonary artery catheter, was maintained at 38°C using a heating pad. The protocol assumed exclusion of animals with haemoglobin concentrations below $10 \text{ g} \cdot \text{dl}^{-1}$ at any stage of observation.

Experimental protocol

The animals were divided into three groups: control group

($n = 5$), D3 and D30 groups ($n = 6$ for each group) treated with two *iv* doses of DEX ($3 \mu\text{g} \cdot \text{kg}^{-1}$ and $30 \mu\text{g} \cdot \text{kg}^{-1}$, respectively) before aortic crossclamping. Dexmedetomidine was infused during 20–30 minutes between completion of surgical preparation and aortic crossclamping. In all three groups the thoracic aorta was occluded for one hour, 30 min after saline (in control) or DEX administration.

Baseline measurements were made after haemodynamic variables stabilized for at least 20 min (Stage 1). Measurements were repeated 30 min after the completion of DEX administration in groups D3 and D30 or saline in the control group (Stage 2). Then, the aorta was clamped just above the diaphragm and the measurements were repeated 10, 20, 30, 45 and 60 min after aortic crossclamping (Stages 3, 4, 5, 6 and 7 respectively); and 10 and 20 min after aortic unclamping (Stages 8 and 9, respectively). The measurements included cardiac output, measured in triplicate by thermodilution with a Gould cardiac output computer (model SP1465; Spectramed Inc, Critical Care Division, Oxnard, CA); heart rate; systolic, diastolic, and mean systemic and pulmonary artery pressures, distal aortic pressure; pulmonary capillary wedge pressure; right atrial pressure; inferior vena cava pressure and flow. All pressures and flows were continuously recorded using a Grass polygraph (model 7, Grass Instrument Co., Quincy, MA). At each stage, arterial, mixed venous (from the pulmonary artery), superior and inferior caval blood samples were obtained and pH, carbon dioxide tension, oxygen tension, haemoglobin, and oxygen saturation were determined in each sample with an Instrumentation Laboratories Arterial Blood Gas Analyzer (model 1301, IL, Lexington; Mass) and Cooximeter (model 282). Lactate concentrations were also measured in the blood samples obtained from the same vessels.

Lactate determinations

Blood lactate concentrations were determined by the method of Henry and Reed.¹⁴ This assay is based on the lactate dehydrogenase (LDH) mediated conversion of lactate to pyruvate with the molar equivalent reduction of NAD to NADH. The increase in absorbance at 340 nm is proportional to the concentration of lactate in the sample. International units of enzyme activity are expressed as micromoles of NADH formed per minute ($E_m = 6.22 \times 10^3 \text{ M}^{-1}\text{cm}^{-1}$ at 37°C). Coefficient of variation equaled 0.8% and sensitivity was less than $1.5 \text{ mg} \cdot \text{dl}^{-1}$.

Calculations

The following derived haemodynamic variables were calculated: superior vena cava (upper body) flow was calculated as the difference between cardiac output and inferior vena cava (lower body) flow, normalized for body

weight. Systemic vascular resistance was calculated as the difference between mean arterial and right atrial pressures divided by cardiac output. Total body, upper body, and lower body oxygen consumption were calculated using the Fick equation: total body oxygen consumption equaled cardiac output times the difference between arterial and mixed venous (from pulmonary artery) blood oxygen contents. Lower body oxygen consumption was computed as lower body flow multiplied by the difference between arterial and inferior vena cava blood oxygen contents. Upper body oxygen consumption equaled upper body flow multiplied by the difference between arterial and superior vena cava blood oxygen contents. Upper body oxygen consumption was also calculated as a difference between total body and lower body oxygen consumption. The values of upper body oxygen consumption calculated in these two different ways were compared. The protocol assumed to exclude observations where the difference between the two values exceed 15% to rule out the possible influence of an inaccurate sampling from superior and inferior caval veins secondary to a streaming effect. Oxygen extraction was calculated as oxygen uptake divided by oxygen delivery which in turn was calculated as a product of flow and oxygen content in arterial blood. Lactate flux in the upper and lower parts of the body were calculated as lactate concentration in the superior caval or inferior caval blood, respectively, times the respective flows.

The results were analyzed as absolute values and expressed as mean $\pm$ SD, unless specified otherwise. Comparisons between groups were performed using one-way analysis of variance. Comparisons among the stages for each group were made with repeated measures analysis of variance. For individual comparisons of a pair of means, Fisher's least protected significant difference test was used. Differences were considered statistically significant if $P < 0.05$.

Results

Effects of dexmedetomidine administration prior to crossclamping of the thoracic aorta

There were no differences in any variable among the groups at baseline, prior to any interventions (Table). Administration of DEX was associated with decreases in mean arterial pressure and heart rate. The decreases were not dose-related. Cardiac output decreased in both DEX groups but there was no difference between the groups. Subsequently, systemic vascular resistance did not change in any of the groups studied. Total body oxygen consumption did not change in either group while oxygen saturation and content in mixed venous blood decreased and calculated oxygen extraction increased in both DEX groups.

TABLE Main baseline cardiovascular, oxygen consumption, and lactate concentration data observed before and after DEX administration, prior to crossclamping of the thoracic aorta (mean $\pm$ SD)

Stage group	Baseline			After DEX administration		
	Control	D3	D30	Control	D3	D30
HR	141 $\pm$ 24	145 $\pm$ 60	142 $\pm$ 43	141 $\pm$ 29	104 $\pm$ 46*	114 $\pm$ 48*
MAP	79 $\pm$ 15	92 $\pm$ 34	104 $\pm$ 31	72 $\pm$ 24	72 $\pm$ 29*	88 $\pm$ 46*
CVP	4 $\pm$ 2	5 $\pm$ 4	4 $\pm$ 3	4 $\pm$ 2	5 $\pm$ 4	4 $\pm$ 3
PCWP	5 $\pm$ 4	6 $\pm$ 5	7 $\pm$ 5	4 $\pm$ 4	7 $\pm$ 5	8 $\pm$ 5
CI	87.0 $\pm$ 13.2	91.1 $\pm$ 29.8	92.6 $\pm$ 43.4	82.1 $\pm$ 13.4	70.6 $\pm$ 20.6*†	66.5 $\pm$ 43.9*†
SVR	0.863 $\pm$ 0.200	0.955 $\pm$ 0.288	1.149 $\pm$ 0.888	0.845 $\pm$ 0.222	0.942 $\pm$ 0.396	1.432 $\pm$ 1.786
UBF	45.0 $\pm$ 12.8	55.7 $\pm$ 26.9	51.1 $\pm$ 42.5	42.6 $\pm$ 7.9	43.2 $\pm$ 21.8*	35.1 $\pm$ 37.4*†
LBF	41.9 $\pm$ 13.9	35.4 $\pm$ 14.2	41.5 $\pm$ 13.0	40.5 $\pm$ 13.4	27.4 $\pm$ 4.6*†	31.4 $\pm$ 20.4*†
$\dot{V}O_2$	5.99 $\pm$ 2.99	5.30 $\pm$ 2.86	5.25 $\pm$ 3.74	5.95 $\pm$ 2.60	5.49 $\pm$ 3.02	4.90 $\pm$ 3.84
TBO ₂ extr	40 $\pm$ 8	32 $\pm$ 8	34 $\pm$ 9	42 $\pm$ 9	42 $\pm$ 9*	44 $\pm$ 10*
La	41 $\pm$ 9	32 $\pm$ 26	34 $\pm$ 21	35 $\pm$ 13	34 $\pm$ 23	31 $\pm$ 31

MAP, mean arterial pressure in mmHg; CVP and PCWP, central venous and pulmonary capillary wedge pressures, respectively, in mmHg; CI, cardiac index in $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; SVR, systemic vascular resistance in $\text{dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$; UBF, LBF, upper body, lower body blood flows, respectively, in $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$; $\dot{V}O_2$, total body oxygen uptake in $\text{mlO}_2 \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$; TBO₂extr, total body oxygen extraction in %; La, arterial lactate concentration in $\text{mg} \cdot \text{dl}^{-1}$.

* $P < 0.05$ compared with baseline values in the same groups.

† $P < 0.05$ compared with control group at the same stage, after dexmedetomidine (or saline in control group) administration.

Flow through the superior caval vein decreased in both DEX groups (possibly in a dose-related fashion); however, the difference in the decrease between the two DEX groups did not reach a level of statistical significance. Oxygen uptake in the upper part of the body did not change while oxygen content and saturation in the superior vena cava decreased in both DEX groups without any difference between them. Similar changes were observed in the lower part of the body, namely, flow through the lower part of the body decreased in both DEX groups while oxygen uptake did not change. Administration of DEX prior to aortic crossclamping was not associated with any changes in lactate concentrations. There were no changes in any variable in the control group (Table).

Effects of crossclamping of the thoracic aorta

Crossclamping of the thoracic aorta was associated with an expected steady substantial increase in mean arterial pressure in all three groups but there were no differences among the groups. Cardiac output decreased in all three groups with the decrease being dose-related: it was relatively minimal in the control group and most pronounced in the D30 group (Figure 1). Subsequently, the vascular resistance increased to the greatest extent in the D30 group and to the least extent in the control group of animals (Figure 2). Filling pressures (central venous pressure – CVP, and pulmonary arterial occluded pressure – PAOP) increased in both DEX groups, and did not change in the control group. The lowest filling pressures were in the control group and the differences between the

FIGURE 1 Changes in cardiac index (CI, mean $\pm$ SE) during crossclamping of the thoracic aorta. Circles identify control group. Squares identify D3 (dexmedetomidine $3 \mu\text{g} \cdot \text{kg}^{-1}$) group and triangles identify D30 (dexmedetomidine $30 \mu\text{g} \cdot \text{kg}^{-1}$) group. * denotes $P < 0.05$ compared to baseline; † represents $P < 0.05$ compared with the control group at the corresponding stage; ‡ identifies $P < 0.05$ compared with D3 group. Drug represents time of D3, D30 or saline injection. AoX and AoUX represent time of clamping and unclamping of the aorta, respectively. Therefore, Stage 1 represents baseline before dexmedetomidine administration. Stage 2 represents values after dexmedetomidine administration prior to crossclamping of the thoracic aorta. Stages 3, 4, 5, 6 and 7 represent values observed in 10, 20, 30, 45, and 60 min of aortic crossclamping, respectively. Stages 8 and 9 represent 10 and 20 min after unclamping of the thoracic aorta.

FIGURE 2 Changes in systemic vascular resistance (SVR). See legend to Figure 1 for symbol identification.

FIGURE 3 Changes in pulmonary capillary wedge pressure (PCWP). See legend to Figure 1 for symbol identification.

control and D3 groups were statistically significant (Figure 3). Total body oxygen uptake substantially decreased without differences among the groups (Figure 4). Oxygen content and saturation in mixed venous blood increased in the control group, did not change in the D3 group and decreased in the D30 group (Figure 5). Subsequently, calculated oxygen extraction decreased in the control and increased in the D30 group.

Blood flow and oxygen uptake in the lower part of the body substantially decreased without any differences

FIGURE 4 Changes in total body oxygen consumption (TBVO₂). See legend to Figure 1 for symbol identification.

FIGURE 5 Changes in mixed venous (pulmonary artery) oxygen saturation (SpaO₂). See legend to Figure 1 for symbol identification.

among the groups (Figures 6, 7). On the other hand, blood flow through the superior caval vein increased in the control group, did not change in the D3 group, and decreased in the D30 group (Figure 8). Oxygen consumption in the upper part of the body decreased in all three groups without differences among the groups (Figure 9). Oxygen content and saturation in the superior caval blood increased in the control and D3 group and did not change in the D30 group. Oxygen extraction in the upper part of the body was the lowest in the control group and the

FIGURE 6 Changes in blood flow through lower part of the body (F_{IVC} -inferior vena caval flow). See legend to Figure 1 for symbol identification.

FIGURE 8 Changes in blood flow through upper part of the body (F_{SVC} -superior vena caval flow). See legend to Figure 1 for symbol identification.

FIGURE 7 Changes in oxygen uptake in the lower part of the body ($LBVO_2$). See legend to Figure 1 for symbol identification.

FIGURE 9 Changes in oxygen uptake in the upper part of the body ($UBVO_2$). See legend to Figure 1 for symbol identification.

largest in the D30 group while in the lower part of the body it was exactly the opposite: oxygen extraction was the highest in the control group and the lowest in the D30 group.

Arterial lactate concentrations increased almost two-fold in the control group while it increased only 30% in animals treated with DEX (Figure 10). Similar changes were observed in the concentrations of lactate in the superior and inferior caval veins, namely, they increased in all groups but the increase was much more prominent in

the control group than in the DEX groups. There were no differences between the two DEX groups. Calculated upper body lactate flux substantially increased in the control group to a much greater extent than in the D30 group (Figure 11). Lower body lactate flux had a tendency to decrease during aortic crossclamping in all three groups which was apparently due to a considerably lower flow; however, immediately after unclamping, the lower body lactate flux was greater in the control group than in either DEX group (Figure 12).

FIGURE 10 Changes in arterial lactate concentrations (La). See legend to Figure 1 for symbol identification.

FIGURE 12 Changes in lactate flux in the lower body (L_{rLB}). See legend to Figure 1 for symbol identification.

FIGURE 11 Changes in lactate flux in the upper body (L_{rUB}). See legend to Figure 1 for symbol identification.

Effect of aortic unclamping

Unclamping of the thoracic aorta was associated with a substantial decrease in arterial blood pressure and an increase in cardiac output without any differences among the groups. The values of cardiac output on unclamping were greater in the control and D3 groups without differences among the groups. Total body oxygen uptake also increased in all three groups (Figure 4). Other main haemodynamic variables returned or had a tendency to return to baseline values (Figures 2–9). Arterial lactate

concentration increased in all three groups. The degree of increase was similar however, the final values of arterial lactate concentration in the control group were greater than in either of the DEX groups. A similar pattern was observed in lactate concentrations in the superior caval vein. In the inferior caval vein, lactate concentrations were also higher in the control group.

Discussion

Haemodynamic changes

Dexmedetomidine administration was associated with a decrease in mean arterial pressure and cardiac output (Table). The decreases were not dose-related and were not associated with changes in systemic vascular resistance. A decrease in cardiac output was mainly due to a decrease in heart rate. These haemodynamic changes were associated with an increase in oxygen extraction which might suggest some degree of inadequacy of cardiac output or opening of additional capillaries, increasing capillary density and oxygen availability. The latter seems to be less likely than the former since oxygen consumption observed after dexmedetomidine administration did not differ from baseline or control values (Table). On the other hand, filling pressures remained unchanged. Also, experimental data suggest that DEX has no intrinsic myocardial contractile effects: no changes in contractility, relaxation, and intracellular Ca^{++} were observed.¹⁵ Thus, the interpretation of these haemodynamic changes are difficult at present but some decrease in myocardial contractility cannot be ruled out.

Aortic crossclamping was associated with an increase in

arterial pressure and vascular resistance in all animals, control as well as those treated with DEX (Figure 2). On the other hand, cardiac output decreased and filling pressures (CVP and PAOP) increased only in those dogs treated with DEX; these changes were dose-related (Figures 1 and 3) and suggested an inability of the heart to respond to an increased afterload and/or preload. Concerning afterload, an increased blood pressure during aortic crossclamping resulted, at least partially, from a sudden increase in impedance to aortic flow. This increased afterload might result in increased left ventricular end-systolic volume and decreased ejection fraction.^{1,3} However, crossclamping of the thoracic aorta might also be associated with increased preload^{6,8} which is presumably due to a passively (elastic venous recoil) and actively (induced venoconstriction) mediated decrease in venous capacitance below the aortic occlusion. Activation of α_2 receptors in animals and humans is also associated with venoconstriction.¹⁶⁻²⁰ The evidence suggests that the postsynaptic vascular α_2 adrenergic receptors play a more prominent role in venous capacitance vessels than in arterial resistance vessels.^{19,20} Therefore, α_2 adrenergic receptor mediated venoconstriction can decrease venous capacitance, thereby increasing venous return to the heart.²¹ Consequently, it is possible that the degree of decrease in venous capacitance and the subsequent increase in venous return was greater in animals pretreated with DEX than in control dogs. Thus, it seems that this increased preload in combination with the myocardium's inability to increase contractility in response to an increased preload and afterload during aortic crossclamping, resulted in a dose-related increase in filling pressures. Such a lack of increase in contractility might be due to a decrease in central sympathetic outflow as well as activation of presynaptic α_2 adrenergic receptors in the myocardium, resulting in the inhibition of the neurotransmitter release.^{19,22,23} Myocardial compromise observed in animals pretreated with DEX also could have been aggravated by halothane which was used as a basic anaesthetic in this study. Although the dose of halothane was not high, this unfavourable drug interaction cannot be ruled out. The constriction of resistive and capacitance vessels alone, without myocardial compromise, can be responsible for the observed simultaneous increase in arterial and filling pressures, and a decrease in cardiac output. After all, an increase in PCWP did not exceed 15–16 mmHg. Such vasoconstriction may result, at least partially, from hypercatecholaminaemia that has been observed during crossclamping of the thoracic aorta.^{24,25} Thus, a moderate increase in PCWP and a decrease in cardiac output in response to aortic crossclamping could result from systemic vasoconstriction or some degree of myocardial compromise or both.

A decrease in blood flow through the lower part of the body during aortic crossclamping is understandable, while an increase in flow through the upper part of the body in the control group of animals (Figure 8) deserves comment. This increase has been demonstrated previously⁵⁻⁷ and probably results from a redistribution of blood volume from the lower part of the body (below the aortic clamp) to the upper part of the body (above the clamp) with a subsequent increase in preload, and possibly the initiation of the Frank-Starling mechanism.⁶ In the D3 group of animals, blood flow through the upper part of the body did not change while it decreased in the D30 group. This dose-related DEX-induced reduction in the increase in blood flow through the upper part of the body is probably due to the reasons responsible for a decrease in cardiac output and an increase in filling pressures, namely, some degree of myocardial compromise or systemic vasoconstriction or both.

It is worth noting that a decrease in cardiac output and an increase in filling pressures were associated with smaller increase in lactate concentrations in the DEX-treated groups than in the control animals. These observations are consistent with the notion that tissue hypoxia was less severe in animals pretreated with DEX suggesting a lesser degree of tissue oxygen deprivation.

Oxygenation

An increase in mixed venous oxygen content and saturation, and a decrease in oxygen consumption in the upper part of the body is an unexpected observation although it has been documented previously.⁷ The reason for this is not clear but might reflect some arteriovenous shunting in the tissues above the aortic clamp. An increase in arteriovenous shunting of microspheres in tissues above the clamp has been demonstrated during infrarenal aortic crossclamping in dogs.²⁶ Crossclamping of the aorta is associated with a substantial increase in sympathoadrenal discharge^{24,25} which may, by itself, constrict nutritive vessels, thereby decreasing oxygen delivery, and subsequently oxygen uptake in the tissues above the aortic clamp. It has been demonstrated that both sympathetic stimulation and norepinephrine infusion decrease capillary density, tissue oxygen extraction, and oxygen uptake in the gut.^{27,28}

Also, an increase in systemic arterial pressure above the aortic occlusion might initiate reflexogenic compensatory mechanisms targeted at decreasing blood pressure. These might cause a rather dramatic dilatation of the vasculature above the aortic occlusion. Such vasodilatation and increase in flow through the microvasculature might reach a degree at which the distance between red cells and the capillary wall is increased to the extent of jeopardizing oxygen exchange. It has been shown that adenosine, which

more than likely accumulates in the ischaemic tissues below aortic occlusion and is washed out into the tissues above the occlusion, increases tissue blood flow but decreases capillary density, oxygen extraction, and oxygen uptake.²⁹ The depressive effect of adenosine on tissue oxygen uptake has been attributed to selective vasodilatation in one region of circulation with flow redistribution resulting in blood flow reduction in other regions.²⁹

Finally, the ischaemic tissues below the aortic occlusion might produce substances that, when reaching tissues above the occlusion, could cause microvascular disturbances, such as an increase in permeability, neutrophil accumulation, or oedema, with subsequent deterioration in normal oxidative processes and decreasing oxygen uptake. Such substances may include xanthine oxidase,³⁰ serotonin, endothelium-derived relaxing factor,³¹ and others. Dexmedetomidine did not affect the decrease in the oxygen uptake in the upper part of the body (Figure 9) and prevented an increase in mixed venous oxygen content and saturation in the D3 group and even decreased mixed venous oxygen content and saturation in the D30 group (Figure 5). The most plausible explanation for these observations is that a decreased flow (cardiac output and flow through the upper part of the body) was associated with an increase in oxygen extraction and subsequent maintenance of oxygen uptake. This effect was dose-related.

In the lower part of the body, below the aortic occlusion, the degree of decrease in blood flow and oxygen uptake in animals pretreated with DEX was the same as in control animals. However, oxygen extraction and lactate concentrations in the inferior vena cava were decreased in a dose-related fashion.

There are several possible explanations for the data. The first is that a decrease in lactate concentrations might result from the interference of the process of pyruvate to lactate conversion, possibly by the inhibition of LDH activity which subsequently might lead to accumulation of pyruvate rather than lactate in response to a similar hypoxic insult. This explanation is not likely because the method of lactate determination used in this study employs addition of excess LDH to the sample. Therefore, if inhibition of LDH occurred, it would not be discovered in this study and would not be reflected in a decrease in lactate concentrations.

The second possibility is that the decrease in lactate concentrations could result from a decrease in glycolysis secondary to an increase in oxygen availability. Total body oxygen delivery was actually decreased by DEX during aortic crossclamping because cardiac output decreased in a dose-related fashion. On the other hand, an improvement in the microcirculation (an increase in perfused capillary

density and nutritive flow) might result in an increase in tissue oxygen availability despite a decrease in total oxygen delivery, calculated as a product of UBF and arterial oxygen content. If this were the case and the decrease in glycolysis were due to an increase in tissue oxygen availability, DEX pretreatment would be associated with an increase in oxygen consumption; however, this did not occur. Therefore, this explanation is unlikely.

The third possibility is that α_2 receptor-mediated vasoconstriction below the aortic clamp could have decreased lactate washout from the lower part of the body. This possibility seems unlikely because the vasculature in the ischaemic tissues below the aortic occlusion is presumably dilated to its maximum due to the metabolic regulation of microcirculation (hypoxia-induced vasodilation).

The fourth possibility is a decrease in tissue metabolism. The decreased oxygen consumption and decreased release of lactate are consistent with this possibility. The mechanism of a DEX-induced reduction in tissue oxygen requirements can be hypothesized as follows: crossclamping of the thoracic aorta is associated with quite dramatic hypercatecholaminaemia.^{24,25} Catecholamines stimulate cellular respiration through activation of adenylate cyclase and formation of adenosine 3',5'-cyclic monophosphate (cAMP) with a resultant activation of a cAMP-dependent protein kinase and triglyceride lipase.^{32,33} The resulting increase in lipolysis leads to an increase in concentrations of free fatty acids, which serves as an oxidizable substrate and also as the intracellular signal for increased mitochondrial respiration.^{32,34} It has been confirmed that epinephrine increases oxygen uptake in different tissues.³⁵⁻⁴⁰ On the other hand, stimulation of α_2 adrenoreceptors inhibits the rate of lipolysis and respiration.^{12,41,42} This inhibition is probably mediated by a decrease in intracellular concentration of cAMP.¹³ It has been confirmed that an α_2 adrenergic agonist, clonidine, inhibited intracellular cAMP accumulation and lipolytic activity; the effect could be antagonized with an α_2 adrenergic antagonist, yohimbine.^{43,44} Clonidine also decreased the accumulation of cAMP induced by isoproterenol or ACTH.⁴⁵

The explanation for a decrease in tissue oxygen demand involving catecholamines is consistent with a decrease in oxygen consumption but may not necessarily explain the decrease in lactate concentration. If oxidative metabolism is stimulated by catecholamines and sufficient NAD^+ is available, the pyruvate should enter the TCA cycle and be converted to lactate. However, it is possible that during ischaemia there is insufficient NAD^+ and that lactate would be formed and in the process regenerate the NAD^+ for oxidative metabolism. Without measuring intermediates of glycolytic metabolism it is impossible to determine whether decreased tissue metabolism and oxygen requirements involve catecholamines or not. Specific studies

devoted to further investigate these possibilities are required. Actually, any option involving a decrease in intracellular cAMP, whether involving catecholamines or not, might play a role in a decrease in tissue metabolism and oxygen requirements after DEX administration.

The differences in response to crossclamping of the thoracic aorta in the majority of the haemodynamic variables were dose-related while the metabolic responses (oxygen uptake, oxygen extraction, and lactate concentrations) differed from control but generally were not different between the two DEX groups. Therefore, one can hypothesize that a dose of DEX which would not be associated with haemodynamic compromise but still would provide a sufficient decrease in tissue oxygen demand could be found. It is important to realize that the haemodynamic response to α_2 adrenergic agonists can vary by species.^{11,19} Therefore, even if a decrease in the myocardium's ability to increase contractility during aortic clamping occurs in dogs, it should not be directly extrapolated to humans. On the other hand, the extrapolation from dogs to humans concerning the metabolic changes observed during administration of an α_2 adrenergic agonist seems to be more reasonable. Thus, the hypothesis, that DEX decreases tissue oxygen demand and possibly increases tolerance to hypoxic insult in tissues, has been supported.

In summary, this study demonstrated that pretreatment with the α_2 adrenergic agonist, DEX, in the doses administered in the study, was associated with an increase in filling pressures and a decrease in cardiac output in response to crossclamping of the thoracic aorta. These observations might be attributed to a decrease in the ability of the myocardium to respond adequately to an increase in preload and/or afterload (associated with crossclamping of the thoracic aorta) or to systemic vasoconstriction which may result from α_2 adrenergic agonist.⁴⁶ The study also demonstrated a decrease in lactate concentrations and oxygen extraction in ischaemic tissues below aortic crossclamping, suggesting that DEX decreases tissue oxygen requirement which might prove particularly useful in clinical situations where tissue hypoxia is expected. Further studies addressing both these issues, namely, haemodynamic compromise and a decrease in tissue oxygen demand, are required.

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