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Effects of Dopexamine in a Rat Model of Supracoeliac Aortic Cross-Clamping and Declamping

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Key Words
Aortic cross-clamping · Dopexamine · Haemodynamics · Intestinal tonometry

Abstract
This experimental study in rats was designed to demonstrate effects of dopexamine (3 μg kg^{-1} min^{-1}, n = 6) or physiologic saline solution (n = 6) on systemic as well as regional perfusion during 30 min of supracoeliac aortic cross-clamping and during 180 min of reperfusion following declamping. Rats were surgically instrumented with arterial, right atrial and portal venous catheters, ultrasonic flow probes around the abdominal aorta, superior mesenteric and carotid artery, and a paediatric tonometer for intestinal mucosal PCO_2 measurement. During 120 min of reperfusion, fluid resuscitation was titrated to keep abdominal aortic blood flow above 80% of baseline values. We found that during cross-clamping, values of arterial lactate (p = 0.002) and intestinal tonometric PCO_2 (p = 0.018) were higher in the dopexamine group than in the control group.

Introduction

Cross-clamping of the abdominal aorta may be applied during aortic reconstructive surgery and during resuscitation of trauma. Acute ischaemia during aortic cross-clamping as well as reperfusion following declamping results in disorders in almost all organ systems both proximal and distal to the aortic clamp [1]. Following abdominal aortic surgery, splanchnic ischaemia was documented histologically in 30% of patients [2], and impaired splanchnic perfusion may contribute to postoperative complications [3]. Recent studies have demonstrated beneficial effects on the splanchnic circulation using dopexamine in animal models of haemorrhagic shock [4], endotoxaemia [5], and during positive pressure ventilation [6]. Accordingly, dopexamine was investigated in patients undergoing abdominal infrarenal aortic surgery [7–9] as a preventive measure to reduce perioperative splanchnic ischaemia.

The rationale to use dopexamine is given by its action on dopaminergic (DA-1) and β_2-adrenoreceptors, resulting in splanchnic vasodilatation [10], and by its indirect action on β_1-adrenoreceptors due to inhibition of norepinephrine reuptake [11], resulting in positive inotropic effects. The combined effects may lead to increased splanchnic as well as systemic blood flows without changing the fractional splanchnic blood flow [12]. Besides haemodynamic effects, adrenergic drugs have metabolic consequences [13, 14], which may limit potentially beneficial haemodynamic effects [15]. Using a rat model of aortic cross-clamping, we recently observed higher blood lactate levels when dopexamine, and lower blood lactate levels when dopamine was continuously infused [16]. The interpretation of these unexpected findings was limited, since the dopexamine dose was higher than in compara-

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ble experimental studies. Furthermore, fluid resuscitation during reperfusion was not adequate to normalize haemodynamic variables following declamping. Therefore, we performed a study using a lower dose of dopexamine and a modified fluid resuscitation protocol, which aimed to keep the aortic blood flow during reperfusion above 80% of respective preclamp baseline values. Based on our previous findings, we hypothesized that continuous infusion of dopexamine might induce higher levels of blood lactate during aortic cross-clamping.

Methods

The studies were approved by the local Animal Care Committee and the procedures fully complied with the Swiss animal protection laws [17].

Animal Preparation

Twelve male Sprague-Dawley rats (Biological Research Laboratories Ltd., Fuellinsdorf, Switzerland), weighing 420 ± 20 g and 3–3.5 months old, were kept in a regulated animal facility, supervised by state veterinarians. Animals were fasted overnight with free access to water before the experiment. Anaesthesia was induced by putting the animals into a chamber which was filled with 3% halothane in 100% oxygen for 5 min, followed by intraperitoneal injection of pentobarbital (45 mg kg^{-1}) and maintained with intravenous pentobarbital (20 mg kg^{-1} h^{-1}) and fentanyl (5 μg kg^{-1} h^{-1}), both diluted in a 5% solution of human albumin (HA) and given as a continuous infusion (8 ml kg^{-1} h^{-1}) throughout the experiment. No neuromuscular blocking drugs were given.

After local anaesthesia with 1% lidocaine hydrochloride, the proximal trachea was surgically exposed and a 14-gauge cannula (Abbocath-T Venosystems, Abbott, Cork, Ireland) was inserted through a tracheotomy. Ventilation was established with tidal volumes of 0.65 ml 100 g^{-1} body weight at a frequency of 80–100 min^{-1} (Model 680, Harvard Biosciences, South Natick, Mass., USA) and an air/oxygen mixture resulting in an FiO_2 of 0.4. End-tidal CO_2 was measured with a side stream infrared CO_2 monitor (CD-102 Normocap, Datex Inc., Helsinki, Finland) at a low flow rate (50 ml min^{-1}) to document adequate ventilatory patterns. The rectal temperature was monitored and kept at 37°C (standard deviation 0.5) using a heating lamp.

Polyethylene cannulas (0.58 mm ID, 0.96 mm OD; Portex, England) were inserted into the left carotid artery for monitoring mean arterial pressure (MAP) and sampling arterial blood, and via the left jugular vein into the right atrium for sampling right atrial venous blood as well as fluid and drug administration. For portal vein blood sampling, an ileocecal vein was isolated under microscope, ligated distally and cannulated with a polyethylene catheter (0.28 mm ID, 0.61 mm OD; Portex). The tip of the catheter was advanced until 1 cm below the liver hilus. Abdominal aortic, superior mesenteric arterial, and right carotid arterial blood flows were measured using a transonic flow meter (T207, Transonic Systems Inc., N.Y., USA). The blood vessels were exposed and separated for a 5- to 8-mm free segment. A 1-mm flow probe (model 1RB1506) was placed around the carotid artery, a 1.5-mm probe (model 1.5RB99) around the superior mesenteric artery close to its origin to the aorta, and a 3-mm probe (model 3SB777) around the abdominal aorta below diaphragm but above branching of the coeliac artery. Surgical dissection of the abdominal aorta was performed such that there was enough space to place the flow probe and a vascular clamp with brackets, covered by rubber tubes to prevent tissue damage, at the supracoeliac level and proximal to the flow probe. A jejunal loop, which is supplied uniquely by the superior mesenteric artery, was identified and a paediatric 5-french nasogastric silicon balloon tonometer (Tonometrics, Charlottenlund, Denmark) was inserted into the intestinal lumen via a small enterotomy. The abdomen was closed with clamps and the animals were allowed to stabilize for 30 min.

Fluid Management

Throughout the experimental procedure, a continuous infusion of HA (8 ml kg^{-1} h^{-1}, see above) together with normal saline 0.9% (4 ml kg^{-1} h^{-1}, for study drug administration) was given. The decision to use a 5% human albumin solution instead of a crystalloid solution was based on a previous experience from pilot studies, where pure crystalloid solution had been associated with difficulties in achieving haemodynamic stability during reperfusion following unclamping. Fluid losses during laparotomy and the surgical preparation were replaced with 24 ml kg^{-1} of HA. Following declamping of the aorta, 10 ml kg^{-1} of HA was infused over 3 min, followed by repeated boluses of 2–4 ml kg^{-1} of HA, and titrated to keep the abdominal aortic blood flow above 80% of the respective baseline values during the first 120 min of reperfusion.

Experimental Protocol

After 30 min recovery from surgery, the animals were randomly allocated to receive normal saline 0.9% (n = 6) or dopexamine (n = 6) at a dose of 3 μg kg^{-1} min^{-1} given at a rate of 4 ml kg^{-1} h^{-1} throughout the experimental procedure until 120 min of reperfusion. After 30 min of infusion, the abdominal aorta above the coeliac artery was clamped for 30 min. Following declamping, the animals were observed for 180 min of reperfusion and then euthanized with intravenous pentobarbital (100 mg). The correct position of catheters and flow probes was confirmed by autopsy.

Measurements

Fifteen minutes after the end of the surgical preparation, the tonometer balloon was filled with 0.6 ml of phosphate-buffered solution (Na_2HPO_4/NaH_2PO_4). Thirty minutes after the end of the surgical preparation, baseline measurements of MAP, heart rate (HR) and blood flows (carotid artery, abdominal aortic, superior mesenteric artery) were recorded. A quantity of 0.3 ml of tonometer balloon fluid was aspirated and discarded as dead space. The remaining 0.3 ml fluid was aspirated using a 1-ml syringe and immediately analyzed for PCO_2 (Model IL 1302, Instrumentation Laboratory Systems Inc., Lexington, Mass., USA). A quantity of 0.3 ml of blood was sampled from the carotid artery, right atrium and the portal vein. Before sampling the blood for analysis, 0.2 ml of dead space of catheters was aspirated and reinjected following aspiration of the blood samples. The sampled blood volume was replaced following each measurement with 1 ml of blood which was harvested the same day from a donor rat. Catheters were then flushed with 0.2 ml of heparinized (2.5 U of bovine heparin per 1 ml) physiologic saline solution. All samples were analyzed for haemoglobin concentration, oxygen saturation (OSM3, Hemoximeter, Radiometer, Copenhagen, Denmark) and lactate concentra-

Table 1. Haemodynamic parameters in the control (CON, n = 6) or dopexamine (DX, n = 6) group

Variable		BL	D30	C30	R15	R30	R60	R120	R180
Mean arterial pressure	CON	123 ± 8	125 ± 15	158 ± 6[a]	95 ± 7[a]	98 ± 13[a]	88 ± 14[a]	77 ± 13[a]	62 ± 12[a]
mm Hg	DX	118 ± 17	127 ± 11	151 ± 10[a]	98 ± 15[a]	96 ± 17[a]	89 ± 20[a]	82 ± 22[a]	67 ± 15[a]
Heart rate	CON	400 ± 41	400 ± 45	350 ± 25[a]	355 ± 23[a]	365 ± 35[a]	378 ± 33	370 ± 25[a]	365 ± 23[a]
beats min^{-1}	DX	410 ± 49	485 ± 30[a, b]	460 ± 25[a, b]	415 ± 35[b]	430 ± 45[b]	430 ± 56	430 ± 68	405 ± 78
Aortic artery blood flow	CON	156 ± 18	153 ± 17		182 ± 32[a]	161 ± 30	137 ± 20	144 ± 21	118 ± 31[a]
ml min^{-1} kg^{-1}	DX	150 ± 13	163 ± 38		164 ± 22	148 ± 19	130 ± 13	141 ± 21	112 ± 27[a]
Mesenteric artery blood flow	CON	37 ± 12	36 ± 11		67 ± 15[a]	52 ± 11[a]	38 ± 7	43 ± 7	33 ± 11
ml min^{-1} kg^{-1}	DX	35 ± 5	37 ± 8		59 ± 9[a]	43 ± 8	39 ± 17	44 ± 19	30 ± 8
Carotid artery blood flow	CON	16 ± 8	16 ± 6	21 ± 5[a]	14 ± 4	11 ± 4[a]	10 ± 4[a]	12 ± 6[a]	10 ± 5[a]
ml min^{-1} kg^{-1}	DX	18 ± 11	14 ± 7	20 ± 9	14 ± 8	11 ± 6[a]	10 ± 5[a]	12 ± 5[a]	10 ± 4[a]

Values are mean ± SD. BL = Baseline; D30 = after 30 min of dopexamine or saline infusion; C30 = after 30 min of aortic cross-clamping; R15 to R180 = after 15–180 min of reperfusion.

[a] $p < 0.05$ versus baseline; [b] $p < 0.05$, CON versus DX.

tion (2300 Stat Plus, Lactate Analyzer, YSI Inc., Ohio, USA). In the arterial sample, a blood gas analysis was performed (Model IL 1302, Instrumentation Laboratory Systems Inc.). Measurements and samplings were performed at baseline, 30 min following the start of the infusion of dopexamine or saline 0.9%, 30 min following aortic cross-clamping, and 15, 30, 60, 120 and 180 min following declamping.

Calculations

Oxygen deliveries and oxygen consumption were calculated using blood flows indexed to body weight. Calculation of oxygen content of arterial (CaO_2) as well as portal venous blood ($CpvO_2$) did not take into account the amount of dissolved oxygen, since a blood gas analysis was not performed in the portal venous sample.

Oxygen content of blood (ml O_2 ml^{-1}) was calculated as:

haemoglobin concentration [g $(100\ ml)^{-1}$] × O_2 saturation $(100)^{-1}$ × (1.34 ml O_2) g^{-1}.

Abdominal aortic oxygen delivery (ml O_2 min^{-1} kg^{-1}) was calculated as: abdominal aortic blood flow (ml min^{-1} kg^{-1}) × CaO_2 (ml O_2 ml^{-1}).

Mesenteric oxygen delivery (ml O_2 min^{-1} kg^{-1}) was calculated as: mesenteric blood flow (ml min^{-1} kg^{-1}) × CaO_2 (ml O_2 ml^{-1}).

Mesenteric oxygen consumption (ml O_2 min^{-1} kg^{-1}) was calculated as: mesenteric blood flow (ml min^{-1} kg^{-1}) × [CaO_2 – $CpvO_2$ (ml O_2 ml^{-1})].

Mesenteric oxygen extraction ratio (%) was calculated as: mesenteric oxygen consumption/mesenteric oxygen delivery × 100.

Regarding tonometric measurements and calculations, the measurements of PCO_2 in the phosphate buffer solution from the tonometric balloon were corrected with the factor 1.17 and named $PtCO_2$. This correction factor, which is different from the correction factors provided by the manufacturer, was determined from our own in vitro study [18], as the equilibration of PCO_2 over the silicon balloon membrane is incomplete after 15 min. The PCO_2 gap was calculated as the difference of tonometric minus arterial PCO_2 ($PtCO_2$ – $PaCO_2$).

Statistical Analysis

All data presented in tables and figures represent mean ± standard deviation (SD). Comparisons of different time points versus baseline within one group were performed using ANOVA for repeated measurements, followed by Dunnett's post test. Differences between two groups at the same time points were analyzed using Student's t test. (GraphPad InStat, version 2.02, San Diego, Calif., USA).

Results

Effects prior to Aortic Cross-Clamping

Thirty minutes infusion of dopexamine induced a significant increase in heart rate in the dopexamine group, different from the control group (table 1).

Effects during Aortic Cross-Clamping

Thirty minutes of aortic cross-clamping increased MAP in both groups and decreased HR in the control group, whereas it remained elevated in the dopexamine group. Carotid blood flow increased in the control group (table 1). Increases in right atrial haemoglobin oxygen saturation were comparable between the two groups (table 2). Arterial lactate concentration (fig. 1) and $PtCO_2$ (table 3) increased in both groups, but to higher levels in the dopexamine group. The PCO_2 gap tended to be higher in the dopexamine group ($p = 0.12$). Arterial pH decreased to a lower level in the dopexamine group (table 3).

Table 2. Oxygen transport parameters in the control (CON, n = 6) or dopexamine (DX, n = 6) group

Variable		BL	D30	C30	R15	R30	R60	R120	R180
Aortic O_2 delivery	CON	28.3 ± 4.2	26.8 ± 2.7		26.3 ± 4.4	25.3 ± 4.1	22.0 ± 2.8*	21.1 ± 2.8*	17.7 ± 4.6*
ml O_2 min^{-1} kg^{-1}	DX	27.5 ± 3.4	29.9 ± 6.6		24.9 ± 4.6	23.5 ± 3.8	20.7 ± 2.8*	21.0 ± 3.9*	17.1 ± 4.6*
Mesenteric O_2 delivery	CON	6.7 ± 2.2	6.3 ± 1.9		9.8 ± 2.8*	8.2 ± 1.7	6.1 ± 1.2	6.3 ± 0.8	5.0 ± 1.6
ml O_2 min^{-1} kg^{-1}	DX	6.4 ± 1.2	6.8 ± 1.6		8.5 ± 1.9*	7.0 ± 1.9	6.1 ± 2.4	6.5 ± 2.9	4.6 ± 1.4
Mesenteric O_2 uptake	CON	0.9 ± 0.3	0.9 ± 0.4		0.6 ± 0.2	0.6 ± 0.3	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.3
ml O_2 min^{-1} kg^{-1}	DX	0.8 ± 0.1	0.8 ± 0.3		0.8 ± 0.3	0.8 ± 0.3	0.9 ± 0.4	0.7 ± 0.3	0.7 ± 0.3
Mesenteric oxygen	CON	14 ± 6	15 ± 7		6 ± 3*	9 ± 5	10 ± 4	10 ± 4	14 ± 8
extraction rate, %	DX	13 ± 3	12 ± 2		9 ± 5	11 ± 2	15 ± 6	12 ± 6	16 ± 5
Haemoglobin	CON	13.6 ± 1.2	13.2 ± 10	12.5 ± 11	11.3 ± 0.6*	12.0 ± 5*	12.3 ± 0.7*	11.6 ± 9*	11.7 ± 0.9*
g 100 ml^{-1}	DX	13.8 ± 1.0	13.9 ± 0.6	12.9 ± 0.5	11.8 ± 0.9*	12.1 ± 1.3*	12.1 ± 0.8*	11.5 ± 1.0*	11.8 ± 1.0*
Right atrial O_2	CON	72 ± 4	69 ± 5	90 ± 7*	65 ± 10	61 ± 10*	58 ± 6*	57 ± 5*	56 ± 10*
saturation, %	DX	70 ± 4	64 ± 9	87 ± 7*	60 ± 14	57 ± 12*	53 ± 8*	55 ± 9*	54 ± 5*

Values are mean ± SD. BL = Baseline; D30 = after 30 min of dopexamine or saline infusion; C30 = after 30 min of aortic cross-clamping; R15 to R180 = after 15–180 min of reperfusion.* $p < 0.05$ versus baseline.

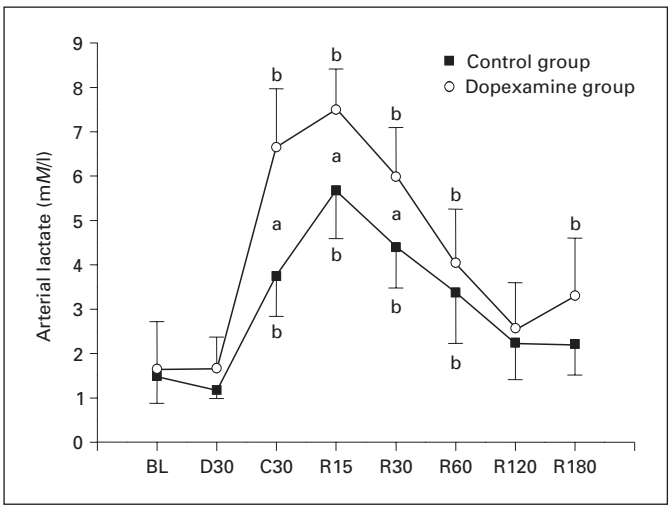

Fig. 1. Arterial lactate concentration in the control (mean – SD, n = 6) or dopexamine group (mean + SD, n = 6) at baseline (BL), after 30 min of dopexamine or saline infusion (D30), after 30 min of supracoeliac aortic cross-clamping (C30), and after 15–180 min of reperfusion (R15–R180) following declamping. [a] $p < 0.05$, control versus dopexamine group; [b] $p < 0.05$ versus baseline.

Effects during Reperfusion following Declamping

MAP decreased in both groups and remained lowered during the reperfusion period. HR remained lowered in the control group and returned to baseline levels in the dopexamine group. Aortic blood flow was kept above 80% of baseline values during 120 min of reperfusion, driven by the fluid resuscitation protocol, and required identical amounts of fluid to reach target values (30 ± 11 ml kg^{-1} in the control group and 36 ± 16 ml kg^{-1} in the dopexamine group; $p = 0.46$). During further reperfusion, aortic blood flow decreased in both groups below baseline values when the infusion of fluid was reduced to 12 ml kg^{-1} h^{-1}. Aortic oxygen delivery steadily decreased in both groups to 75% of baseline values mainly due to haemodilution effects (accounting for approximately 60% of the decrease in aortic oxygen delivery) and further dropped to 62% of baseline when fluid resuscitation was reduced (table 2). Right atrial oxygen saturation decreased comparably in both groups, indicating increased oxygen extraction (table 2). Mesenteric blood flow was higher than at baseline early following declamping and decreased steadily towards baseline values during further reperfusion in both groups. The resulting mesenteric oxygen delivery remained preserved around baseline levels, with the exception of the increase immediately following declamping (table 2). Mesenteric oxygen uptake remained preserved throughout the reperfusion period. The resulting mesenteric oxygen extraction ratio dropped significantly in the control group immediately following declamping and recovered to baseline levels during further reperfusion. Carotid blood flow was decreased below baseline values during the entire reperfusion period in

Table 3. Tonometer and blood gas parameters in the control (CON, n = 6) or dopexamine (DX, n = 6) group

Variable		BL	D30	C30	R15	R30	R60	R120	R180
$PtCO_2$ kPa	CON	6.0 ± 0.7	6.5 ± 0.2	10.5 ± 0.7[a]	8.1 ± 0.4[a]	6.9 ± 0.4[a]	6.4 ± 0.7	7.1 ± 0.5[a]	7.5 ± 0.7[a]
	DX	6.1 ± 0.5	6.7 ± 0.3	11.6 ± 0.6[a, b]	8.9 ± 0.6[a, b]	7.8 ± 1.4[a]	7.0 ± 0.4	7.5 ± 0.5[a]	7.5 ± 0.6[a]
PCO_2 gap kPa	CON	1.4 ± 0.5	1.3 ± 0.5	6.7 ± 1.0[a]	2.7 ± 0.5[a]	2.0 ± 0.4	1.5 ± 0.7	1.8 ± 0.2	2.1 ± 0.8
	DX	1.5 ± 0.8	1.5 ± 0.6	7.5 ± 0.5[a]	3.4 ± 0.3[a, b]	3.1 ± 1.4[a]	2.0 ± 0.4	2.3 ± 0.7	2.1 ± 0.8
PCO_2 arterial kPa	CON	4.7 ± 0.4	5.1 ± 0.5	3.8 ± 0.4[a]	5.4 ± 0.4	5.0 ± 0.5	5.0 ± 0.3	5.3 ± 0.5	5.4 ± 0.6
	DX	4.6 ± 0.4	5.1 ± 0.4	4.1 ± 0.3[a]	5.5 ± 0.5	4.8 ± 0.3	5.0 ± 0.4	5.2 ± 0.5	5.4 ± 0.3
pH art units	CON	7.40 ± 0.03	7.37 ± 0.04	7.41 ± 0.05	7.19 ± 0.03[a]	7.23 ± 0.02[a]	7.25 ± 0.03[a]	7.25 ± 0.02[a]	7.23 ± 0.02[a]
	DX	7.39 ± 0.04	7.34 ± 0.05[a]	7.27 ± 0.06[a, b]	7.12 ± 0.06[a, b]	7.18 ± 0.05[a]	7.22 ± 0.07[a]	7.24 ± 0.05[a]	7.21 ± 0.04[a]

Values are mean ± SD. BL = Baseline; D30 = after 30 min of dopexamine or saline infusion; C30 = after 30 min of aortic cross-clamping; R15 to R180 = after 15–180 min of reperfusion.

[a] $p < 0.05$ versus baseline; [b] $p < 0.05$, CON versus DX.

both groups. The dopexamine group differed from the control group by the transiently higher values of arterial lactate concentration, $PtCO_2$ and PCO_2 gap early following declamping (table 3; fig. 1).

Discussion

The main finding of this experimental study is that dopexamine, infused during aortic cross-clamping, is associated with higher blood lactate levels and higher tonometer PCO_2 during induced ischaemia by aortic cross-clamping and during the first 15 min of reperfusion following declamping. We confirmed the finding of higher lactate levels from our previous study [16], where we had given a higher dose of dopexamine (10 vs. 3 μg kg^{-1} min^{-1} in the present study) and lesser fluid during reperfusion. Since increased plasma levels of lactate may principally depend on increased production or decreased metabolism and clearance, primarily by the liver, several potential mechanisms may account for the observed differences in the dopexamine group.

First, there is a systemic, metabolic effect, mediated by adrenergic receptors, and acting on all tissues, which are susceptible to adrenergic stimulation. Systemic metabolic effects have been demonstrated for dopexamine [14], noradrenaline, adrenaline and dopamine [13] in awake, healthy volunteers. These metabolic effects resulted in an increased systemic oxygen uptake without an increase in lactate. In contrast to these data from healthy, unstressed subjects, dopexamine at moderate doses induced a reversible increase in systemic oxygen uptake together with an increase in lactate levels [19] in patients immediately following cardiopulmonary bypass. Most of the recent data regarding metabolic effects of adrenergic drugs come from experimental and clinical studies in sepsis, where the effects of adrenergic drugs on metabolism, perfusion and lactate generation are complex [15] and may not apply to our model. We did not measure systemic oxygen uptake in our model, but we may assume that right atrial oxygen saturation reflects changes in systemic oxygen uptake, if aortic blood flow and haemoglobin do not change. In fact, our results do not show significant differences in right atrial haemoglobin oxygen saturation between the two groups at identical values for aortic blood flow and haemoglobin, which suggests that dopexamine has no major effects on systemic oxygen uptake.

Second, there is a regional, metabolic effect due to dopexamine treatment in tissues distal to the aortic cross-clamp, enhancing ischaemia during the period of induced ischaemia by aortic cross-clamping. This effect would affect not only the visceral organs, but also tissues of the lower body, which are not supplied by collateral blood flow. In contrast to our previous study, we demonstrated significantly higher intestinal tonometer PCO_2 values during ischaemia, induced by aortic cross-clamping, as well as during early reperfusion following declamping in the dopexamine group. Higher intestinal tonometer PCO_2 values in the dopexamine group suggest that more anaerobic metabolism occurs within the intestinal mucosa and that part of the increased lactate might be generated

within the splanchnic region. There is supporting evidence from an experimental model in pigs [20], in which a combination of measurements including jejunal laser Doppler flowmetry, microoxymetry, mucosal PCO_2 tonometry and luminal microdialysis for lactate, pyruvate and glucose was applied. By inducing graded mesenteric hypoperfusion, it could be demonstrated that dopexamine induced increased mesenteric lactate production below a perfusion pressure of 30 mm Hg despite having favourable effects on mesenteric blood flow. Combining flow measurements with metabolic measurements at the regional level added information to this study, which would have been missed. Whether intestinal CO_2 tonometry represents a precise tool to evaluate regional splanchnic ischaemia is widely debated [21], but nevertheless, it is applied in numerous clinical and experimental studies. Increased accuracy of measurements may be achieved using a phosphate-buffered solution [22] as well as calculating the PCO_2 gap which better reflects splanchnic ischaemia [23–25], instead of intramural pH which may vary, depending on systemic arterial PCO_2. Alternatively, mesenteric ischaemia can be estimated using polarographic electrodes to measure surface oxygen tension. Using both polarographic and tonometric methods, we previously demonstrated in pigs a linear relationship between changes in intramural pH and changes in jejunal serosal and mucosal surface oxygen tensions, when mesenteric flow was gradually reduced [26]. Similar findings are reported from a study in dogs, using hypocapnia as a vasoconstricting stimulus [27].

Third, collateral blood flow to the ischaemic tissues distal to the aortic cross-clamp might have been decreased by dopexamine, either by systemic vasodilatation, as demonstrated in earlier studies using nitroprussid [28], or by effects on microvascular blood flow distribution, as demonstrated using prostaglandin during aortic cross-clamping [29]. Since we found identical values for MAP in both groups, we have no evidence that vasodilating effects of dopexamine proximal to the clamp might have decreased collateral blood flow by decreasing perfusion pressure. Distal to the clamp, microvascular effects may well have occurred within the splanchnic area, as described above, and may not be excluded in other tissues.

Finally, metabolism of dopexamine might be severely disturbed during supracoeliac cross-clamping, since the liver plays a significant role in the clearance of dopexamine. Up to a fourfold increase in plasma concentrations has been measured in patients undergoing orthoptic liver transplantation during the anhepatic phase [30]. Accordingly, liver ischaemia during the period of supracoeliac aortic cross-clamping might therefore result in higher plasma levels of dopexamine, which may have effects on tissues proximal to the clamp. These effects may differ from those observed during the preclamp period and may probably affect cardiac metabolism. In our model, dopexamine induces an increase in heart rate without a concomitant increase in aortic and carotid blood flow; further chronotropic stimulation may therefore not be tolerated adequately. We do not know whether myocardial blood flow was enhanced and whether myocardial oxygen consumption was increased. However, the experimental design of our study does not allow drawing conclusions on cardiac function in the absence of differences in measured variables except heart rate.

Further reperfusion following the early period of 30 min after declamping demonstrated no differences between the dopexamine and the control group. In contrast with our previous study [16], lactate levels recovered to baseline levels within 2 h of reperfusion in both groups, most probably due to higher amounts of intravenous fluid.

Favourable effects of dopexamine on organ damage are reported from experimental studies, probably due to dopexamine-associated anti-inflammatory properties [31], or by prevention of free radical formation [32]. These effects would not have been evident in our model, since the observation period was too short. However, these mechanisms may well be involved to explain the protective effect on colonic mucosa, which are described in patients undergoing aortic surgery [9].

This study is limited by several factors. First, using a rodent model, which is economically attractive, may limit the number of monitoring devices being applied simultaneously and the amount of blood sampling due to the size of the animals. Furthermore, complex surgical preparations and protocols induce haemodynamic changes, which are easier to control in larger animals. Variability of results may therefore be greater than expected and requires larger series. Second, our data and similar findings during graded mesenteric hypoperfusion [20] result from experimental studies in animals, and conclusions for the clinical setting may not be drawn. Moreover, the observed effects associated with dopexamine treatment are limited to the induced ischaemic and the immediate reperfusion period and may therefore not be of clinical importance.

In conclusion, during supracoeliac aortic cross-clamping, we demonstrated that dopexamine was associated with higher values of arterial lactate and intestinal tonometric PCO_2. This finding may be explained by complex

interactions of dopexamine effects and the effects of aortic cross-clamping, occurring systemically, as well as regionally. The significance of this finding remains unclear.

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