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Inotropic treatment and intestinal mucosal tissue oxygenation in a model of porcine endotoxemia

Reinhard Germann, MD; Markus Haisjackl, MD; Birgit Schwarz, MD; Engelbert Deusch, MD; Stefan Meusburger, MD; Eva Gruber, MD; Werner Pajk; Hans Hausdorfer, MD; Johannes Bonatti, MD; Bernhard Furtner, MD; Hanno Ulmer, MD; Walter Hasibeder, MD, PhD

From the Department of Anesthesia and General Intensive Care Medicine (Drs. Germann, Haisjackl, Schwarz, Deusch, Meusburger, Gruber, Furtner, and Hasibeder), the Department of Histology (Dr. Hausdorfer), First Department of Surgery (Dr. Bonatti), and the Department of Biostatistics and Documentation (Dr. Ulmer), University of Innsbruck, Innsbruck, Austria. Supported, in part, by Leopold Inc. (Graz, Austria), Ely Lilly (Vienna, Austria), and Speywood Pharmaceuticals Ltd (Berkshire, UK).

Address requests for reprints to: Reinhard Germann, MD, Department of Anesthesia and General Intensive Care Medicine, University of Innsbruck, Anichstra beta e 35, A-6020 Innsbruck, Austria.

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Objective: To evaluate the dose-related effects of dopamine, dopexamine, and dobutamine on intestinal mucosal tissue oxygenation following short-time Infusion of Escherichia coli lipopolysaccharide, which has previously been shown to decrease mucosal tissue oxygenation by 60% of control values.

Design: Prospective, randomized, unblinded study.

Setting: Animal research laboratory.

Subjects: Anesthetized, mechanically ventilated domestic pigs.

Interventions: Pigs were infused with 2 micro g/kg of E. coli lipopolysaccharide over 20 mins via the superior mesenteric artery. Pulmonary artery occlusion pressure was maintained near 15 mm Hg, using a mixed infusion regimen of Ringer's lactate solution and hydroxyethyl starch. Following endotoxemia, a small segment of the jejunal mucosa was exposed by midline laparotomy and antimesenteric incision. The control group (n = 7) received no further interventions. Pigs in the dopamine (n = 7), dopexamine (n = 7), and dobutamine (n = 7) groups were infused with 2.5, 5, 10, and 20 micro g/kg/min of the respective drug via a central venous catheter.

Measurements and Main Results: Systemic hemodynamics as well as systemic, mesenteric, and femoral blood gas variables were measured using an arterial, a thermodilution pulmonary artery, a superior mesenteric venous, and a femoral venous catheter. Jejunal mucosal tissue PO_2 was measured by means of two Clark-type surface oxygen electrodes. Oxygen saturation of jejunal mucosal microvascular hemoglobin was determined by tissue reflectance spectrophotometry.

Infusion of endotoxin resulted in pulmonary hypertension. Systemic hemodynamics remained unchanged except for brief decreases in cardiac output and arterial blood pressure. Dopamine, dopexamine, and dobutamine increased systemic oxygen delivery in a dose-related manner by 80% ($p < .01$), 96% ($p = .00$), and 129% ($p = .00$) of values before inotropic treatment. Dopamine increased mucosal tissue PO_2 by 109% (10-micro g dose, $p < .01$) and 164% (20-micro g dose, p

= .00), and mucosal hemoglobin oxygen saturation by 61% (5-micro g dose, p < .05), 102% (10-micro g dose, p < 01) and 121% (20-micro g dose, p = .00). Dopexamine increased mucosal tissue PO_2 by 89% (20-micro g dose, p < .01) and mucosal hemoglobin oxygen saturation by 26% (2.5-micro g dose, p < .05) and 35% (5-, 10-, and 20-micro g dose, p < .05). In the dobutamine and control groups, no significant effect on either mucosal tissue PO_2 or hemoglobin oxygen saturation was observed.

Conclusions: In this model of porcine endotoxemia, dopamine and, to a lesser extent, dopexamine increase intestinal mucosal tissue oxygenation. Of all three inotropes used, dobutamine has the most pronounced effect on systemic oxygen delivery, but it does not improve mucosal tissue oxygenation. Selective vasodilation within the intestinal mucosa, mediated mainly by dopamine-1 receptors, seems to explain the observed intestinal mucosal effect of dopamine and dopexamine. (Crit Care Med 1997; 25:1191-1197)

Key Words: endotoxin; dopamine; dobutamine; dopexamine; intestinal mucosa; tissue PO_2; spectrophotometry; tissue oxygenation; oxygen delivery

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Tissue oxygen debt has been identified as a major determinant of organ failure and mortality in critical illness [1]. Based on observations that oxygen delivery (DO_2) values in patients who survived critical illness were higher than in those who died, and higher than standard physiologic values, treatment strategies evolved that intended to achieve supranormal values for systemic DO_2 in order to prevent or reverse tissue oxygen debt [2]. However, large randomized trials in mixed populations of critically ill patients have recently questioned the benefit of such treatment, as mortality was either unchanged [3] or increased [4].

Apart from adequate fluid and blood replacement, inotropic support is the main therapeutic maneuver in increasing DO_2. If it is assumed that tissue oxygen debt can be reversed by inotropic support, blood flow and oxygen must be distributed to tissues where hypoxia is present. The gut, and specifically the gut mucosal layer, have been reported to be a microcirculatory region which is centrally involved in the cascade of hypoperfusion and organ failure [5,6]. However, no or confounding experimental information is available on vasoactive properties of currently used inotropes within the gut mucosal microcirculation.

Dopamine, for example, has been reported to either produce intestinal mucosal vasodilation and increased mucosal tissue PO_2 due to the stimulation of dopaminergic receptors [7,8] or to cause mucosal vasoconstriction attributed to the stimulation of alpha-adrenergic receptors meant [9]. Dobutamine, the predominant inotrope both in clinical practice and in the above cited outcome trials [3,4], has never been investigated in terms of oxygen supply to the gastrointestinal mucosa. A single study addressed mucosal vasoactive properties of dopexamine, a $beta_2$- and DA_1-receptor agonist [10], which combines known mucosal vasodilating properties of other $beta_2$- and DA_1-agonistic drugs [11,12]. In this study, prevention of vasoconstriction in mucosal villus arterioles during normotensive endotoxemia is reported [13].

The present animal experiments therefore addressed the question whether increasing DO_2 with either dopamine, dobutamine, or dopexamine may improve intestinal mucosal tissue oxygenation in a model of short-time infusion of endotoxin via the mesenteric artery, a procedure that has previously been shown to decrease mucosal tissue PO_2 to 40% of control values [14].

MATERIALS AND METHODS

The experiments were approved by the Federal Ministry of Science and Research. The study included 36 domestic pigs weighing 35 to 42 kg of either gender, which were anesthetized with ketamine hydrochloride (20 mg/kg im), orally intubated, and mechanically ventilated with a positive end-expiratory pressure of 5 cm H_2 O. Tidal volume and ventilatory frequency were adjusted to keep $PaCO_2$ constant between 35 and 43 torr (4.7 and 5.7 kPa). FIO_2 was adjusted to maintain PaO sub 2 values between 100 and 120 torr (13.3 and 16.0 kPa). Anesthesia was maintained with a continuous infusion of fentanyl (20 micro g/kg/hr) and midazolam (0.8 mg/kg/hr). Adequate muscle relaxation was achieved by bolus injections of vecuronium (0.15 mg/kg).

Surgical Preparation (Two-Step System).

Following the induction of anesthesia, the right carotid artery was cannulated for systemic mean arterial pressure measurements and for blood sampling. A balloon-tip thermodilution catheter (Baxter Edwards Critical-Care, Irvine, CA) was inserted into the pulmonary artery via the right internal jugular vein for measurement of cardiac output, pulmonary arterial pressure, and pulmonary artery occlusion pressure (PAOP), as well as for obtaining mixed venous blood samples. A separate 14-gauge catheter was inserted into the right internal jugular vein for infusion of inotropes. A 4-Fr radiographical catheter (Cordis Medical, Miami, FL) was fluoroscopically guided into the root of the superior mesenteric artery via the right femoral artery for infusion of Escherichia coli lipopolysaccharide (serotype O111:B4, Difco Laboratories, Detroit, MI). A 16-gauge catheter was inserted into the left femoral vein for blood sampling. Seventy minutes after starting the experimental protocol, a midline laparotomy was performed (Figure 1), and a 16-gauge catheter was placed in a branch of the superior mesenteric vein. A small part of jejunal mucosa was exposed by antimesenteric enterotomy. The boundary of the mucosa was sutured to the oval opening of a cork plate. The intestine was reintroduced into the abdominal cavity with the exception of the exposed mucosa. Jejunal mucosal temperature was maintained at 36 +/- 1 [degree sign]C by means of an infrared heating lamp and by covering the surface of the jejunum with sponges moistened with warm physiologic saline.

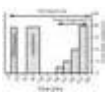

Figure 1. Experimental protocol. All animals were infused with 2 micro g/kg of Escherichia coli lipopolysaccharide (LPS) via the mesenteric artery. Following laparotomy and positioning of the Erlangen microlightguide spectrophotometer and two Clark-type surface oxygen electrodes on top of the jejunal mucosa, animals in groups 2 to 4 were infused with either dopamine, dopexamine, or dobutamine in exponential steps, whereas group 1 animals served as controls and received no inotropic treatment.

Determination of Systemic Hemodynamics and Blood Gases.

Arterial, pulmonary artery, and central venous pressures were measured using Statham P10EZ pressure tranducers (Spectramed-Statham, Bilthoven, The Netherlands). Cardiac output was determined by the thermodilution method, using triplicate measurements with 10-mL injections of ice-cooled saline. Arterial, mixed venous, femoral venous, and mesenteric venous blood gases were measured by means of an automatic blood gas analyzer (AVL Biomedical Instruments, Graz, Austria) and a hemoximeter (OSM2, Radiometer, Copenhagen, Denmark).

Determination of Intestinal Mucosal Tissue Oxygenation.

The methodology applied has already been described in detail in previous reports [8,15]. Two Clark-type multiwire surface electrodes (Eschweiler, Kiel, Germany) were positioned on the exposed mucosa, recording mucosal tissue oxygen tension (mucosal PO_2). A single electrode consists of eight platinum wires, each 15 micro m in diameter representing eight individual measuring points, and a silver/silver chloride reference electrode. The electrodes were kept in place by small polyvinyl chloride caps surrounded by a transparent thin rubber patch with a diameter of 2 cm each. At each time point of the experimental protocol, mucosal PO_2 was continuously recorded for a period of 150 secs with a frequency of 1 Hz.

An Erlangen microlightguide spectrophotometer (EMPHO II, BGT, Uberlingen, Germany) was used to measure oxygen saturation of mucosal microvascular hemoglobin (mucosal HbO_2). The spectrophotometer includes one illuminating microlightguide and six circumferentially arranged detecting microlightguides with a diameter of 250 micro m each and a rapidly rotating bandpass interference filter disk for the generation of monochromated light within the spectral range of 502 to 628 nm. The microlightguide array was fixed to the mucosal surface in a manner identical to that used for the PO_2 electrode. At each time point, mucosal HbO_2 was recorded for 150 secs with a frequency of 7 Hz. The algorithm used to calculate oxygen saturation of microvascular hemoglobin was validated for intestinal mucosal tissue [15].

Experimental Protocol.

(Figure 1) A total of 36 animals were randomly assigned to four treatment groups. Following the initial part of surgery, a 30-min resting period, and baseline measurements of hemodynamics and blood gases (at 0 min), all four groups were infused with 2 micro g/kg of E. coli lipopolysaccharide for a period of 20 mins, followed by a second and third set of measurements at 30 and 60 mins. Animals were then laparotomized and allowed to stabilize until a second baseline (at 180 mins), which included parameters of jejunal mucosal tissue oxygenation and jejunal venous blood gases. Group 1 animals served as controls and received no further treatment, whereas the remaining animals were infused with 2.5, 5, 10, and 20 micro g/kg/min of dopamine (Leopold, Graz, Austria) (group 2), dopexamine (Speywood Pharmaceutical, Berkshire, England) (group 3) or dobutamine (Ely Lilly, Vienna, Austria) (group 4). Single doses were infused for a period of 30 mins. All measurements were obtained within the last 10 mins of each dosing interval (at 210, 240, 270, and 300 mins). The short plasma half-lives of the three inotropes used ensure that, first, after changing the infusion rate, plasma steady-state concentrations are reached before the next measurement period and, secondly, plasma concentrations remain proportional to the dosing rate.

All four groups of animals were infused throughout the experiment to an equal extent with Ringer's lactate solution and a 6% solution of hydroxyethyl starch (molecular weight 200,000) aimed at keeping PAOP near 15 mm Hg.

Fifty milligrams of methylene blue (Neopharma, Aschau, Germany) was injected into the mesenteric artery catheter to confirm correct catheter position by blue colorization of the enterotomized jejunal segment before killing the animals by a central venous injection of 40 mmol of potassium chloride in deep anesthesia.

Calculations and Statistical Analysis.

Systemic DO_2 was calculated as the product of cardiac index (mL/kg body weight) times arterial oxygen content, and regional oxygen extraction ratios as the ratio of arteriovenous to arterial oxygen content. Results are expressed as mean +/- SEM. Overall effects within and between

groups were evaluated by analysis of variance for repeated measurements. In case of significant time within group differences, comparisons within group to baseline were made by paired t-test. Linear regression was used to delineate the relationship between systemic DO_2 and jejunal mucosal tissue oxygen tension. A $p < .05$ was considered statistically significant. For correction of multiple comparisons, the Bonferroni-Holm procedure was used.

RESULTS

A total of 28 pigs evenly distributed to the four treatment groups were used for statistical analysis. Five animals died of right heart failure within 10 mins after terminating the endotoxin infusion. Three animals had to be excluded from further analysis because of either hemorrhage during surgery (one pig) or dislocation of the mesenteric artery catheter as indicated by missing colorization of the enterotomized jejunal segment (two pigs).

Prelaparotomy Period-Hemodynamic Effect of Endotoxin (from 0 to 60 mins).

(Figure 2) The initial systemic hemodynamic response to infusion of E. coli lipopolysaccharide via the mesenteric artery was characterized by a brief decrease in cardiac output, pulmonary hypertension, and a delayed decrease in mean arterial blood pressure, as compared with baseline values (time 0 min).

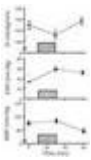

Figure 2. Initial systemic hemodynamic effect of endotoxin infusion via the mesenteric artery. The shaded bar marks the endotoxin infusion period. Cardiac index (CI) showed a reversible and slight decrease as a result of right heart insufficiency due to pulmonary hypertension (pulmonary artery pressure [PAP]). Mean arterial blood pressure (MAP) decreased slightly. *$p < .05$ vs. time 0 min by paired t-test ($n = 28$).

Postlaparotomy Period-Inotropic Treatment (from 180 to 300 mins): Hemodynamics.

(Table 1) No statistically significant differences in hemodynamic variables occurred between groups before starting inotropic treatment (time 180 mins). Control animals subjected to endotoxemia, but no further drug therapy, maintained mean arterial blood pressure, PAOP, systemic DO_2, and heart rate compared with baseline (time 0 min) and time 180 mins. Pulmonary hypertension persisted throughout the observation period. All three groups treated with inotropes showed significant increases in systemic DO_2 compared with pretreatment (time 180 mins), reaching peak values at doses of 20 micro g. Only dopexamine produced a decrease in mean arterial blood pressure (all doses) and in pulmonary arterial pressure (2.5-, 10-, and 20-micro g doses). All drugs increased heart rate in a dose-related manner. The volume of fluid required to keep PAOP at 15 mm Hg did not differ between groups and ranged between 5.2 +/- 0.7 L (dopamine group) and 6.5 +/- 0.5 L (dopexamine group).

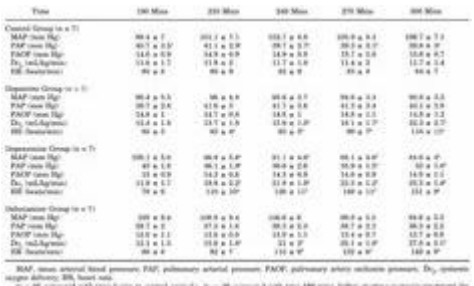

Table 1. Hemodynamic parameters following laparotomy (mean +/- SEM)

Intestinal Mucosal Tissue Oxygenation.

(Figure 3, Figure 4) Mucosal tissue oxygen tension at 180 mins ranged between 12.4 +/- 3.5 torr (1.7 +/- 0.5 kPa; control group) and 14.7 +/- 3.2 torr (2.0 +/- 0.4 kPa; dopexamine group) and did not differ between groups. Both dopamine (10- and 20-micro g doses) and dopexamine (20-micro g dose) increased mucosal PO sub 2, as compared with pretreatment. However, no change in mucosal PO_2 was observed in dobutamine-treated animals and controls (Figure 3, top). Oxygen saturation of mucosal microvascular hemoglobin at time 180 mins ranged between 30.7 +/- 2.3% (dopamine group) and 38.7 +/- 5.5% (dobutamine group) and did not differ between groups. Similar to mucosal PO_2, mucosal HbO_2 increased during infusion of dopamine (5-, 10-, and 20-micro g doses) and dopexamine (all doses). No changes in mucosal HbO_2 were observed in dobutamine-treated animals and controls (Figure 3, bottom).

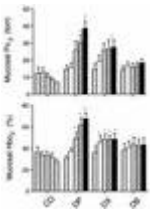

Figure 3. Effects of inotropes on jejunal mucosal tissue oxygenation significantly differed between groups (group by dose interaction, p = .00 by analysis of variance). Mucosal tissue PO_2 increased with dopamine (DP) at doses of 10 and 20 micro g/kg/min and with dopexamine (DX) at 20 micro g/kg/min, whereas it remained unchanged in control animals (CO) and dobutamine (DB)-treated animals. Oxygen saturation of mucosal microvascular hemoglobin (Mucosal HbO_2) increased at 5, 10, and 20 micro g/kg/min of dopamine and all doses of dopexamine, whereas it remained unchanged in control animals and dobutamine-treated animals. *p <.05 vs. pretreatment (time of 180 mins) by paired t-test (n = 7 for all groups). Spotted bars, 0; open bars, 2.5 micro g; hatched bars, 5 micro g; cross-hatched bars, 10 micro g; solid bars, 20 micro g.

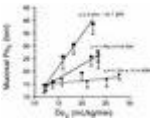

Figure 4. Multiple linear regressions for systemic oxygen delivery (DO_2) vs. mucosal tissue PO_2 in groups treated with inotropes. Dopamine (DP) had the smallest effect on DO_2, but the largest effect on mucosal PO_2 (p = .002) and thus, the most selectively distributed blood flow and oxygen to the small intestinal mucosa. In contrast, despite a prominent increase in DO_2, dobutamine (DB) did not change mucosal PO_2 (p = .1), suggesting that blood flow was distributed to tissues other than the intestinal mucosa. Dopexamine (DX) ranged between dopamine and dobutamine (p = .02) (n = 7 for all groups).

Multiple linear regressions were performed, comparing systemic DO_2 with mucosal PO_2 in the groups treated with inotropes. Dopamine had the smallest effect on systemic DO_2, but the most pronounced effect on jejunal mucosal tissue PO_2, suggesting selective mucosal vasodilation (Figure 4). In contrast, dobutamine had the most pronounced effect on systemic DO_2, but no effect on mucosal tissue PO_2.

Regional Oxygen Extraction Ratios.

(Figure 5) Mesenteric oxygen extraction ratio at time 180 mins ranged between 0.30 +/- 0.03

(dopamine group) and 0.38 +/- 0.06 (control group) and did not differ between groups. While the mesenteric oxygen extraction ratio decreased in animals treated with dopamine (10- and 20-micro g doses) and dopexamine (2.5- and 5-micro g doses), it remained unchanged in animals given dobutamine and in controls (Figure 5, top). Skeletal muscle oxygen extraction ratio at time 180 mins ranged between 0.35 +/- 0.04 (dopamine group) and 0.43 +/- 0.06 (dopexamine group) and did not differ between groups. In control animals, skeletal muscle oxygen extraction ratio remained constant over time. Dopamine (2.5- and 5-micro g doses) increased skeletal muscle oxygen extraction ratio, whereas dopexamine (2.5- and 20-micro g doses) and dobutamine (5-, 10-, and 20-micro g doses) led to a decrease in skeletal muscle oxygen extraction ratio (Figure 5, bottom).

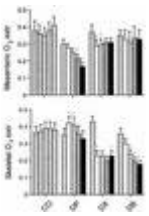

Figure 5. Calculated regional oxygen extraction ratios following inotropic treatment significantly differed between groups (group by dose interaction, p = .00 by analysis of variance). Mesenteric oxygen extraction ratio decreased with dopamine (DP) at 10 and 20 micro g/kg/min and with dopexamine (DX) at 2.5 and 5 micro g/kg/min, whereas it remained unchanged in dobutamine (DB)-treated animals and controls (CO). Skeletal muscle oxygen extraction ratio increased with dopamine at 2.5 and 5 micro g/kg/min, decreased with dopexamine at 2.5 and 20 micro g/kg/min, and with dobutamine at 5, 10, and 20 micro g/kg/min, and remained unchanged in controls. *p < .05 vs. pretreatment (time of 180 mins) by paired t-test (n = 7 for all groups). Spotted bars, 0 micro g; open bars, 2.5 micro g; hatched bars, 5 micro g; cross-hatched bars, 10 micro g solid bars, 20 micro g.

DISCUSSION

In this model of porcine endotoxemia, of the three inotropes used, only dopamine and dopexamine improved jejunal mucosal tissue oxygenation, measured as surface tissue oxygen tension and oxygen saturation of mucosal microvascular hemoglobin (Figure 3). Although dobutamine most effectively increased systemic DO_2 (Table 1, Figure 4), no local effect on tissue oxygenation was observed (Figure 3 and Figure 4), which suggests distribution of oxygen to microcirculatory regions other than the intestinal mucosa.

Before inotropic treatment, animals were infused with 2 micro g/kg of E. coli lipopolysaccharide via the superior mesenteric artery over a period of 20 mins. This procedure has previously been demonstrated to decrease jejunal mucosal tissue PO_2 in this porcine preparation to 40% of values observed in sham treated animals [14]. As infusion of the same dose of lipopolysac-charide via a central venous catheter did not significantly alter mucosal tissue PO_2, the mesenteric route of application of endotoxin may play an important role in determining the degree of mucosal hypoxia by increasing local vascular concentrations of endotoxin [14]. This marked effect of lipopolysac-charide on mucosal oxygenation is not a consequence of systemic hemodynamic alterations induced by endotoxin, since both in these (Figure 2, Table 1) and the previous experiments [14] systemic DO_2 and mean arterial blood pressure were preserved over the experimental period, with the exception of a brief decrease at the end of the endotoxin infusion (Figure 2). More likely, the observed effect of endotoxin on mucosal oxygenation is mediated by a regional vasoconstrictive mechanism. In support of this concept, endotoxin has been reported to reduce the density of perfused capillaries in small intestinal mucosal villi and crypts [16] and to decrease mucosal villous blood flow [13] without changing perfusion pressure.

Following pretreatment with endotoxin, both dopamine and dopexamine increased mucosal PO_2

and mucosal HbO_2 to values >or=to20 torr (>or=to2.67 kPa) and >or=to50%, respectively (Figure 3), which have previously been reported to be normal values in this preparation [11,14,15]. Such increases are likely to reflect an enhanced blood flow to the intestinal mucosal layer, since both mucosal PO_2 and mucosal HbO_2 are a function of mucosal blood flow [17,18].

In relation to concomitant increments in systemic DO_2, dopamine seems to act as the most selective inotrope in increasing mucosal tissue PO_2 (Figure 4). A selective vasodilatory effect of dopamine within the intestinal mucosa has previously been demonstrated in cats, where intravenous infusion of 10 and 25 micro g/kg/min increased jejunal blood flow to the mucosa and submucosa, whereas serosal and muscularis blood flow decreased [7]. Likewise in pigs, intravenous doses of 2 to 32 micro g/kg/min of dopamine induced dose-related increases in mucosal PO_2 but no changes in serosal PO_2 [8]. There is growing evidence that mucosal vasodilation is mainly mediated by postsynaptic vascular DA_1-receptors since, first, blockade of DA_1-receptors by specific antagonists prevents dopamine-induced mucosal vasodilation [19], and second, DA_1-specific agonists such as fenoldopam exhibit a potency to increase mucosal PO_2 similar to that of dopamine [11].

Dopexamine not only stimulates DA_1-receptors but also $beta_2$-receptors. At the DA_1-receptor, the potency of dopexamine is about one third that of dopamine. However, at the $beta_2$-receptor, the potency is 60 times that of dopamine [10]. $beta_2$-receptors have been reported to mediate vasodilation both in the gastric [20] and small intestinal mucosal circulation [12]. Therefore, we assumed that stimulation of both DA_1- and $beta_2$-receptors by dopexamine may have an additive effect on mucosal vasodilation. However, absolute values for mucosal PO_2 and mucosal HbO_2, as well as PO_2 values in relation to changes in systemic DO_2, were lower in the dopexamine group than in the dopamine group (Figure 3 and Figure 4). Consequently, stimulation of the DA_1-receptor seems to play a dominant role in mediating vasodilation in this preparation. In addition, the potent $beta_2$-agonism of dopexamine may have forced a considerable part of blood flow to other microcirculatory regions rich in $beta_2$-receptors, such as skeletal muscle [21]. Although regional oxygen extraction ratios, calculated in these experiments for the skeletal muscle and superior mesenteric circulation (Figure 5), do not merely reflect regional blood flow and DO_2, but also regional oxygen uptake, they may illustrate different vasoactive properties of drugs used in this study. Within the mesenteric circulation, oxygen extraction ratios decreased in both dopexamine- and dopamine-treated animals (Figure 5, top), which together with concomitant increases in mucosal PO_2 (Figure 3, top) indicate a substantial increase in mesenteric blood flow in the case of both drugs. Looking at the skeletal muscle circulation, which is devoid of dopaminergic receptors, the picture is different (Figure 5, bottom). Here, dopamine tended to increase oxygen extraction ratio, suggesting a decrease in muscle blood flow. In contrast, dopexamine provoked a large decrease in muscle oxygen extraction ratio (Figure 5, bottom), indicating a considerable increase in blood flow to the skeletal muscle circulation. Powerful and dose-related vasodilation within the skeletal muscle vasculature has already been observed in dogs [21].

Although dobutamine provoked the largest increase in systemic DO_2 of all three drugs used, it did not improve intestinal mucosal tissue oxygenation (Table 1, Figure 3 and Figure 4). This finding is not surprising in terms of receptor affinity, since dobutamine is primarily a potent $beta_1$ agonist with mild balancing alpha- and $beta_2$-adrenergic receptor agonist properties within the peripheral

vasculature [22]. In dogs, intravenous doses of up to 32 micro g/kg/min produced no significant change in blood flow to the superior mesenteric artery. Expressed in percent changes of cardiac output, superior mesenteric artery blood flow decreased [23]. Similarly, a 13-micro g/kg/min dose in pigs did not change superior mesenteric artery blood flow [24] and decreased the ratio of superior mesenteric blood flow to cardiac output by 34%, indicating that the drug has no selective effect within the mesenteric circulation. Dose-related decreases in skeletal muscle oxygen extraction ratio in this study and a previous report [23] of enhanced blood flow to the femoral artery suggest that the skeletal muscle circulation may specifically benefit from dobutamine infusion.

Clinical Implications and Limitations of the Model.

The present results suggest that mere boosting of systemic DO_2 by use of dobutamine does not restore regional tissue oxygenation within the intestinal mucosa. In a direct comparison of all three inotropes used, dopamine may be the drug of choice in the treatment of patients who are suspected to present with intestinal mucosal ischemia.

However, an application of these results to humans and critically ill patients in particular has to be viewed with caution. First, responses of the peripheral vasculature to dopamine vary between different mammals. Studies [23,25] in dogs suggest that the vasodilator effect of dopamine within the superior mesenteric circulation can be overridden by concurrent stimulation of alpha-adrenergic receptors at doses of >10 micro g/kg/min. Yet, this vasoconstrictor effect noticed in dogs is not representative of other mammals, since in pigs, cats, and rabbits vasodilation persists at intravenous doses of 20, 25, and 60 micro g/kg/min, respectively [7,19,26]. In humans, this mesenteric vasoconstrictor threshold is still completely unknown. In general, experiments [27] in isolated monkey arteries, which follow more closely the responses of human arteries to dopamine than feline or canine arteries suggest that, compared with renal or coronary vessels, the superior mesenteric artery responds more consistently to dopamine with dopamine receptor-mediated relaxation than with alpha-adrenergic receptor-mediated contraction. In those species where direct measurements of parameters related to blood flow within the mesenteric mucosal circulation have been obtained (pig, cat, and dog), dopamine does produce dose-related vasodilation in the pig at doses between 2 and 32 micro g/kg/min [8] and in the cat at doses between 10 and 25 micro g/kg/min [7]. It causes vasoconstriction only in the dog [9]. In the dog study [9], 0.1 and 0.5 micro g/kg/min of dopamine were directly infused into the superior mesenteric artery, producing an increase in mesenteric arterial blood flow, but a decrease in mucosal blood flow as measured by radio-iodine absorption from the gut lumen. However, the results obtained were only descriptive, since the sample size of two dogs at each dose did not allow statistical analysis.

Secondly, pretreatment with endotoxin, as was the case in this model, has been observed to attenuate the vasoconstrictor response to alpha-agonistic drugs. In pigs infused with endotoxin, the doses of noradrenaline or dopamine that need to be infused in order to achieve a predefined increase in arterial blood pressure are higher than in control animals [28]. Thus, the intestinal mucosal vascular response to dopamine may be different in pigs not subjected to endotoxin. In this model, however, both under resting conditions [8] and following endotoxin infusion, a similar increase in intestinal mucosal tissue oxygenation and also in mean arterial blood pressure is observed with dopamine infused at doses of as much as 20 micro g/kg/min. Hence, a depressed vascular reactivity does not seem to occur in this endotoxin model.

In conclusion, this study shows that dopamine considerably increases tissue oxygenation of the small intestinal mucosa during normotensive endotoxemia and should therefore be carefully evaluated in patients presenting with intestinal mucosal ischemia. In contrast, dobutamine does not improve tissue oxygenation within the intestinal mucosa. Dopexamine may theoretically constitute an attractive alternative to dopamine, since it does not hold the risk of alpha-receptor-

mediated mesenteric vasoconstriction. However, in this preparation the effects of dopexamine on mucosal tissue oxygenation were less pronounced than those effects of dopamine, which is most likely attributable to the lower affinity of dopexamine at the vascular DA_1-receptor.

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