Effects of α- and β-adrenergic stimulation on hepatosplanchnic perfusion and oxygen extraction in endotoxic shock

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Objective: To examine the effects of adrenergic stimulation on hepatosplanchnic perfusion, oxygen extraction, and tumor necrosis factor–α production during endotoxic shock.

Design: In vivo, prospective, randomized, controlled, repeated-measures, experimental study.

Setting: Experimental physiology laboratory in a university teaching hospital.

Subjects: Twenty-one anesthetized and mechanically ventilated dogs.

Interventions: An intrapericardial catheter was positioned. Catheters for blood sampling were inserted into the right femoral artery, hepatic vein, portal vein, and pulmonary artery. Ultrasonic flow probes were placed around the portal vein, the hepatic artery, the mesenteric artery, the left renal artery, and the left femoral artery. Animals received 2 mg/kg of Escherichia coli endotoxin, followed by fluid resuscitation. Seven dogs received intravenous isoproterenol (0.1 μg/kg·min⁻¹), seven received phenylephrine (1 μg/kg·min⁻¹), and seven served as controls. Thirty minutes later, cardiac tamponade was introduced to study organ perfusion and tissue oxygen extraction capabilities.

Main Results: The isoproterenol group had a higher cardiac index and stroke index and lower systemic vascular resistance than the other groups. The phenylephrine group had a higher arterial pressure but a lower cardiac index than the isoproterenol group. The isoproterenol group had a higher hepatic artery blood flow than the other groups and a higher portal and mesenteric flow than the control group. Liver and gut mucosal blood flow was greater in the isoproterenol than in the phenylephrine group. The isoproterenol group had a lower global critical oxygen delivery than the other groups (8.8 ± 1.3 vs. 13.1 ± 2.0 (control) and 11.8 ± 3.3 mL/kg·min⁻¹ (phenylephrine); both p < .05) and a higher liver critical oxygen extraction ratio than the control group. Iso- proterenol tended to attenuate, but phenylephrine significantly increased, blood tumor necrosis factor levels.

Conclusions: During endotoxic shock, β-stimulation can improve hepatosplanchnic perfusion and enhance tissue oxygen extraction capabilities, whereas α-stimulation does not. In addition, α-adrenergic stimulation can increase tumor necrosis factor levels. (Crit Care Med 2001; 29:581–588)

Key Words: vasodistension; vasodilation; oxygen delivery; oxygen uptake; hepatic blood flow; gut mucosa; tumor necrosis factor; septic shock

To deliver adequate amounts of oxygen to the tissues in relation to their metabolic demands, blood flow to the organs is adjusted by a balance between generalized vasoconstrictor tone involving the adrenergic system and local metabolic vasodilation within tissues. Under physiologic conditions, β-adrenergic stimulation may promote gastrointestinal mucosal blood flow and improve its oxygenation, whereas α-adrenergic agonists can maintain arterial pressure and increase tissue perfusion pressure. The adrenergic system plays a fundamental role in the maintenance of optimal oxygen extraction (1, 2) but can be altered in septic conditions (3-6) when endotoxin and other bacterial products can alter adrenergic receptors (6). If the oxygen delivery (DO₂) cannot meet the body's oxygen demands, blood flow distribution can be an important mechanism to prevent hypoxia in vital organs. The hepatosplanchnic vasculature may play a particular role in these alterations (7), even though the gut may be quite susceptible to a reduced oxygen supply. After endotoxemia, intestinal mucosal blood flow may decrease more than muscularis flow (8), and ischemia may render the gut mucosa more permeable to bacteria and their products (9). These, in turn, may stimulate the release of cytokines and other mediators, which can increase oxygen demand and simultaneously alter tissue oxygen extraction capabilities by altering vascular tone, capillary recruitment, and endothelial cell function (10-12). Maintenance of splanchnic blood flow can prevent increased intestinal mucosal permeability in endotoxic conditions (13) and, therefore, seems to represent a valuable therapeutic option.

Adrenergic agents in common use may have significant effects on hepatosplanchnic blood flow and oxygen extraction capabilities in septic conditions. Norepinephrine could maintain splanchnic blood flow and improve gut mucosal oxygenation in sepsis (14,15). We also recently found that norepinephrine can even increase hepatic arterial blood flow and improve liver oxygen extraction capabilities in a dog model of endotoxic shock (15). Because this agent combines the effects on both α- and β-adrenoceptors, the mechanisms by which norepinephrine can improve tissue oxygen delivery could not be defined.
Recent studies have also indicated that adrenergic agents may modulate the inflammatory response. β-adrenergic agonists can inhibit, but α-stimulation can promote, endotoxin-induced tumor necrosis factor (TNF-α) production in vitro (16-19).

To differentiate the effects of β-adrenergic from α-adrenergic stimulation on hepatosplanchnic blood flow and tissue oxygen extraction capabilities, we investigated the effects of the β-adrenergic agonist isoproteanol and the α-adrenergic agonist phenylephrine during acute canine endotoxemic shock. In the first phase, we studied the effects of these agents on global and hepatosplanchnic hemodynamics, and in the second phase, we explored their effects on oxygen extraction capabilities by inducing cardiac tamponade. We also studied the effects of β- and α-adrenergic stimulation on plasma TNF concentrations.

**MATERIALS AND METHODS**

This study was approved by the Ethical Committee of Animal Research of the Erasmus University Hospital. In conducting the research described in this report, the investigators adhered to the National Institutes of Health's guidelines for the use of experimental animals.

**Surgical Preparation.** Twenty-one mongrel dogs of either gender, weighing 29.5 ± 5.1 kg, were anesthetized with pentobarbital sodium at a loading dose of 30 mg/kg, followed by an intravenous infusion of 4 mg/kg-hr⁻¹ (pump Infusomat II, B.Braun, Melsungen AG, Germany) through the right forelimb vein. After endotracheal intubation with a cuffed endotracheal tube, the dog was mechanically ventilated with room air using a Servo ventilator 900B (Siemens-Elema, Solna, Sweden). The animals were paralyzed with pancuronium bromide, given as an initial bolus of 0.15 mg/kg, followed by an infusion of 0.075 mg/kg-hr⁻¹. The respiratory rate was set at 12 breaths/min, and the tidal volume was adjusted to obtain an end-tidal CO₂ between 28 and 34 mm Hg. These ventilatory conditions were not changed thereafter. A right femoral arterial catheter was inserted and connected to a pressure transducer for arterial pressure monitoring. The left forelimb vein was cannulated for infusing normal saline and adrenergic agents. A balloon-tipped pulmonary artery catheter (93A-131-7-F, Baxter, Irvine, CA) was inserted through the right external jugular vein under the guidance of pressure waves, as determined from a four-channel monitor (Sirecust 302A, Siemens, Erlangen, Germany). A left thoracotomy between the fourth and fifth intercostal space was performed, with bleeding controlled by electrocautery. Via a 2- to 3-mm incision in the anterior pericardium, a 16-gauge polyethylene catheter (Intercath, Deseret Medical, Sandy, UT) with multiple side holes around the tip was positioned in the pericardial space with its tip adjacent to the diaphragmatic surface of the left ventricle. The catheter was secured with purse-string sutures. The needle of a warm sterile syringe was injected into the pericardial cavity to ensure no leakage. The saline was then drained before sealing. The thoracic cavity was carefully closed in three layers, and a chest tube (Argyle Trocar catheter A75, 28Ch-40cm, Sherwood Medical, Tullamore, Ireland) was placed through the seventh intercostal space to allow gentle evacuation of the chest. Through a midline laparotomy, a splenectomy was performed after maximal splenic contraction to 1 mg of epinephrine (spread on the surface of the spleen), to prevent autotransfusion of erythrocytes during hypotension. There was no difference in baseline hemoglobin levels in the three groups of dogs after splenectomy. Ultrasonic flow probes (R-series, Transonic Systems, Ithaca, NY; positioned at a 45° angle to the vessel under study for optimum resolution) were placed around the common hepatic artery (3–4 mm), the portal vein (10–12 mm), the mesenteric artery (4–6 mm), the left renal artery (3–4 mm), and the left femoral artery (4–6 mm) for simultaneous measurement of blood flow in these vessels. Care was taken to disrupt the nervous sheath of the common hepatic artery as little as possible. The probes were chosen to produce a good fit to the vessels. The space between the vessel and probe was then filled with an acoustic gel. All flow probes were correctly calibrated for dog blood, Radiometer). All flow rates were determined from a strip-chart recording technique (cardiac output computer, COM-2, Baxter) using three to five 5-ml injections of cold 5% glucose in ice water. Each injection was started at end-inspiration. A temperature probe was used on-line to control for variations in Inj ectate temperature. Respiration was monitored using a breathing bag and a respiratory flow meter (Medex, Amsterdam, The Netherlands). Whole-body D₂O was calculated as the product of arterial oxygen content and cardiac index. Whole-body oxygen uptake (VO₂) was measured from the expired gases as previously described (21). Hepatic artery and portal D₂O were calculated as the product of the flow in the hepatic artery and the oxygen content of the artery and the flow in the portal vein and the oxygen content of the portal vein, respectively. Liver D₂O was calculated as the sum of the D₂O measured at the hepatic artery and the D₂O measured at the portal vein (20). Hepatic artery and portal VO₂ were calculated as the product of hepatic arterial blood flow (QH) and arterial-hepatic venous oxygen content difference and the product of portal ve-
nous blood flow (Qpv) and portal venous-hepatic venous oxygen content difference, respectively. Liver V̇O₂ was calculated as the sum of the V̇O₂ measured in the hepatic artery and the V̇O₂ measured in the portal vein (20). The following formulas were used:

\[ \frac{D_\text{O}_2}{(\text{mL/min})} = \left( \frac{QHA \times \text{CaO}_2 + \text{Qpv} \times \text{CpvO}_2}{0.9} \right) \times 0.9 \]

\[ \frac{V_\text{O}_2}{(\text{mL/min})} = \left( \frac{QHA \times (\text{CaO}_2 - \text{ChvO}_2) + \text{Qpv} \times (\text{CpvO}_2 - \text{ChvO}_2)}{0.9} \right) \times 0.9 \]

where CaO₂, CpvO₂, and ChvO₂ are arterial, portal venous, and hepatic venous oxygen content, respectively. The constant value, 0.9, corrects for the common hepatic arterial blood flow directed toward the gastroduodenal artery in normal conditions (20). In the present study, we did not determine the blood flow through either the hepatic artery or the gastroduodenal artery under endotoxic conditions. However, we used an endotoxin-alone group as our control to compare specifically the effects of the adrenergic agents on regional blood flow after endotoxin, assuming that any changes in blood flow were the result of the adrenergic intervention. The oxygen extraction ratio (O₂ER) was derived from the ratio of each individual V̇O₂/ḊO₂.

Plasma TNF was measured by an enzyme-linked immunosorbent assay technique using specific polyclonal rabbit antibodies to recombinant human TNF-α. These antibodies to human TNF see canine TNF in Western blot (W. Buurman, unpublished data) and inhibit the biological activity of canine TNF to a lesser degree than they inhibit human TNF. In brief, immuno-Maxisorb plates (96-well, Nunc, Roskilde, Denmark) were coated with monoclonal anti-human TNF-α. Nonattached sites were blocked with 1% human serum albumin in phosphate-buffered saline. Goat polyclonal rabbit antibodies along with peroxidase were used for detecting antibodies. Developments were carried out with 3,3'-5,5'-tetramethylbenzidine, and the reaction was stopped with H₂SO₄. The activity was measured at 450 nm spectrophotometrically (Molecular Devices, Menlo Park, CA).

**Experimental Protocol.** After surgical preparation, the dog was placed in the supine position and left to stabilize for 30 mins. The pericardial cavity was then emptied using a 5-mL syringe to ensure a slightly negative intrapericardial pressure before the control measurements (B) started. The animals received a slow bolus of 2 mg/kg of Escherichia coli endotoxin (055:B5, control 3120-10-7, Difco, Detroit, MI) over 2 mins through the pulmonary artery catheter. Endotoxin was dissolved in normal saline to obtain a 10-mg/mL solution. A second set of measurements was obtained 30 mins after endotoxin administration (E). The dogs were then randomly divided into three groups: endotoxin alone (n = 7), endotoxin plus isoproterenol (n = 7), and endotoxin plus phenylephrine (n = 7). Isoproterenol (Isuprel, isoprenaline hydrochloridum, Sanofi Winthrop, Brussels, Belgium) was prepared as a 10-μg/mL solution in a 50-mL syringe (Perfusor Akkuputo, ED-EDL, Melsungen AG, Germany) and administered as a continuous infusion at 0.1 μg/kg-min⁻¹ throughout the study. Phenylephrine (Neosynephrine, Boehrener, Barcelona, Spain) was prepared as a 100-μg/mL solution in a 50-mL syringe (Perfusor Akkuputo, ED-EDL) and administered at 1 μg/kg-min⁻¹ until the end of the study. A normal saline infusion was simultaneously started and titrated to restore pulmonary artery occlusion pressure to baseline, and a third set of measurements was made after 30 mins (D). The saline infusion was then kept constant at a rate of 20 mL/kg-hr⁻¹ in all animals throughout the study. Cardiac tamponade was then induced by repeated injections into the pericardial sac of normal saline heated to 37°C. The amount of saline injected was 30 mL for the first two injections, then 10 mL until V̇O₂ started to fall from baseline levels, and finally 2.5 mL until the mean arterial pressure fell by 80% from baseline. After each injection, a time interval of 20 mins was allowed for a steady state to be reached, characterized by a stable expired oxygen fraction, end tidal CO₂, arterial pressure, and heart rate, before the next measurements were obtained. Core temperature was kept constant at its initial level with warming lamps and a heating blanket during the study. The total length of the experiment was 4 hrs.

**Statistics.** A dual-line regression method was used to determine the whole-body and liver critical ḊO₂ (ḊO₂crit) from a plot of V̇O₂ vs. ḊO₂ in each individual animal. For each plot, linear regression by best fit was used to calculate straight lines for the supply-independency and -dependency (22). The point of intersection of their regression lines defined the ḊO₂crit and the corresponding critical V̇O₂. The critical O₂ER (O₂ERcrit) was defined as the V̇O₂/ḊO₂ ratio at ḊO₂crit and derived from each individual V̇O₂/ḊO₂ plot. Statistical analysis included an analysis of variance for repeated measurements (for intrapericardial pressures and groups together), followed by a Dunnett test. The predominant effect of each treatment was considered, and when the F test was significant, a Student’s t-test was performed. Differences in ḊO₂crit and O₂ERcrit between the control and the adrenergic agent-treated groups were explored using a two-tailed Student’s t-test. A p < .05 was considered statistically significant. Values are expressed as mean ± SD.

**RESULTS**

Effects of Endotoxin Alone. Endotoxin administration resulted in more than a 50% decrease in mean arterial pressure, cardiac filling pressures, cardiac index, and left ventricular stroke work index (Table 1 and Fig. 1). Systemic vascular resistance increased by 20%, and pulmonary vascular resistance doubled (Table 1 and Fig. 1). Blood flow was reduced by approximately 50% in all vasculatures studied (Fig. 2). Tissue perfusion assessed by the laser Doppler technique decreased by approximately 25% in the liver and ileum mucosa (Fig. 3).

After initial fluid resuscitation, mean arterial pressure was restored from near 40 to approximately 60 mm Hg and remained low, but cardiac index and regional blood flows increased to, or above, baseline levels, so that systemic vascular resistance was reduced profoundly (Figs. 1 and 2). Liver perfusion and ileum mucosal perfusion were restored slightly above the baseline level (Fig. 3).

Hemodynamic Effects of Isoproterenol and Phenylephrine. When isoproterenol was infused in addition to fluids, the cardiac index dramatically increased from approximately 50 to near 300 mL/kg-min⁻¹ by combined increases in heart rate and stroke index. Arterial pressure did not change, and systemic vascular resistance fell to very low levels (Table 1 and Fig. 1). Hepatic, portal and mesenteric blood flows were significantly greater than in the control group, but renal and femoral blood flows were not significantly influenced (Fig. 2).

When phenylephrine was infused in addition to fluids, mean arterial pressure increased from approximately 45 to near 80 mm Hg, but cardiac index or regional blood flow were not significantly influenced (Figs. 1 and 2). Liver and ileum mucosal perfusion increased more with isoproterenol than with phenylephrine (Fig. 3).

During cardiac tamponade, the isoproterenol-treated group initially maintained a higher cardiac index and stroke index and a lower systemic vascular resistance than the other groups. However, at intrapericardial pressures >6 mm Hg, the rate of decrease of these hemodynamic variables was greater in the isoproterenol group than in the other groups (Fig. 1). At high intrapericardial pressure, hepatic and femoral blood flows were higher in the isoproterenol group than in the phenylephrine group (Fig. 2). Laser Doppler blood flow in the liver and the ileum mucosa remained greater in the isoproterenol than in the phenylephrine group (Fig. 3).
Table 1. Selected hemodynamic and blood gas variables

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<th>Baseline</th>
<th>Endotoxin</th>
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<td><strong>Intrapericardial Pressure (mm Hg)</strong></td>
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<td>Endotoxin</td>
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<td>Endotoxin + isoproterenol</td>
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<td>Endotoxin + phenylephrine</td>
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<td>Endotoxin</td>
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<td>Endotoxin + phenylephrine</td>
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<td>Endotoxin</td>
<td>13.1 ± 2.8</td>
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<td>phenylephrine</td>
<td>5.4 ± 6.0</td>
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<td><strong>Arterial oxygen saturation (%)</strong></td>
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<td>ShO2</td>
<td>74.6 ± 10.8</td>
<td>31.3 ± 15.4</td>
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<td>LVSWI (gcm/kg)</td>
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<td>166.4 ± 43.2</td>
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<td>PVR (dynes⋅sec/cm−5)</td>
<td>168 ± 24</td>
<td>505 ± 268</td>
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<td><strong>Arterial pH</strong></td>
<td>7.34 ± 0.03</td>
<td>7.19 ± 0.03</td>
<td>7.13 ± 0.05</td>
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<td>Lactate (mM/L)</td>
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<td>Hemoglobin (g/dL)</td>
<td>16.5 ± 3.0</td>
<td>17.5 ± 3.3</td>
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PAOP, pulmonary arterial occlusion pressure; RAP, right atrial pressure; MPAP, mean pulmonary artery pressure; LVSWI, left ventricular stroke work index; PVR, pulmonary vascular resistance; ShO₂, hepatic venous oxygen saturation; SpO₂, portal venous oxygen saturation.

*p < .05 vs. phenylephrine; †p < .05 vs. endotoxin. Data are shown as mean ± sd.
There was no significant difference in the amount of fluid infused in the three groups (5.1 ± 1.6 l in control group vs. 4.6 ± 0.5 l in the isoproterenol group and 4.3 ± 0.5 l in the phenylephrine group; both p = NS).

**Effects on Oxygen Extraction Capabilities.** Figure 4 shows the global $\dot{V}O_2$/ $\dot{V}O_2_{crit}$ relation of the three groups of animals. Isoproterenol tended to decrease liver $\dot{V}O_2_{crit}$ and to increase liver $O_2$ER$_{crit}$.

**TNF Levels.** TNF levels were significantly lower in the isoproterenol-treated group than in the control group 3 hrs after endotoxin administration, but they were somewhat lower already at baseline. On the other hand, the phenylephrine-treated animals showed higher TNF levels than the isoproterenol-treated group 2 hrs after endotoxin and than the other two groups 3 hrs after endotoxin (Fig. 5).

**DISCUSSION**

Septic shock is characterized by severe systemic hypotension associated with a loss of microvascular integrity. Fluid resuscitation is one of the major means of improving tissue perfusion in the treatment of septic shock. However, in most cases, fluids alone are not sufficient to maintain tissue perfusion, and vasoactive agents are required. Moreover, low tissue blood flow followed by fluid resuscitation may lead to tissue injury by recruitment and activation of neutrophils, resulting in the release of cytotoxic mediators. Vasoactive agents, which also have some anti-inflammatory effects, may help to attenuate the systemic inflammatory response.

We used an acute endotoxic shock model combining an initial hyperdynamic state after fluid resuscitation and a late hypodynamic state induced by cardiac tamponade. The present study indicates that in a model of fluid resuscitated endotoxic shock, isoproterenol increased macro- and microhepatosplanchnic blood flow...
and improved whole-body and liver oxygen extraction capabilities. Phenylephrine did not exert these beneficial hemodynamic effects, but rather increased TNF release.

We did not measure the endogenous levels of catecholamines in this endotoxic shock model. During endotoxic shock in the rat, there is a dose- and time-dependent change in plasma catecholamine levels in response to endotoxin. That is, catecholamine levels increase in the early phase and decrease over time after endotoxin (23). However, adrenergic hyporesponsiveness has been described, even in early endotoxic conditions. The mechanism of desensitization may be involved in the interference between exogenous catecholamines themselves and the functioning of the adrenergic receptor system. Therefore, in the present study, we investigated the responses to α- and β-adrenergic stimulation separately. An early study demonstrated that the response and sensitivity to catecholamines were not significantly affected by moderate doses (up to 45 mg/kg) of sodium pentobarbital for anesthesia in dogs (10). We conclude, therefore, that the differences observed in the present study in response to α- and β-adrenergic stimulation were the result of the adrenergic receptor system and not the use of anesthesia.

Because the present model was unable to obtain repetitive baseline hemodynamic variables in the same animal, a dose response curve study was not possible. We, thus, chose the adrenergic agents at the doses commonly used in hypoxic or circulatory shock models in the dog (24-26). Also, the doses of the adrenergic agents, isoproterenol and phenylephrine, used were roughly equivalent with respect to hemodynamics in anesthetized dogs. Spiess et al. (27, 28) demonstrated that isoproterenol can redistribute intestinal blood flow, favoring mucosal over muscularis blood flow. In anesthetized dogs, Richardson et al. (30) showed that isoproterenol increased both the blood flow and the capillary filtration coefficient in the innervated small intestine. The persistence of a vasodilator response after practolol indicated that β2-adrenoceptors were primarily responsible for these effects.

In septic conditions, Cain and Curtis (1) demonstrated that dopexamine, which exerts primarily β2-adrenergic effects, improved intestinal blood flow in fluid-resuscitated endotoxic dogs. Van Lambergen et al. (33) and Schmidt et al. (8) also showed that dopexamine maintained intestinal villus perfusion and prevented vasoconstriction in villus arterioles in endotoxic rats. However, adrenergic stimulation may be less likely to influence relative regional blood flow. This has been supported by several studies. In a porcine model of fluid-resuscitated endotoxic shock, Breslow et al. (34) observed no major differences among dopamine, norepinephrine, and phenylephrine in regional blood flow. All adrenergic agents infused for 30 mins increased arterial pressure without affecting either cardiac output or splanchnic blood flow. Because the adrenergic agents were titrated to achieve a mean arterial blood pressure of between 70 and 80 mm Hg, the doses used were much greater than in the present study (dopamine, 147 ± 54 μg/kg·min⁻¹; norepinephrine, 3.0 ± 1.6 μg/kg·min⁻¹; and phenylephrine, 5.9 ± 2.7 μg/kg·min⁻¹), also resulting in greater regional vascular resistance. This may explain the lack of increase in regional blood flow in that study (34). In a sheep model of sepsis induced by cecal ligation and perforation, Bersten et al. (35) found that dopamine, dopexamine, dobutamine, or norepinephrine had no significant ef-
fect on hepatosplanchnic blood flow. Adrenergic agents were titrated to achieve a 20% increase in the cardiac index in the absence of fluid resuscitation, and regional blood flow was assessed after 3 hrs of infusion (35). Thus, the use of different models, species, adrenergic agonists, doses, and timing may result in different observations.

To more clearly clarify the issues, we used a model in which some features observed in clinical septic shock could be reproduced and investigated separately the effects of an \( \alpha \)- and a \( \beta \)-adrenergic agent on regional blood flow after endotoxic shock. To study the effects of adrenergic agents on regional blood flow and oxygen extraction capabilities after endotoxic challenge, we used an endotoxin group as the control so that any changes seen in the treated groups could be assumed to be the result of the adrenergic agent. Whether endotoxin can alter the normal hepatic/gastroduodenal arterial blood flow ratio was not determined. We demonstrated that the \( \beta \)-adrenergic agent isoproterenol improved hepatosplanchnic blood flow without significantly influencing blood flow distribution among organs. Isoproterenol also improved liver and intestinal mucosal blood flow as assessed by the laser Doppler technique. Shepherd et al. (31, 32) using a modified Gore-Bohlen model of intestinal circulation demonstrated that isoproterenol selectively vasodilates the intestinal mucosa and, at the same time, reduces blood flow to the muscularis. Cain and Curtis (1) observed in fluid-resuscitated endotoxic dogs that the \( \beta \)-agonist doxapamine did not alter the distribution of cardiac output between intestine and muscle but favored mucosal over muscularis blood flow in the gut.

We further showed that isoproterenol improved tissue oxygen extraction capabilities. In septic conditions, there is an increase in stopped-flow capillary density while continuous, perfused, and total capillary density is decreased. The intercapillary distance is larger than normal in septic conditions (12). Drazenovic et al. (11) demonstrated that endotoxin challenge significantly lowered the perfused capillary density of mucosal villi in dogs. When perfused capillary percentage was considered as a function of \( O_2 \)ER for control and endotoxin-challenged gut loops, a significant relationship was found in the control group, but no relationship was detected in the endotoxin group. This suggests that gut adjustments in perfused capillary density in response to changes in \( O_2 \)ER are impaired after endotoxin administration. Impaired oxygen extraction capabilities might arise from a failure to regulate capillary density in accord with the local oxygen supply-to-demand ratio. Both \( \beta_1 \)- and \( \beta_2 \)-adrenergic stimulation can increase perfused capillary density by vasodilating effects primarily mediated by cyclic adenosine monophosphate (36). Isoproterenol has been shown to prevent vascular permeability and to increase capillary recruitment primarily by \( \beta_2 \)-adrenergic properties. Indeed, ICI 118551, a specific \( \beta_2 \)-antagonist, blunted this action, but ICI 89406, a specific \( \beta_1 \)-antagonist, did not (37). Capillary recruitment in response to local hypoxia can effectively reduce intercapillary spacing, thereby allowing tissues to extract more oxygen. Hence, although this was not specifically studied here, the improved oxygen extraction capabilities of isoproterenol were probably predominantly the result of its \( \beta_2 \)-adreceptors effects.

Isoproterenol administration resulted in a decrease in arterial pH and an increase in blood lactate concentration, which were probably secondary to enhanced glycolysis (38). Acidosis may also help to maintain tissue oxygen extraction (39). It is unlikely that acidosis was the result of organ ischemia because for a given mean arterial pressure, the isoproterenol-treated group showed a higher cardiac index and a better preserved organ perfusion.

Phenylephrine did not influence either hepatosplanchnic blood flow or global and liver oxygen extraction capabilities after endotoxemia. Samsel and Schumacker (40) demonstrated that the \( \alpha \)-adrenergic antagonist phenoxybenzamine markedly reduced gut vascular resistance but did not alter oxygen extraction capabilities when blood flow was acutely reduced by hemorrhage in dogs. This observation suggests that a functional difference exists between the vessels controlling microvascular distribution of capillary blood flow and those responsible for local vascular resistance. Vasoconstrictors can reduce the density of the perfused capillary bed, so that the oxygen flux from capillary to cell becomes diffusion limited, even under constant flow conditions (31). In the present study, phenylephrine did not show any effects on tissue oxygen extraction capabilities.

Recent clinical studies (14, 41) have underlined the value of norepinephrine in the treatment of septic shock. We recently observed in the same dog model that norepinephrine at a dose of 1 \( \mu \)g/kg/min\(^{-1}\) decreased \( O_2 \)ERcrit and increased \( O_2 \)ERcrit (15). Importantly, norepinephrine increased both arterial pressure and cardiac index, as well as hepatic arterial blood flow, but it was impossible to separate what was the result of \( \alpha \)- or \( \beta \)-adrenoceptor effects (15). The present investigation shows that the increased global, hepatic arterial blood flow and \( O_2 \)ERcrit seen with norepinephrine were the result of its \( \beta_1 \)- and \( \beta_2 \)-stimulating rather than its \( \alpha \) effects. Also, the \( \beta \)-adrenergic response may become predominant in endotoxic animals, as the result of a reduction in the number of \( \alpha \)-adrenergic receptors (5) and a relative increase in the number of \( \beta \)-receptors (5, 42, 43). Although both phenylephrine and norepinephrine increased arterial pressure in this model, only norepinephrine improved \( O_2 \)ERcrit. These observations stress the importance of \( \beta \)-adrenergic stimulation in the maintenance of oxygen extraction capabilities.

We observed that isoproterenol slightly attenuated endotoxin-induced TNF release, but phenylephrine significantly increased TNF production. The isoproterenol-attenuated TNF release seems to be specifically related to the \( \beta_2 \)-adrenergic effect, although the secondary increase in blood flow itself may have played a role in our study. Several studies have established that stimulation of \( \beta \)-adrenergic receptors can inhibit endotoxin-induced TNF production \textit{in vitro} (16, 17, 19) or \textit{in vivo} (16,18) by increasing intracellular cyclic adenine monophosphate levels (19). Other studies showed that \( \alpha_1 \)-receptor stimulation increases TNF release after endotoxin in macrophages (44) and that \( \alpha_1 \)-adrenoceptor blockade can decrease TNF production (45, 46) after endotoxemia in rats and mice. Our results suggest that \( \alpha \)-adrenergic receptors may influence cytokine release even more than \( \beta \)-adrenergic receptors. Because an increased TNF release may be associated with a worse outcome from septic shock, these observations caution against the liberal administration of \( \alpha \)-adrenergic agents in septic shock.

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