Epinephrine induces tissue perfusion deficit in porcine endotoxin shock: evaluation by regional CO₂ content gradients and lactate-to-pyruvate ratios

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Epinephrine induces tissue perfusion deficit in porcine endotoxin shock: evaluation by regional CO₂ content gradients and lactate-to-pyruvate ratios. Am J Physiol Gastrointest Liver Physiol 288: G586–G592, 2005. First published October 28, 2004; doi:10.1152/ajpgi.00378.2004.——Epinephrine is widely used as a vasoconstrictor or inotrope in shock, although it may typically induce or augment lactic acidosis. Ongoing debate addresses the question of whether hyperlactatemia per se is a sign of tissue perfusion deficit or aerobic glycolysis. We wanted to test the hypothesis that epinephrine has selective detrimental effects on visceral perfusion and metabolism. We performed rigorous regional venous blood gas analyses as well as intraperitoneal microdialysis. We used a mathematical model to calculate regional arteriovenous CO₂ content gradients and estimated the magnitude of the Haldane effect in a porcine model of prolonged hypotensive shock induced by endotoxin infusion (mean arterial blood pressure < 60 mmHg). Subsequently, vasopressors (epinephrine or norepinephrine) were administered and adjusted to maintain systemic mean arterial pressure > 70 mmHg for 4 h. Epinephrine caused systemic hyperlactatemia and acidosis. Importantly, both systemic and regional venous lactate-to-pyruvate ratios increased. Epinephrine was associated with decreasing portal blood flow despite apparently maintained total splanchnic blood flow. Epinephrine increased gastric venous-to-arterial PCO₂ gradients and CO₂ content gradients with decreasing magnitude of the Haldane effect, and the regional gastric respiratory quotient remained higher after epinephrine as opposed to norepinephrine infusion. In addition, epinephrine induced intraperitoneal lactate and glycerol release. We did not observe these adverse hemodynamic or metabolic changes related to norepinephrine with the same arterial pressure goal. We conclude that high CO₂ content gradients with decreasing magnitude of the Haldane effect pinpoint the most pronounced perfusion deficiency to the gastric wall when epinephrine, as opposed to norepinephrine, is used in experimental endotoxin shock.

Haldane effect; lactate; microdialysis; norepinephrine

Both epinephrine and norepinephrine are widely used as vasopressors in septic shock (20, 22, 23). Epinephrine, as opposed to norepinephrine, is known to induce arterial hyperlactatemia and systemic acidosis when used as treatment for shock to increase perfusion pressure or as an inotrope (11, 17). Numerous investigators have focused the question on whether this effect is caused by tissue hypoperfusion and dysoxia or whether it is merely a metabolic alteration related to aerobic glycolysis (5, 13, 16). Previously, the tissue perfusion and metabolic changes induced by epinephrine compared with other vasoactive drugs have been studied by measuring regional blood flows, oxygen transport, and lactate metabolism, or by using tonometry and tissue perfusion measurements in both animal models and in a clinical setting (2, 5, 16). Results remain controversial (4, 5, 24). We wanted to address this question by evaluating tissue perfusion and metabolism by regional lactate concentrations and lactate-to-pyruvate ratios as well as by using intraperitoneal microdialysis. We intended to use the regional venous blood gas analysis data to estimate tissue perfusion and metabolism, to calculate regional venous-to-arterial PCO₂ gradients, CO₂ content gradients (8, 12), and the magnitude of the Haldane effect on venous-to-arterial CO₂ gradients (8).

MATERIALS AND METHODS

The institutional animal care and use committee of the University of Kuopio approved the study protocol.

Anesthesia. Twelve domestic female pigs (27 ± 1 kg) were used in the study. Animals were fasted for 24 h before the experiment with free access to water. The gastrointestinal tract was emptied with osmotic laxative (Colostereil; Orion, Espoo, Finland). For the experiment, the animals were premedicated with an intramuscular injection of atropine 0.05 mg/kg. Sedation was induced with ketamine 10 mg/kg and xylazine 2 mg/kg. The ear vein was cannulated, and anesthesia was induced with sodium thiopentone 5–15 mg/kg. Anesthesia and analgesia were maintained with continuous infusions of sodium thiopentone 5 mg·kg⁻¹·h⁻¹ and fentanyl 30 µg·kg⁻¹·h⁻¹ during the surgical manipulation, after which the fentanyl infusion rate was reduced to 5 µg·kg⁻¹·h⁻¹. Tracheotomy was performed, and the lungs were ventilated with a tidal volume of 10–15 ml/kg to maintain normocapnia (arterial CO₂ 33.8–41.3 mmHg) and FIO₂ was adjusted to keep arterial partial pressure of O₂ above 13.3 kPa. Positive end expiratory pressure of 5–8 cmH₂O was applied during the experiment. Cefuroxime (Zinacef; 750 mg) was given intravenously at the beginning of the surgical procedures. Neuromuscular blockade was established with continuous infusion of pancuronium (1–4 mg/h). To limit the number of animals to a minimum, we did not randomize control groups (endotoxin without drug intervention and operated animals without endotoxin or drug intervention) for this experiment. Instead, we referred to the control animals from earlier experiments, which were completed during the same time period (18).

Animal preparation. The left femoral artery was cannulated for arterial blood sampling and for monitoring of systemic arterial blood pressure. The right jugular vein was dissected free and cannulated for pulmonary artery catheter (Arrow; Arrow International, Reading, PA) and hepatic vein catheter (model MPA2 Angiographic catheter; Boston Scientific, Maple Grove, MN) to measure pulmonary artery occlusion pressure (PAOP) and to collect blood samples. Probes for ECG and O₂ saturation were inserted. A full midline laparotomy was performed.

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performed, and the urinary bladder was catheterized and drained. The stomach was emptied with orogastric drain. The position of the hepatic catheter was confirmed manually.

The portal vein and hepatic arteries were dissected free. Precalibrated ultrasonic flow probes were inserted around the vessels. Mesenteric, colonic, portal, and gastric veins were cannulated (single lumen catheter; Arrow) for regional blood sampling. Microdialysis capillaries were inserted on the surface of the jejunum for intraperitoneal lactate measurement. The laparotomy was closed in two layers.

**Hemodynamic monitoring.** Systemic and pulmonary arterial pressures were recorded with quartz pressure transducers, and displayed continuously on a multimodular monitor and recorder (model CS3; DATEX-OHMEDA Instrumentarium, Helsinki, Finland). Automated data filtering (2-min median) was used when the continuous parameters were collected (Deio Instrumentarium). Heart rate was measured from the ECG. PAOP was measured hourly. Cardiac output was measured by the thermodilution technique (mean value of 3 measurements) with room temperature saline injections of 5 ml.

**Blood flow measurements.** Regional blood flows were measured with ultrasonic transit-time flow probes (Transonic Systems, Ithaca, NY) from the hepatic artery and portal vein. Signals were recorded by flow meters (Flowmeters T108 and T208; Transonic Systems, Ithaca, NY). The flow data were stored with computer software (Windaq; DATAQ instruments, Akron, OH). In vivo zero flow signals were recorded at the end of each experiment.

**Fluid management.** For maintenance fluid therapy, 5 ml·kg⁻¹·h⁻¹ saline 0.9% was infused throughout the experiment. Fluid resuscitation with Ringer’s acetate and hydroxyethyl starch 1:1 (Hemohes; Braun, Melsungen, Germany) was performed to achieve PAOP > 5 mmHg withput allowing central venous pressure to exceed 12 mmHg. Blood glucose was maintained between 4.5 and 7.0 mM with a 30% glucose infusion throughout the experiment.

**Microdialysis.** Microdialysis capillaries were manufactured in our laboratory (25). Dialysate (2 μl/min) was collected for half an hour before endotoxin infusion, before vasopressor infusion, and at the end of the experiment in 30-min fractions. Microdialysate lactate concentrations were analyzed within 15 min (model 2300 Stat Plus; Yellow Springs Instruments, Yellow Springs, OH). Microdialysate glycerol concentrations were determined (model CMA600; CMA, Stockholm, Sweden) after the samples had been stored at −20°C.

**Experimental protocol.** After the surgical procedures, the animals were stabilized for 6 h and randomized into epinephrine (n = 6) and norepinephrine (norepinephrine, n = 6) groups. *Escherichia coli* endotoxin (lipopolysaccharide O111:B4; Difco Laboratories, Detroit, MI) infusion was started at a rate of 0.25 μg·kg⁻¹·h⁻¹, and after 1–3 h, the infusion rate was doubled repeatedly every 30–45 min to achieve hypotensive shock [mean systemic arterial pressure (SAPm) < 60 mmHg]. When hypotensive shock was achieved, either epinephrine or norepinephrine infusion was started (randomization using sealed opaque envelopes). We adjusted the infusion rate for 4 h aiming to maintain SAPm at >70 mmHg. Two animals in both groups received additional epinephrine (0.02 ± 0.01 mg) to prevent hemodynamic collapse during the first hour of endotoxin infusion. Duration of endotoxin infusion before hypotensive shock was 17 ± 2 h in the epinephrine group and 20 ± 1 h in the norepinephrine group (not significant).

**Blood samples.** Arterial blood samples were drawn hourly for hemoglobin, arterial blood gases, and glucose measurements. Arterial, colonic, mesenteric, portal, hepatic, gastric, and mixed venous blood samples were collected at baseline and at 0, 2, 3, and 4 h of vasopressor infusion (shock 0 h to shock 4 h), and hemoglobin concentration, blood gases (model ABL 520; Radiometer, Copenhagen, Denmark), lactate (model 2300 Stat Plus; Yellow Springs Instruments), and pyruvate (model UV-706 kit; Sigma, St. Louis, MO) concentrations were analyzed. The blood gas analysis of the samples was performed on whole blood immediately after collecting samples into syringes. Care was taken to remove any air bubbles from the syringes.

**Plasma (actual) bicarbonate was calculated by the analyzer according to the formula given by the supplier.** Lactate measurements were performed immediately after collecting the samples. The pyruvate samples were analyzed within 48 h of collection. Before analysis, the samples were frozen and kept at −20°C. Hemoglobin concentration and hemoglobin oxygen saturation were determined by using an analyzer (Hemoxymeter OSM3, Radiometer) in porcine mode.

**Calculations and statistical analysis.** All data are presented as medians with interquartile ranges. Data are truncated to baseline, hypotensive endotoxin shock before drug intervention (0 h), and at 4 h from the beginning of drug infusion (4 h). The Mann-Whitney U-test was done to evaluate differences between groups at the baseline, before vasopressor infusions, and at 4 h when appropriate. Within-group analysis (changes from shock 0 h to shock 4 h) was done with nonparametric analysis of variance for repeated measurements (Friedman test). A P value of <0.05 was used to indicate statistical significance. Blood carbon dioxide contents and regional CO₂ content gradients were calculated as first devised by Giovannini et al. (8) and applied by Jakob et al. (12). First, we calculated the arterial CO₂ content from the bound form of carbon dioxide in plasma (CaCO₂p) and red blood cells (CaCO₂r), dissolved carbon dioxide, and hematocrit. We used the Henderson-Hasselbalch equation to determine CaCO₂p from the partial tension of carbon dioxide in arterial blood and arterial pH. CaCO₂r was then determined, because it is known that the ratio between CaCO₂r and CaCO₂p is a function of pH and oxygen saturation. Venous-to-arterial CO₂ content gradient was then determined from its two components by using the mathematical model described by Giovannini et al. (8): 1) the increase related to change in partial tension of CO₂ from arterial to venous blood, and 2) the increase in CO₂ content related to change in hemoglobin oxygen saturation from arterial to venous blood (Haldane effect). Regional respiratory quotient (RQ) was calculated as the ratio of regional venous-to-arterial CO₂ content gradient to arterial-to-venous CO₂ content gradient. Blood O₂ content was calculated with the standard formula of CO₂ = [Hb (g/dl)·SO₂ (%)·1.34 (ml O₂/g Hb)] + [0.0031 (ml O₂·mmHg⁻¹·dl⁻¹)·P0₂].

**RESULTS**

All animals survived to the end of the experiment. The initial infusion rate of epinephrine and norepinephrine was 0.01 μg·kg⁻¹·min⁻¹ and the infusion rates of vasopressors necessary to reverse hypotension were 0.93 ± 0.4 μg·kg⁻¹·min⁻¹ in the epinephrine and 0.66 ± 0.1 μg·kg⁻¹·min⁻¹ in the norepinephrine group. The total amounts of epinephrine and norepinephrine infused were 6.7 ± 2.7 and 4.1 ± 0.6 mg.

**Systemic and regional hemodynamics and oxygen transport.** Both epinephrine and norepinephrine effectively reversed hypotension. Norepinephrine, but not epinephrine infusion increased cardiac output. The total splanchnic blood flow (sum of portal venous and hepatic arterial blood flows) increased in response to norepinephrine infusion (P = 0.016, Table 1). Epinephrine decreased portal venous blood flow in five of six animals over the 4-h study period, regardless of the direction of change in cardiac output (Fig. 1). Concomitantly, epinephrine maintained the total splanchnic blood flow. Epinephrine was associated with modestly higher splanchnic oxygen extraction (P = 0.078, Mann-Whitney U-test) (Table 2). In addition, regional gastric RQ increased from 0.95 ± 0.01 at baseline to 1.59 ± 0.20 after 4 h of infusion in the epinephrine group, whereas norepinephrine was associated with a lower RQ after shock and a 4-h norepinephrine infusion of 0.81 ± 0.02 at baseline and 1.07 ± 0.07 (P = 0.016 between the groups) after infusion.
Table 1. Systemic blood pressure, cardiac output (CO), and regional blood flows in epinephrine-treated (Epi) and norepinephrine-treated (NE) animals

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Shock 0 h</th>
<th>Shock 4 h</th>
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<tr>
<td>SAPm, mmHg</td>
<td></td>
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<tr>
<td>Epi</td>
<td>103±8</td>
<td>57±1</td>
<td>73±1*</td>
</tr>
<tr>
<td>NE</td>
<td>109±10</td>
<td>58±2</td>
<td>74±2*</td>
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<tr>
<td>CO l/min</td>
<td></td>
<td></td>
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<tr>
<td>Epi</td>
<td>3.6±0.3</td>
<td>3.6±0.2†</td>
<td>3.9±0.7</td>
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<tr>
<td>NE</td>
<td>2.8±0.3</td>
<td>2.6±0.3</td>
<td>5.2±0.7*</td>
</tr>
<tr>
<td>Qsplanch, ml/min</td>
<td></td>
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</tr>
<tr>
<td>Epi</td>
<td>998±90§</td>
<td>985±65§</td>
<td>950±110</td>
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<tr>
<td>NE</td>
<td>668±59</td>
<td>688±103</td>
<td>1010±91*</td>
</tr>
<tr>
<td>Qporta, ml/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>896±85</td>
<td>888±64§</td>
<td>825±98</td>
</tr>
<tr>
<td>NE</td>
<td>601±59</td>
<td>521±57</td>
<td>834±73*</td>
</tr>
<tr>
<td>Qha, ml/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>102±13</td>
<td>97±11</td>
<td>124±16</td>
</tr>
<tr>
<td>NE</td>
<td>67±10</td>
<td>167±47</td>
<td>176±49</td>
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</table>

Values are means ± SE; n = 6 animals per group. SAPm, mean systemic arterial pressure; Qsplanch, splanchnic blood flow; Qporta, portal vein blood flow; Qha, hepatic arterial blood flow. *P < 0.05, within the group (shock 4 h–0 h, Friedman test); †P < 0.05, between the groups (Mann-Whitney U-test).

Systemic and regional CO₂ exchange. Arterial PCO₂ increased gradually and comparably in the two groups. Contrary to partial tension of carbon dioxide, arterial CO₂ content decreased markedly in the epinephrine group compared with norepinephrine-treated animals (Fig. 2). Concomitantly, arterial plasma bicarbonate decreased by 30 ± 3% in the epinephrine group as opposed to stable bicarbonate in norepinephrine group (Fig. 2). Arterial CO₂ content was highly correlated with the bicarbonate concentration in the epinephrine (r² = 0.94) but not in the norepinephrine group (r² = 0.55) (Fig. 2).

Epinephrine infusion was associated with more than twofold increase of a portal venous-to-arterial PCO₂ gradient (from 6.9 ± 0.7 at baseline to 15.6 ± 2.5 mmHg at the end of the experiment, P < 0.05), whereas during the infusion of norepinephrine, the portal venous-to-arterial PCO₂ gap remained low and stable (8.3 ± 0.9 at baseline vs. 9.2 ± 0.6 mmHg the end of the experiment). There was, however, only a minor (25%) increase in portal venous-to-arterial CO₂ content gradient from 3.9 ± 0.3 to 4.9 ± 0.7 ml/dl in the epinephrine, compared with stable CO₂ content gradient over the prehepatic tissues in the norepinephrine group (from 4.4 ± 0.4 to 3.8 ± 0.4 ml/dl). In the epinephrine group, at the end of the experiment, 20 ± 1% and in the norepinephrine group, 23 ± 2% of the CO₂ content gradient over prehepatic tissues could be explained by the Haldane effect only (changing hemoglobin oxygen saturation over the tissue).

A more detailed evaluation of three regions within the visceral tissues revealed that epinephrine induced a marked increase in venous-to-arterial PCO₂ gradient in the stomach and a true increase in CO₂ content gradient with only 16 ± 3% accounted for by the Haldane effect compared with norepinephrine-treated animals in which both PCO₂ gradient and CO₂ content gradient remained low with 25 ± 1% accounted for by the Haldane effect (Fig. 3).

Mesenteric venous-to-arterial PCO₂ gradient had a tendency to increase (P = 0.075) twofold after 4 h of epinephrine, whereas norepinephrine was associated with a low mesenteric PCO₂ gradient. CO₂ content gradient was constant in both epinephrine and norepinephrine groups (Fig. 3). The Haldane effect explained 19 ± 1 and 25 ± 1% of CO₂ content gradient at the end of the experiment in the epinephrine and norepinephrine groups, respectively.

We detected a 75 ± 19% increase in portal venous-to-arterial PCO₂ gradient in the colon after 4 h of epinephrine infusion during endotoxin shock. Norepinephrine was associated with stable and low colonic venous-to-arterial PCO₂ gradient. In the epinephrine group venous-to-arterial CO₂ content gradient remained constant, whereas in the norepinephrine group CO₂ content gradient decreased by 15 with 20 ± 2% explained by the Haldane effect.

Systemic and regional lactate and pyruvate metabolism. During the 4-h period of epinephrine infusion, arterial lactate increased fivefold (P < 0.001), whereas norepinephrine did not change arterial lactate concentration. The gastric venous-to-arterial lactate gradient had a tendency to increase in animals treated with epinephrine (P = 0.075). Regional venous-to-arterial lactate gradients did not increase in any of the regions during infusion of norepinephrine (Table 3). Intraperitoneal lactate release occurred on the surface of the jejunum in the epinephrine group. Infusion of norepinephrine was not associated with intraperitoneal lactate release. (Fig. 4). Furthermore, epinephrine increased intraperitoneal glycerol concentration to
Fig. 2. Arterial partial tension of CO₂ (PCO₂), arterial CO₂ content, arterial (plasma) bicarbonate (HCO₃⁻), and CO₂ content-HCO₃⁻ concentration relation in epinephrine (black, n = 6)- or norepinephrine (gray, n = 6)-treated animals at the baseline, after hypotensive endotoxin shock was established (0 h) and after 4 h of vasopressor infusion (4 h). *P < 0.05, within the group (shock 4–0 h, Friedman test). §P < 0.05, between the groups (Mann-Whitney U-test).

Fig. 3. Regional gastric (top row), jejunal (middle row), and colonic (bottom row) venaarterial (v-a) CO₂ partial tension gradients (left panels), venoarterial CO₂ content gradients (middle panels), and proportional magnitude of Haldane effect (right panels) in epinephrine (black, n = 6)- and norepinephrine (gray, n = 6)-treated animals at the baseline, after hypotensive endotoxin shock was established (0 h) and after 4 h of vasopressor infusion (4 h). *P < 0.05, within the group (shock 4–0 h, Friedman test). §P < 0.05, between the groups (Mann-Whitney U-test).
518 ± 107 μM, whereas after norepinephrine infusion, glycerol remained low at 27 ± 8 μM (P < 0.05 between the groups).

The arterial lactate-to-pyruvate ratio as well as regional venous lactate-to-pyruvate ratios increased in all monitored areas in the epinephrine group, whereas there were no changes in lactate-to-pyruvate ratios in the norepinephrine group (Table 4).

**DISCUSSION**

The main findings of the present study may be summarized as follows. As expected, both epinephrine and norepinephrine reversed systemic hypotension induced by prolonged endotoxin challenge, and epinephrine infusion was associated with systemic hyperlactatemia and acidosis. Moreover, we assume that high systemic lactate concentration, apparently released from tissues other than the viscera, masked the effect of epinephrine on lactate metabolism in visceral tissues, and therefore, evaluation of tissue perfusion and metabolism by means of lactate only is limited. However, both systemic and regional venous lactate-to-pyruvate ratios (a marker of cytosolic redox status) do suggest that epinephrine may, indeed, have untoward effects on tissue perfusion and/or metabolism. In support of this concept is the increase of, not only regional venous-to-arterial PCO₂ gradients, but also CO₂ content gradients with a low magnitude of the Haldane effect. In addition, intraperitoneal lactate and glycerol release may indicate anaerobic visceral metabolism and degrading cellular membranes, respectively. We suggest that epinephrine does have "superselective" regional adverse effects on gastric perfusion and metabolism within an otherwise preserved splanchic circulation.

The limitations of this experiment must be considered: small sample size, endotoxin shock as a limited model of sepsis, and possible species differences. Furthermore, our protocol focused strictly on gradually developing hypotensive shock (mean arterial pressure > 60 mmHg, regardless of the other hemodynamic parameters) as a trigger for vasoactive drug intervention. Apparently by chance, the systemic and regional blood flow patterns varied between the groups at the time when it became necessary to start the vasopressor infusion. However, because cardiac output and splanchic blood flow were higher in the epinephrine group before drug intervention, it is likely that the effect, if any, of the different blood flow patterns would be favoring the epinephrine group. Secondly, all the metabolic markers indicate that the groups were comparable or favoring the epinephrine group at this time point. Finally, we cannot rule out the possibility that the increase in intraperitoneal lactate merely reflects systemic hyperlactatemia. Also, increasing glycerol may signal lipolysis rather than cellular membrane disintegration (7). More specifically, epinephrine may have stimulated glycerol transport from omental adipocytes through one of the aquaporins (15).

Both epinephrine and norepinephrine are widely used in septic shock to reverse hypotension and preserve perfusion pressure. Even recently, several investigators have addressed the question of whether epinephrine, as opposed to other vasoactive drugs, exerts harmful effects on tissue perfusion. This concern is on the basis of clinically common arterial hyperlactatemia and acidosis in conjunction with epinephrine infusion. Methods by which the assumed adverse effects have...
been evaluated are various, including measurements of lactate, lactate-to-pyruvate ratio, ketone-to-body ratio, tonometry, regional blood flow, oxygen transport, and tissue perfusion (16, 17, 21, 27). We wanted to add to the knowledge of the effects of both norepinephrine and epinephrine by rigorous regional venous sampling, intraperitoneal microdialysis, and above all, regional venous-to-arterial CO₂ content gradients with an estimation of the Haldane effect in a controlled randomized model of endotoxin shock.

**Systemic and regional blood flow and oxygen transport.** Systemic and splanchic blood flows increased during norepinephrine infusion as opposed to epinephrine, which had no major effect on either. On the basis of these findings, one could argue that systemic and splanchic perfusions were by and large maintained in both the epinephrine and norepinephrine groups. On the other hand, portal venous blood flow decreased in five of six animals, regardless of the direction of change in cardiac output during epinephrine infusion. Splanchnic and systemic oxygen consumption remained at the same level as before vasopressor infusions. However, systemic oxygen extraction increased up to 52% and splanchic oxygen extraction up to 78% during epinephrine infusion. Therefore, we suggest that oxygen delivery was nearly marginal, especially in parts of the splanchic vascular region when epinephrine was used for increasing perfusion pressure. Additionally, the calculated regional gastric RQ remained markedly higher in the epinephrine-treated animals. This adds to the findings supporting the assumed anaerobic metabolism in gastric tissue.

**Systemic and regional lactate, pyruvate, and CO₂.** It is well known that systemic hyperlactatemia may occur when epinephrine is used as treatment of hypotension or as an inotrope. Several investigators have implicated that this may not necessarily be a sign of tissue hypoperfusion or anaerobic metabolism. Indeed, hyperlactatemia may be related to aerobic glycolysis. Epinephrine stimulates the Na⁺-K⁺ pump activity; thus lactate is released from well-oxygenated tissue (14, 19). In the present experiment, we observed a high arterial lactate-to-pyruvate ratio in addition to arterial hyperlactatemia. This should, to our understanding, indicate cytosolic dysoxia within some vascular region of an organism. A closer look at the splanchic region revealed an increasing venous-to-arterial lactate gradient in the gastric wall, whereas prehepatic tissues as a whole seemed to turn to a negative gradient, indicating overall lactate uptake. Intraperitoneal lactate release occurred, but this may have merely reflected systemic hyperlactatemia. Intraperitoneal lactate concentrations never exceeded the arterial concentrations. Our major concern in this experimental setting was that systemic hyperlactatemia originating from tissues other than visceral may interfere with the simple measurement of regional lactate gradients. Moreover, compartmentalization of lactate metabolism may occur with simultaneous lactate uptake and lactate release (for review, see Ref. 3). Therefore, we calculated regional lactate-to-pyruvate ratios, which were higher in the epinephrine group over all the tissues we monitored, especially in the gastric wall. Because we have previously observed increasing uptake of pyruvate over visceral tissues in endotoxin shock (26), one may speculate whether regional venous lactate-to-pyruvate ratio is a reliable measure of tissue dysoxia.

Regional arterial-to-venous or mucosal-to-arterial PCO₂ gradients should reflect the adequacy of tissue perfusion (1, 6). In the present experiment, when epinephrine was used as a vasoconstrictor, we did observe increasing PCO₂ gradients in prehepatic tissues in general, but also in gastric, jejunal, and colonic tissue. The Haldane effect, however, may hinder the value of PCO₂ gradient as a marker of tissue perfusion and metabolism (8, 12). In other words, partial tension of CO₂ with higher hemoglobin oxygen saturation will be higher at any given CO₂ content. The majority of chemically bound forms of CO₂ is carried as bicarbonate in the blood. Accordingly, in this experiment, we observed a high correlation between decreasing CO₂ content and bicarbonate concentration. In addition to the Haldane effect, changes in hemoglobin concentration and pH, in effect, H⁺ concentration and binding of H⁺ to hemoglobin, have their impact in the PCO₂-CO₂ content relation. Also, the data herein support this concept, because from the baseline to the end of the experiment, systemic acidosis occurs, and thereby, the effect of high H⁺ concentration on the hemoglobin binding capacity of CO₂ increases. Thus the PCO₂-CO₂ content relationship changes, and high PCO₂ occurs during low CO₂ content. As for regional CO₂ content gradients, we observed a marked CO₂ content gradient increase only in the gastric wall. Concomitantly, the proportional magnitude of the Haldane effect diminished, indicating that increasing PCO₂ gradient over the gastric wall was indeed caused by either CO₂ stagnation or increasing production. Considering the concomitant increase in venous-to-arterial lactate gradient, and gastric venous lactate-to-pyruvate ratio, we interpret these findings as an indication of inadequate perfusion in gastric tissue when epinephrine is used to treat endotoxin-related hypotension. Finally, the marked increase in gastric RQ is consistent with the presence of regional hypoperfusion and hypoxia during epinephrine administration. Indeed, in these conditions, the RQ is better defined as an “exchange ratio,” because its value does not reflect a true RQ, but a series of gas exchange interactions, which commonly occur in low blood flow and tissue hypoxia (9). Another aspect and interpretation of the results is that the decreasing proportional magnitude of the Haldane effect over gastric tissue represents low-CO₂ buffering capacity of hemoglobin and other proteins as suggested by Giovannini et al. (10).

In conclusion, epinephrine induced a marked increase in lactate-to-pyruvate ratio in various visceral tissues. More importantly, increasing venous-to-arterial PCO₂ gradients indicated that visceral perfusion defect might be present. High CO₂ content gradients with decreasing Haldane effect and high regional venous lactate-to-pyruvate ratios together with high regional RQ pinpointed the most pronounced perfusion deficiency in the gastric wall when epinephrine, as opposed to norepinephrine, was used in endotoxin shock. In addition, intraperitoneal glycerol, a possible marker of cell membrane disintegration, increased when epinephrine was used as the vasopressor. As a clinical implication, we suggest that epinephrine may induce selective visceral tissue hypoperfusion and therefore should not be considered as a first line vasopressor.

**GRANTS**

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REFERENCES


