Vasopressin vs. norepinephrine in endotoxic shock: systemic, renal, and splanchnic hemodynamic and oxygen transport effects

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Guzman, Jorge A., Ariosto E. Rosado, and James A. Kruse. Vasopressin vs. norepinephrine in endotoxic shock: systemic, renal, and splanchnic hemodynamic and oxygen transport effects. J Appl Physiol 95: 803–809, 2003; 10.1152/japplphysiol.00017.2003.—The effects of intravenous norepinephrine (NE, group 1) and vasopressin (AVP, group 2) infusions on systemic, splanchnic, and renal circulations were studied in anesthetized dogs under basal conditions and during endotoxic shock. Under basal conditions, AVP infusion induced a 12 ± 7% drop in left ventricular stroke work, a 45 ± 5% fall in portal venous blood flow, and a 31 ± 13% decrease in intestinal mucosal blood flow (P < 0.05). AVP also decreased splanchnic oxygen delivery (D O2) and increased splanchnic and renal oxygen extraction significantly during basal conditions. Except for more pronounced bradycardia among animals in group 2, the systemic and splanchnic changes were comparable between study groups during endotoxic shock. AVP infusion restored renal blood flow and D O2 in endotoxic shock compared with animals resuscitated with NE, which had persistently low renal blood flow and D O2. Our data demonstrate that, in contrast to NE, administration of AVP effectively restores renal blood flow and D O2 with comparable systemic and splanchnic hemodynamic and metabolic effects in endotoxin-induced circulatory shock.

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time were displaced to expose the portal vein. After careful dissection, an 8-mm ultrasonic transit-time flow probe (model 8RS; Transonic Systems; Ithaca, NY) was placed around the vessel and secured with sutures to the adjacent lymphatic tissue. A 7-Fr catheter was advanced through the splenic vein to the portal vein for blood sampling and pressure (Ppv) recording. Its position was confirmed by palpating the tip of the catheter through the wall of the portal vein. Ileal mucosal blood flow was measured continuously by laser-Doppler flowmetry. Through a second small ileostomy, a laser-Doppler flow probe (type R; Transonic Systems) was sewn to the antimesenteric mucosal surface, and the ileostomy was closed. The manufacturer modified the probe so that it could be secured to the mucosa without compromising perfusion in the area of interest. This methodology does not provide measurements of microvascular perfusion in absolute terms, but it has been validated previously as a reliable means of estimating relative changes in mucosal perfusion (26). A 7-Fr curved-tip catheter was advanced though the femoral vein to the renal vein for blood sampling and pressure (Prv) measurements. After identification of the main renal artery (either side), a 2-mm ultrasonic flow probe (model 2RS; Transonic Systems) was placed around the vessel and secured with sutures to the adjacent adipose tissue. After hemostasis was ensured, the laparotomy was closed and the animals were allowed to stabilize for 45 min, during which time minute ventilation was readjusted, if necessary, to maintain arterial PaO2 at \( \sim 40 \) Torr. Core temperature was monitored via the thermistor of the pulmonary artery catheter and maintained at \( 38.0 \pm 0.5^\circ \text{C} \) by use of heating pads and overhead infrared lamps as necessary.

**Measurements and calculations.** Systemic arterial, mixed venous, portal, and renal venous blood samples were analyzed for PO2, PCO2, pH, and lactate concentration by using an automated blood-gas analyzer (model 260; Bayer Diagnostics; Medfield, MA). Total hemoglobin concentration and oxyhemoglobin fraction were assayed spectrophotometrically by using a multilength wavelength oximeter calibrated for canine blood (OSM-3; Radiometer; Westlake, OH). Cardiac output was measured by continuous thermodilution (Vigilance; Baxter Healthcare) and indexed to body mass \((\text{l} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\). Hemodynamic pressures (mmHg) were measured by fluid-coupled electronic transduction (Transpac; Abbott Laboratories; North Chicago, IL). Portal vein (Ppv) and renal artery (Qra) blood flow were measured ultrasonically (model T206; Transonic Systems) and indexed to total organ mass \((\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1})\) (20). Systemic arterial (CaO2), mixed venous (CmvO2), portal venous (CpvO2), and renal venous (CrvO2) blood oxygen content; systemic, splanchic, and renal oxygen extraction (Oex); and systemic, splanchic, and renal oxygen delivery (Do2) were calculated from gas tensions (Torr) and fractional oxyhemoglobin saturations of systemic arterial (PaO2 and SaO2, respectively), pulmonary arterial (PmvO2 and SmvO2, respectively), portal venous (PpvO2 and SpvO2, respectively), and renal venous blood (PrvO2 and SrvO2, respectively) and total hemoglobin concentration (Hb, g/dl) according to:

\[
\text{CaO}_2 = (\text{Hb} \times 1.39 \times \text{SaO}_2) + (\text{PaO}_2 \times 0.00314)
\]

\[
\text{CmvO}_2 = (\text{Hb} \times 1.39 \times \text{SmvO}_2) + (\text{PmvO}_2 \times 0.00314)
\]

\[
\text{CpvO}_2 = (\text{Hb} \times 1.39 \times \text{SpvO}_2) + (\text{PpvO}_2 \times 0.00314)
\]

Systemic Oex = \((\text{CaO}_2 - \text{CmvO}_2) / \text{CaO}_2\)

Splanchnic Oex = \((\text{CaO}_2 - \text{CpvO}_2) / \text{CaO}_2\)

Renal Oex = \((\text{CaO}_2 - \text{CrvO}_2) / \text{CaO}_2\)

Systemic Do2 = \(\text{CaO}_2 \times \text{Qra} / 100\)

Splanchnic Do2 = \(\text{CaO}_2 \times \text{Qpv} / 100\)

Renal Do2 = \(\text{CaO}_2 \times \text{Qra} / 100\)

Systemic (Rsys), mesenteric (Rspl), and renal (Rren) vascular resistance and left ventricular stroke work (LVSW) were calculated from heart rate \((f\), beats/min\), indexed blood flows, and intravascular pressures according to:

\[
\text{Rs} = (\text{Pao} - \text{Pcv}) \times 79.9/(\text{Qt})
\]

\[
\text{Rspl} = (\text{Pao} - \text{Ppv}) \times 79.9/(\text{Qpv})
\]

\[
\text{Rren} = (\text{Pao} - \text{Prv}) \times 79.9/(\text{Qra})
\]

LVSW = \(0.0136 \times (\text{Pao} - \text{Ppao}) \times \text{Qt} / f\)

**Experimental procedure.** After two consecutive sets of baseline measurements were obtained (vital signs; arterial, mixed venous, portal venous, and renal venous blood-gas, acid-base, and lactate values; portal, mucosal, and renal blood flow; and cardiac output), animals were assigned to receive either NE (group 1) or AVP (group 2). The study protocol consisted of two parts: During the first part, a continuous intravenous infusion of NE (norepinephrine bitartrate; Abbott Laboratories) at 0.2 \(\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) or AVP (V0377; Sigma-Aldrich; St. Louis, MO) at 0.08 U/min was started and maintained for 30 min, during which time measurements were obtained at 15-min intervals. The vasopressor infusion was then discontinued, and a washout period of 45 min was allowed to reverse the drug-induced hemodynamic changes. During this washout period, a set of measurements was obtained at 15 and 45 min after drug discontinuation. During the second part, the animals were subjected to endotoxic shock by intravenous infusion of 4 \(\text{mg} / \text{kg}\) *Escherichia coli* (serotype 0111:B4) lipopolysaccharide (LPS; Sigma-Aldrich) over 20 min followed by a resuscitation period of 30 min. Animals in both groups were resuscitated by use of an intravenous infusion of isotonic saline solution titrated to maintain Ppao within \(\pm 1\) mmHg of their initial baseline value. In addition to fluid resuscitation, a continuous intravenous infusion of NE (0.2 \(\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) ) was restarted in group 1 animals, whereas a continuous intravenous infusion of AVP (0.08 U/min) was restarted in group 2 animals. The vasopressor doses remained fixed as long as Pao increased to \(\geq 80\%\) of the pre-LPS value or were otherwise increased as necessary to achieve that minimum systemic arterial pressure. After the 30-min resuscitation period, vasopressors were discontinued and the animals were followed for another 15 min. Measurements were obtained at 10-min intervals during and at 15-min intervals after LPS infusion. Animals were then euthanized by intravenous injection of a saturated solution of potassium chloride.

**Statistical analysis.** Summary values are expressed as means ± SE. One-factor repeated-measures analysis of variance (ANOVA) was used to compare sequential measurements for each tested variable obtained between baseline and the end of the washout period and between the end of washout period and the end of resuscitation. Dunnett’s test was used to make further comparisons if ANOVA revealed significant differences. The control values for Dunnett’s test were designated as the last measurement obtained at the end of the washout period and the last measurement obtained at the end of the washout period. Two-way (one factorial and one repeated-measures factor) ANOVA was used to compare sequential measurements obtained between baseline and the end of the washout period and between the end of the washout period and the end of the experiment between the two.
groups. Probability values (2-tailed) of <0.05 were considered statistically significant. Statistical calculations were performed by using Excel (version 7.0; Microsoft; Redmond, WA) and SigmaStat (version 2.0; Jandel; San Rafael, CA) software.

RESULTS

Twelve animals were studied (6 per group). Mean weight was 22 ± 1 kg in both groups (P = not significant). Systemic hemodynamic and oxygen transport variables and arterial lactate concentrations over the course of the experiment for both groups are shown in Table 1. For each study group, Ppao was maintained at or near baseline levels throughout the experiments. Both vasopressors decreased heart rate during pre-LPS conditions. Although animals in group 2 had less tachycardia post-LPS and resuscitation, this was not statistically different from group 1. Similarly, variations in Pao throughout the study were comparable between groups. Both AVP and NE induced a significant drop in Qt and a concomitant increase in Rspl during pre-LPS conditions. Although the trends in these changes were more pronounced in animals receiving AVP, they were not statistically different from animals receiving NE. Changes in Qt during LPS infusion and resuscitation were similar in both study groups. Changes in systemic Do2 were not significantly different between groups throughout the experiment.

Changes in portal, intestinal mucosal, and renal blood flow are shown in Fig. 1. Portal blood flow decreased significantly shortly after AVP infusion was initiated and returned to near baseline levels by the end of the washout period. Concomitantly, AVP decreased portal venous pressure by 12 ± 9% and increased Rspl by 125 ± 9%. Contrary to animals in group 2, NE infusion increased portal venous pressure by 19 ± 5% and Rspl by 29 ± 13% (P < 0.05 for both compared with AVP). On the other hand, changes observed in portal blood flow and venous pressure and in Rspl post-LPS and during resuscitation were comparable between study groups. Mucosal blood flow changes paralleled changes in Qpv. Qra remained essentially unchanged during pre-LPS conditions, irrespective of study group, and decreased by 60% post-LPS. AVP resuscitation restored Qra to near-pre-LPS levels in contrast to NE, which had no effect on Qra. NE significantly increased Prv and Rren during resuscitation in comparison to AVP and end-of-washout levels.

Table 2 shows the results of selected splanchnic variables throughout the experiment. Pre-LPS, AVP induced a significant reduction in splanchnic Do2. This coincided with a significant decrease in Ppvo2 and an increase in splanchnic O2ex. Judging by the essentially unchanged PpCO2 and portal lactate concentration, the drop in splanchnic delivery Do2 was not of sufficient magnitude to cause a detectable shift to anaerobic metabolism. On the other hand, observed changes in splanchnic variables during LPS administration and resuscitation were all comparable between groups.

Selected renal variables are shown in Table 3. Similar to the effects noted on the splanchnic vasculature,
AVP administration induced a significant increase in renal oxygen consumption. This occurred without an adverse effect on renal baseline levels and resulted in lower renal O2ex compared with NE. Despite restoration of renal O2ex to near basal levels, renal lactate levels remained above pre-LPS values in both study groups. Post-LPS, AVP infusion restored renal O2ex to near basal levels and resulted in lower renal O2ex compared with NE. Despite restoration of renal O2ex in group 2, renal venous lactate levels remained above pre-LPS values in both study groups.

Fig. 1. Changes (△) in portal, intestinal mucosal, and renal blood flow during experiment. Group 1, ○, group 2, ●. Arrows indicate periods of vasopressor infusion. Shading indicates duration of endotoxin infusion. *P < 0.05 compared with baseline. †P < 0.05 compared with end of washout. ‡P < 0.05 between groups from time 0 to end of experiment. §P < 0.05 between groups from immediately preendotoxin to end of experiment.

Table 2. Portal venous blood-gas and lactate levels and selected splanchnic oxygen transport variables at major experimental time points

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>End of Drug</th>
<th>End of Washout</th>
<th>End of LPS</th>
<th>End of Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
</tr>
<tr>
<td>Ppvo2, Torr</td>
<td>57.0 ± 4.3</td>
<td>60.8 ± 6.1</td>
<td>58.1 ± 4.8</td>
<td>49.8 ± 3.5*</td>
<td>54.8 ± 4.5</td>
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<tr>
<td></td>
<td>45.1 ± 2.8</td>
<td>43.5 ± 3.3</td>
<td>44.1 ± 4.8</td>
<td>46.0 ± 2.4</td>
<td>49.6 ± 4.5</td>
</tr>
<tr>
<td>Portal venous lactate, mmol/l</td>
<td>2.2 ± 0.3</td>
<td>2.4 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>2.0 ± 0.2</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>Splanchnic DO2, ml-100 g^-1 min^-1</td>
<td>22.5 ± 1.2</td>
<td>20.6 ± 3.8</td>
<td>21.1 ± 3.3</td>
<td>11.9 ± 2.9*</td>
<td>20.9 ± 2.9</td>
</tr>
<tr>
<td>Splanchnic O2ex</td>
<td>0.21 ± 0.06</td>
<td>0.15 ± 0.05</td>
<td>0.19 ± 0.07</td>
<td>0.29 ± 0.05*</td>
<td>0.22 ± 0.07</td>
</tr>
</tbody>
</table>

Values are means ± SE. Ppvo2, portal venous blood PO2; PpvoCO2, portal venous blood PCO2; DO2, oxygen delivery. *P < 0.05 compared with baseline. †P < 0.05 compared with end of washout.
Table 3. Renal venous blood-gas and lactate levels and selected renal oxygen transport variables at major experimental time points

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Baseline</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Baseline</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Baseline</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Baseline</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrvO2, Torr</td>
<td>38.0 ± 2.3</td>
<td>54.9 ± 2.3</td>
<td>52.9 ± 4.3</td>
<td>47.3 ± 3.6</td>
<td>46.2 ± 2.5</td>
<td>48.0 ± 2.2</td>
<td>47.3 ± 3.6</td>
<td>46.1 ± 2.5</td>
<td>48.0 ± 2.2</td>
<td>46.2 ± 2.5</td>
<td>47.3 ± 3.6</td>
<td>46.1 ± 2.5</td>
<td>48.0 ± 2.2</td>
<td>46.2 ± 2.5</td>
<td>47.3 ± 3.6</td>
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<td>PrvCO2, Torr</td>
<td>4.9 ± 0.5</td>
<td>5.5 ± 0.2</td>
<td>4.9 ± 0.5</td>
<td>6.1 ± 0.6</td>
<td>5.5 ± 0.2</td>
<td>4.9 ± 0.5</td>
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<td>5.5 ± 0.2</td>
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<td>5.5 ± 0.2</td>
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<td>6.1 ± 0.6</td>
<td>5.5 ± 0.2</td>
<td>4.9 ± 0.5</td>
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<tr>
<td>Renal venous lactate, mmol/l</td>
<td>1.9 ± 0.1</td>
<td>0.1 ± 0.0</td>
<td>2.2 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>2.2 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>2.2 ± 0.0</td>
<td>0.1 ± 0.0</td>
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<td>2.2 ± 0.0</td>
<td>0.1 ± 0.0</td>
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<tr>
<td>Renal venous blood PO2, mmHg</td>
<td>100 ± 10</td>
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<tr>
<td>Renal venous blood PCO2, mmHg</td>
<td>4.9 ± 0.5</td>
<td>5.5 ± 0.2</td>
<td>4.9 ± 0.5</td>
<td>6.1 ± 0.6</td>
<td>5.5 ± 0.2</td>
<td>4.9 ± 0.5</td>
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<td>6.1 ± 0.6</td>
<td>5.5 ± 0.2</td>
<td>4.9 ± 0.5</td>
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<td>Renal O2ex, %</td>
<td>41.5 ± 8.5</td>
<td>43.0 ± 8.5</td>
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<td>Renal DO2, m l.min⁻¹ 100 g⁻¹</td>
<td>0.04 ± 0.01</td>
<td>0.08 ± 0.02</td>
<td>0.20 ± 0.04</td>
<td>0.08 ± 0.02</td>
<td>0.20 ± 0.04</td>
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<td>DISCUSSION</td>
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Although vasopressor therapy remains a mainstay of clinical treatment of septic shock, selection of the most appropriate pressor agent continues to be debated (31). Our data demonstrate that despite undesirable changes being induced in regional perfusion during basal conditions, AVP administration effectively restores renal blood flow during endotoxic-induced circulatory shock, with systemic and splanchnic effects that are comparable to NE.

Except for a more pronounced drop in Qt and a decrease in LVSW in animals receiving AVP, systemic circulatory effects during basal conditions were comparable between the two study groups. Because of a left shift of the heart rate-arterial pressure baroreflex curve, AVP is a weak vasopressor agent in animals with intact autonomic nervous system (15). This baroreflex effect explains why, under physiological conditions, rate-related decreases in Qt preclude vasoconstriction from yielding proportional increases in blood pressure. However, pentobarbital anesthesia and surgical stress can alter central nervous system reflexes and vascular reactivity and enhance vascular sensitivity to exogenous AVP administration, thus explaining the significant rise in Pao we observed after initiation of AVP (3, 24). On the other hand, the NE-induced increase in Pao pre-LPS was predictable because of its known vasoconstrictor and inotropic effects. To our knowledge, the effects of AVP on LVSW have not been previously described. During basal conditions, AVP induced a significant decrease in LVSW compared with NE. Differences in Rsys and Qt observed in our model can explain these findings, although AVP-induced coronary vasoconstriction and myocardial ischemia could also be involved (9, 14). Although hypothetical, the increase in renal oxygen extraction observed after AVP infusion could represent increased metabolic expenditure associated with AVP-induced activation of aquaporins in the distal nephron.

Attempting to avoid any confounding effects of drug titration on our results, our protocol allowed for fixed starting doses of either AVP or NE as long as Pao remained within 20% of pre-LPS values. The starting doses were chosen on the basis of previous clinical and experimental work (1, 14, 18, 19, 23, 29). Because the initial infusion dose increased Pao to the preselected target range, titration was not necessary in either group.

The effects of AVP administration on renal perfusion and oxygen transport were more striking during resuscitation from endotoxic shock. Although the renal effects of AVP are complex, the observed improvement in renal blood flow was likely secondary to nitric oxide-mediated afferent arteriolar vasodilatation and selective efferent arteriolar vasoconstriction (4, 25). However, with higher exogenous AVP doses, profound vasoconstriction and decreased renal blood flow should be expected (8). It could be postulated that a dose-response increase in renal blood flow might have been achieved if higher NE doses were used. Arguing...
against this, Treggiari and colleagues (28) demonstrated in a porcine model of endotoxin shock that the administration of NE to increase Pao to 20 mmHg above shock levels did not increase renal or splanchnic blood flows compared with lower doses. However, caution should be exercised in extrapolating this data to human sepsis.

Although the effects of AVP on Qpv and Ppv have been previously studied, the comparative effects of AVP and NE on the splanchnic circulation have not. During basal conditions, a significant decrease in portal and mucosal blood flow was observed during AVP infusion. This resulted in a marked reduction in splanchnic oxygen delivery accompanied by a rise in gut O₂-ex. However, the absence of changes suggestive of anaerobic metabolism, such as detectable increases in PpvCO₂ or portal venous lactate concentration place these hemodynamic findings in perspective and imply that regional oxygen delivery was not critically impaired. More importantly, during endotoxin shock we did not find appreciable differences in the effects of the two drugs on the splanchnic circulation at the doses studied.

Patterns of endogenous AVP release during clinical septic shock may differ from that observed in animal models. Although plasma levels of endogenous AVP appear to be inappropriately low in patients with septic shock, they remain persistently elevated for up to 12 h after shock induction in laboratory investigations (10, 27, 34). This difference may only reflect variations in the timing of AVP measurements with respect to the temporal stage of shock. Nevertheless, despite the likelihood that plasma levels of endogenous AVP were high in our model, we found that exogenous AVP administration has desirable vasoconstrictor effects in early endotoxic shock. Even in the presence of high endogenous AVP levels, this observation may be secondary to an AVP-induced enhancement of catecholamine-mediated vasoconstriction (7, 17). In addition, it is possible that AVP-induced dose-dependent blockade of K⁺-sensitive adenosine triphosphate channels may have helped to restore vascular tone in this model of septic shock (12, 32).

In summary, our data demonstrate that, in contrast to NE, exogenous AVP administration effectively restores renal blood flow and renal oxygen delivery with comparable systemic and splanchnic hemodynamic and metabolic effects in endotoxin-induced circulatory shock. These findings suggest that AVP alone, or perhaps in combination with other catecholamines, may enhance renal perfusion and facilitate the clinical management of septic shock.

REFERENCES


