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

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Submitted 8 January 2003; accepted in final form 17 April 2003

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 (DO2) 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 DO2 in endotoxic shock compared with animals resuscitated with NE, which had persistently low renal blood flow and DO2. Our data demonstrate that, in contrast to NE, administration of AVP effectively restores renal blood flow and DO2 with comparable systemic and splanchnic hemodynamic and metabolic effects in endotoxin-induced circulatory shock.

SEPTIC SHOCK IS A FORM OF distributive circulatory collapse caused by severe infections (6, 22). The hallmark of clinical septic shock is marked peripheral arteriolar vasodilatation, which results in low systemic vascular resistance, elevated cardiac output, hypotension, and inadequate tissue perfusion. Although the mechanism of the vasodilatation of septic shock remains incompletely understood, growing evidence implicates abnormalities of vasomotor regulation (11, 31). In addition, inappropriately low plasma vasopressin levels have been suggested as contributory to the hypotension in advanced vasodilatory septic shock (10).

Therapy for septic shock typically includes administration of intravenous fluids, antibiotics, and vasopressor agents (33). However, development of adrenergic hyposensitivity with gradual loss of catecholamine pressor responsiveness resulting in refractory hypotension is a frequent clinical challenge (2, 21). Arginine vasopressin (AVP), a potent endogenous vasoconstric-

tor, has been proposed as a vasopressor alternative or adjuvant to conventional catecholamine treatment for management of septic shock (16, 23, 29). In this setting, AVP infusion improved mean arterial blood pressure, facilitated withdrawal of catecholamine vasopressor support, and improved some measures of renal function (16, 23, 29). However, organ-specific heterogeneity in the vascular responsiveness to AVP has been described. For example, AVP causes cerebral and pulmonary vasodilatation (9, 30), whereas increases in systemic vascular resistance and reduction of skeletal muscle and skin blood flow have been described as well (5). The effects of AVP on intestinal and renal blood flow during sepsis-induced circulatory shock remain largely unknown.

We conducted the present animal investigation to assess the systemic, splanchnic, and renal hemodynamic and metabolic effects of AVP infusion compared with norepinephrine (NE) administration during basal conditions and during resuscitation from endotoxic shock.

MATERIALS AND METHODS

Surgical preparation. This protocol was approved by the Animal Investigation Committee of Wayne State University. Mongrel dogs (17–24 kg) were fasted overnight and then anesthetized with an intravenous injection of pentobarbital sodium (30 mg/kg), endotracheally intubated, and placed on mechanical ventilation (model MA-1; Puritan-Bennett; Carlsbad, CA) using a constant tidal volume (15 ml/kg). Respiratory rate was adjusted to achieve a baseline arterial PaCO2 of ~40 Torr. A femoral vein and artery were exposed by surgical dissection and cannulated with vascular catheters for continuous intravenous infusions of pentobarbital sodium (0.06 mg·kg⁻¹·min⁻¹) and normal saline solution, as well as for continuous monitoring of mean arterial blood pressure (Pao) and intermittent blood sampling for blood-gas, lactate, and hemoglobin assays. A balloon-tipped, multilumen, continuous-thermodilution pulmonary artery catheter (746HF8; Baxter Healthcare; Irvine, CA) was advanced through the femoral vein and guided into the pulmonary artery by pressure waveform analysis for measurement of cardiac output (Qt), central venous pressure (Pcv), pulmonary artery pressure (Ppa), and pulmonary artery occlusion pressure (Ppao). After a midline laparotomy, the duodenum and small intesti-
tine 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 PCO2 at 40 Torr. Core temperature was monitored via the thermistor of the pulmonary artery catheter and maintained at 38.0 ± 0.5°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 860; Bayer Diagnostics; Medfield, MA). Total hemoglobin concentration and oxyhemoglobin fraction were assayed spectrophotometrically by monitoring via the thermistor of the pulmonary artery catheter and the tip of the catheter through the wall of the portal vein. Rspl (Pao – Pcv) × 79.9/Qt

**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 μg·kg⁻¹·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 mg/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 ±1 mmHg of their initial baseline value. In addition to fluid resuscitation, a continuous intravenous infusion of NE (0.2 μg·kg⁻¹·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 ≥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 baseline 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 Rsys 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 groups, and decreased by 60% post-LPS. AVP resuscitation restored Qra to 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 PpCO2 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 $O_2_{\text{ex}}$ and a trend toward decreased $PrvO_2$ during pre-LPS conditions. This occurred without an adverse affect on renal $D O_2$, suggesting an increase in renal oxygen consumption. Post-LPS, AVP infusion restored renal $D O_2$ to near basal levels and resulted in lower renal $O_2_{\text{ex}}$ compared with NE. Despite restoration of renal $D O_2$ in group 2, renal venous lactate levels remained above pre-LPS values in both study groups.

**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>Group 1</th>
<th>Group 2</th>
<th>End of Drug</th>
<th>End of Washout</th>
<th>End of LPS</th>
<th>Group 1</th>
<th>Group 2</th>
<th>End of Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$PpvO_2$, Torr</td>
<td>57.0±4.3</td>
<td>49.8±3.5*</td>
<td>54.8±4.5</td>
<td>50.4±3.8*</td>
<td>47.8±3.4†</td>
<td>48.7±3.4†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$PpvCO_2$, Torr</td>
<td>58.1±2.8</td>
<td>50.4±2.3</td>
<td>67.6±3.8</td>
<td>65.6±3.3</td>
<td>58.3±3.9</td>
<td>57.8±3.9</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Portal venous lactate, mmol/l</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splanchnic $DO_2$, ml/min</td>
<td>122.5</td>
<td>20.6</td>
<td>21.1</td>
<td>11.9</td>
<td>20.9</td>
<td>18.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splanchnic $O_2_{\text{ex}}$</td>
<td>0.15</td>
<td>0.05*</td>
<td>0.15</td>
<td>0.05</td>
<td>0.2</td>
<td>0.37</td>
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<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. $PpvO_2$, portal venous blood $P O_2$; $PpvCO_2$, portal venous blood $P CO_2$; $D O_2$, oxygen delivery. *$P < 0.05$ compared with baseline. †$P < 0.05$ compared with end of washout. §$P < 0.05$ between groups from immediately preendotoxin to end of experiment.
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>Group 1</th>
<th>Group 2</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrvO2, Torr</td>
<td>54.9 ± 4.3</td>
<td>52.2 ± 3.8</td>
<td>45.3 ± 4.6</td>
<td>47.3 ± 3.6</td>
<td>47 ± 3.6</td>
<td>46 ± 3.6</td>
<td>47 ± 3.6</td>
<td>46 ± 3.6</td>
<td>47 ± 3.6</td>
<td>46 ± 3.6</td>
</tr>
<tr>
<td>PrvCO2, Torr</td>
<td>38.0 ± 2.3</td>
<td>42.0 ± 2.6</td>
<td>38.0 ± 2.3</td>
<td>42.0 ± 2.6</td>
<td>38.0 ± 2.3</td>
<td>42.0 ± 2.6</td>
<td>38.0 ± 2.3</td>
<td>42.0 ± 2.6</td>
<td>38.0 ± 2.3</td>
<td>42.0 ± 2.6</td>
</tr>
<tr>
<td>Renal venous lactate, mmol/l</td>
<td>1.9 ± 0.1</td>
<td>2.2 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>Renal O2ex</td>
<td>0.42 ± 0.04</td>
<td>0.32 ± 0.04</td>
<td>0.25 ± 0.03</td>
<td>0.32 ± 0.04</td>
<td>0.25 ± 0.03</td>
<td>0.32 ± 0.04</td>
<td>0.25 ± 0.03</td>
<td>0.32 ± 0.04</td>
<td>0.25 ± 0.03</td>
<td>0.32 ± 0.04</td>
</tr>
</tbody>
</table>

Values are means ± SE. PrvO2, renal venous blood PO2; PrvCO2, renal venous blood PCO2. *P < 0.05 compared with baseline. †P < 0.05 compared with end of washout.

DISCUSSION

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 endotoxin-induced circulatory shock, with systemic and splanchic 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 vasocostriction 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 splanchic 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 splanchic oxygen delivery accompanied by a rise in gut O₂ex. 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 splanchic 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 splanchic 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


