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

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SEPTIC SHOCK IS A FORM OF distributary 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 vasconstrictor, 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 PCO$_2$ 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...


tone 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
(Pv) 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 ileos-
tomy 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 abso-
lute 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 pres-
sure (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 ves-

tel 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 cath-
ether 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 ana-
lyzed for PO2, PCO2, pH, and lactate concentration by using an
automated blood-gas analyzer (model 860; Bayer Diagnos-
tics; Medfield, MA). Total hemoglobin concentration and oxy-
hemoglobin fraction were assayed spectrophotometrically by
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hemoglobin fraction were assayed spectrophotometrically by

- Systemic DO2 = CaO2 × Qt/100
- Splanchnic DO2 = CaO2 × Qpv/100
- Renal DO2 = CaO2 × 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

\[
\text{Rsys} = (Pao - Pcv) \times 79.9/Qt \\
\text{Rspl} = (Pao - Ppv) \times 79.9/Qpv \\
\text{Rren} = (Pao - Prv) \times 79.9/Qra \\
\text{LVSW} = 0.0136 \times (Pao - Ppao) \times Qt/f
\]

**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 bi-
tartrate; 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 mea-
surements were obtained at 15-min intervals. The vasopres-
sor infusion was then discontinued, and a washout period
of 45 min was allowed to reverse the drug-induced hemody-
namic changes. During this washout period, a set of measure-
ments was obtained at 15 and 45 min after drug discontinu-
ance. 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 pe-
riod 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 continu-
ous intravenous infusion of NE (0.2 μg·kg\(^{-1}\)·min\(^{-1}\)) was
restarted in group 1 animals, whereas a continuous intraves-
sor infusion of AVP (0.08 U/min) was restarted in group 2
animals. The vasopressor doses remained fixed as long as
Ppao increased to ≥80% of the pre-LPS value or were other-
wise increased as necessary to achieve that minimum sys-
temic arterial pressure. After the 30-min resuscitation pe-
riod, 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 in-
jection of a saturated solution of potassium chloride.

**Statistical analysis.** Summary values are expressed as
means ± SE. One-factor repeated-measures analysis of vari-
ance (ANOVA) was used to compare sequential measure-
ments for each tested variable obtained between baseline and
the end of the washout period and between the end of wash-
out period and the end of resuscitation. Dunnett’s test was
used to make further comparisons if ANOVA revealed signif-
ant 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 se-
quential measurements obtained between baseline and the end
of the washout period and between the end of the wash-
out period and the end of the experiment between the two

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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, PpaO2 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 Qs were similar to the effects noted on the splanchnic vasculature, unchanged Ppv CO2 and portal lactate concentration, 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 infusions 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 PpvCO2 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 O2ex and a trend toward decreased PrvO2 during pre-LPS conditions. This occurred without an adverse affect on renal DO2, suggesting an increase in renal oxygen consumption. Post-LPS, AVP infusion restored renal DO2 to near basal levels and resulted in lower renal O2ex compared with NE. Despite restoration of renal DO2 in group 2, renal venous lactate levels remained above pre-LPS values in both study groups.

Fig. 1. Changes (Δ) 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.

| Table 2. Portal venous blood-gas and lactate levels and selected splanchnic oxygen transport variables at major experimental time points |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable       | Baseline        | End of Drug     | End of Washout  | End of LPS      | End of Resuscitation |
|                | Group 1         | Group 2         | Group 1         | Group 2         | Group 1         | Group 2         |
| PpvO2, Torr    | 57.0 ± 4.3      | 60.8 ± 6.1      | 58.1 ± 4.8      | 49.8 ± 3.5      | 54.8 ± 4.5      | 63.8 ± 4.7      | 45.3 ± 4.4      | 44.2 ± 3.4      | 46.7 ± 3.4      | 48.4 ± 4.8      |
| PpvCO2, Torr   | 45.1 ± 2.8      | 43.5 ± 3.3      | 44.1 ± 4.8      | 46.0 ± 2.4      | 49.6 ± 4.5      | 45.1 ± 2.3      | 61.8 ± 5.9      | 55.4 ± 4.9      | 67.6 ± 6.8      | 53.5 ± 3.9      |
| Portal venous lactate, mmol/l | 2.2 ± 0.3      | 2.4 ± 0.2      | 2.1 ± 0.3      | 2.0 ± 0.2      | 1.9 ± 0.3      | 1.7 ± 0.2      | 3.4 ± 0.6      | 3.0 ± 0.3      | 3.7 ± 0.6      | 3.4 ± 0.6      |
| Splanchnic DO2 ml/100 g·min⁻¹ | 20.5 ± 1.2     | 20.6 ± 3.8     | 21.1 ± 3.3     | 11.9 ± 2.9      | 20.9 ± 2.9     | 18.8 ± 3.7     | 9.0 ± 1.3      | 7.6 ± 2.5      | 9.4 ± 0.7      | 8.4 ± 3.2      |
| Splanchnic O2ex | 0.21 ± 0.06     | 0.15 ± 0.05     | 0.19 ± 0.07     | 0.29 ± 0.05      | 0.22 ± 0.07     | 0.16 ± 0.03     | 0.31 ± 0.08     | 0.40 ± 0.04     | 0.42 ± 0.09     | 0.36 ± 0.07     |

Values are means ± SE. PpvO2, portal venous blood PO2; PpvCO2, 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>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>47.3 ± 3.6</td>
<td>54.0 ± 3.3</td>
<td>46.2 ± 2.8</td>
<td>53.1 ± 4.2</td>
<td>46.4 ± 2.5</td>
</tr>
<tr>
<td>PrvCO₂, Torr</td>
<td>38.0 ± 2.3</td>
<td>47.3 ± 3.6</td>
<td>45.0 ± 2.8</td>
<td>35.8 ± 2.5</td>
<td>45.0 ± 2.8</td>
<td>34.5 ± 2.5</td>
</tr>
<tr>
<td>Renal Venous lactate, mmol/l</td>
<td>0.10 ± 0.05</td>
<td>0.10 ± 0.05</td>
<td>0.10 ± 0.05</td>
<td>0.10 ± 0.05</td>
<td>0.10 ± 0.05</td>
<td>0.10 ± 0.05</td>
</tr>
<tr>
<td>Renal O₂ex, ml/min/100 g body wt</td>
<td>0.04 ± 0.04</td>
<td>0.08 ± 0.08</td>
<td>0.03 ± 0.03</td>
<td>0.09 ± 0.09</td>
<td>0.03 ± 0.03</td>
<td>0.09 ± 0.09</td>
</tr>
</tbody>
</table>

Values are means ± SE. PrvO₂, renal venous blood PO₂; PrvCO₂, renal venous blood PCO₂.

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 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 O$_2$ex. However, the absence of changes suggestive of anaerobic metabolism, such as detectable increases in PpvCO$_2$ 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