Beneficial Effects of Short-term Vasopressin Infusion during Severe Septic Shock


Background: Septic shock is associated with vasopressin deficiency and a hypersensitivity to its exogenous administration. The goal of the current study was to determine whether short-term vasopressin infusion in patients experiencing severe septic shock has a vasopressor sparing effect while maintaining hemodynamic stability and adequate end-organ perfusion.

Methods: Patients experiencing septic shock that required high-dose vasopressor support were randomized to a double-blinded 4-h infusion of either norepinephrine (n = 11) or vasopressin (n = 13), and open-label vasopressors were titrated to maintain blood pressure. To assess end-organ perfusion, urine output and creatinine clearance, gastric mucosal carbon dioxide tension, and electrocardiogram ST segment position were measured.

Results: Patients randomized to norepinephrine went from a median prestudy norepinephrine infusion of 20.0 μg/min to a blinded infusion of 17.0 μg/min at 4 h, whereas those randomized to vasopressin went from a median prestudy norepinephrine infusion of 25.0 μg/min to 5.3 μg/min at 4 h (P < 0.001). Mean arterial pressure and cardiac index were maintained in both groups. Urine output did not change in the norepinephrine group (median, 25 to 15 ml/h) but increased substantially in the vasopressin group (median, 32.5 to 65 ml/h; P < 0.05). Similarly, creatinine clearance did not change in the norepinephrine group but increased by 75% in the vasopressin group (P < 0.05). Gastric mucosal carbon dioxide tension and electrocardiogram ST segments did not change significantly in either group.

Conclusions: The authors conclude that short-term vasopressin infusion spared conventional vasopressor use and improved some measures of renal function in patients with severe septic shock.

EFFECTIVE cardiovascular support plays an essential role in the management of patients with septic shock. Oxygen delivery must be maintained above a critical threshold, and arterial pressure must exceed a level that allows appropriate distribution of cardiac output for adequate regional perfusion. Combinations of catecholamines, including norepinephrine, epinephrine, dopamine, and dobutamine, are currently used to achieve these goals. A number of studies favor norepinephrine as an effective vasopressor to maintain an adequate mean arterial pressure during septic shock. However, at high doses, norepinephrine has several potential adverse effects, including increased tissue oxygen demand, decreased renal and mesenteric blood flow, increased pulmonary vascular resistance, and arrhythmias resulting from β-adrenergic effects of norepinephrine. Over a short time, vascular responsiveness to norepinephrine and other catecholamines diminishes. Thus, potential problems arise when high-dose catecholamines are required to treat septic shock. Furthermore, mortality from septic shock remains high despite the availability of norepinephrine and other catecholamine vasopressors. Thus, it is conceivable that alternative vasopressors used alone or in combination with standard therapies may further improve organ perfusion and function.

In view of these concerns, vasopressin may be a rational additional therapy in septic shock. During hypotension, vasopressin normally helps maintain arterial blood pressure by acting as a potent vasoconstrictor. In contrast to cardiogenic and hypovolemic shock, during which vasopressin concentrations increase substantially, vasopressin concentrations are not elevated during established septic shock, which has been interpreted as vasopressin deficiency. During septic shock, there is enhanced vasopressin sensitivity despite this relative vasopressin deficiency. Thus, there is a physiologic rationale for restoring endogenous vasopressin concentrations during septic shock. As with all vasoconstricting agents, there is organ-specific heterogeneity in the vascular responsiveness to vasopressin. Vasopressin causes vasodilation of cerebral, coronary, and pulmonary vasculature in animal models and has little effect on afferent glomerular renal arterioles. Vasopressin significantly increases systemic vascular resistance overall by reducing blood flow to other organs, including skeletal muscle and skin. During cardiac arrest in humans, vasopressin increases cerebral blood flow. These organ-specific vascular effects of vasopressin may be beneficial compared with the effects of norepinephrine.

Accordingly, we tested the hypothesis that vasopressin infusion has a vasopressor-sparing effect while maintaining hemodynamic stability and adequate end-organ perfusion. To test this hypothesis, we compared the short-term physiologic effects of vasopressin versus norepinephrine.
epinephrine in patients who had hyperdynamic septic shock requiring high-dose vasopressors. The study drug (either vasopressin or norepinephrine) was titrated to maintain mean arterial pressure while we measured cardiac index and surrogate markers of specific organ perfusion, including urine output and creatinine clearance (renal), gastric–arterial carbon dioxide tension (Paco₂) gradient (gastric), and ST segment changes (heart).

**Materials and Methods**

Our goal was to determine whether short-term vasopressin infusion in patients experiencing severe septic shock has a vasopressor-sparing effect while maintaining hemodynamic stability and adequate end-organ perfusion using a prospective, double-blind, randomized, controlled study design. Either vasopressin or norepinephrine was infused for 4 h in patients with severe septic shock who required high-dose vasopressors despite adequate fluid resuscitation. This study was approved by the ethical review boards of St. Paul’s Hospital and Vancouver Hospital. Informed consent was obtained from the next of kin before study enrollment. Studies were conducted in the multidisciplinary intensive care units of these two university-affiliated tertiary care hospitals.

**Inclusion Criteria**

Patients with severe septic shock were recruited if they fulfilled the diagnosis of sepsis plus end-organ dysfunction unrelated to the primary septic focus, were adequately volume resuscitated, were on high-dose vasopressors, and had a pulmonary artery catheter in place. All patients were required to have a cardiac index greater than 2.01·min⁻¹·m⁻². Sepsis was defined using standard criteria (table 1), which, together with end-organ dysfunction, define septic shock. Adequate volume resuscitation was defined as 500 ml crystalloid bolus or 250 ml 5% albumin (or other equivalent colloid) and pulmonary capillary wedge pressure greater than 12 mmHg, failing to reverse hypotension and vasopressor requirement. High-dose vasopressor support was defined as follows: norepinephrine dose (micrograms per minute) plus epinephrine dose (micrograms per minute) plus dopamine dose divided by 4 (micrograms per kilogram per minute) greater than 5 for a minimum of 1 h. These criteria fulfill the definition of septic shock and approximately correspond to severe cardiovascular failure as defined by the Sequential Organ Failure Assessment score.

**Exclusion Criteria**

Patients were excluded if they were pregnant, had a hypersensitivity to exogenously administered vasopressin or norepinephrine, had acute coronary artery disease present or suspected, had acute mesenteric ischemia present or suspected, had severe hyponatremia (serum sodium <125 mmol/L) not responding to water restriction, or if the patient had Raynaud phenomenon, systemic sclerosis, or a vasospastic diathesis.

**Measurements**

All patients were mechanically ventilated, had ST segments monitored, had a systemic arterial catheter to measure mean arterial pressure, and had a pulmonary artery catheter to measure pulmonary artery pressure, pulmonary artery occlusion pressure, and thermodilution cardiac output in triplicate. Systemic vascular resistance index was calculated as the mean systemic arterial pressure minus right atrial pressure divided by cardiac index. Pulmonary vascular resistance index was calculated as the mean pulmonary artery pressure minus pulmonary artery occlusion pressure divided by cardiac index.

We measured gastric mucosal Paco₂ using a nasogastric tonometer (Tonometrics, Worcester, MA) after the correct position of the tonometer in the stomach was confirmed by radiography. The tonometer balloon was filled with 2.5 ml normal saline at room temperature 60 min before measurement. After this 60-min equilibration time, the saline sample was removed from the tonometer. The first 1 ml was discarded as catheter dead space, and blood gas analysis (IL-482; Radiometer, Copenhagen, Denmark) was performed on the remainder. Paco₂ measurements were temperature corrected to 37°C. Note that body temperature did not change during the course of this 4-h study. In four patients an automated gas tonometer system was used. The gradient between gastric mucosal and arterial Paco₂, ΔP_g-aCO₂, was calculated as gastric mucosal Paco₂ minus arterial Paco₂. Histamine receptor antagonists, which have no effect on the reproducibility of ΔP_g-aCO₂, were not routinely used.

Urine output per hour was averaged over 4 h before the study, and the repeat measure was averaged over 4 h during study drug infusion. Simultaneously in blood and in a 4-h urine collection, we measured creatinine, sodium, and osmolality at baseline and after the 4-h study drug infusion. Serum vasopressin concentration was measured using a radioimmunoassay.

**Patients**

Twenty-four patients were enrolled. The etiology of septic shock was documented infection in 22 patients...
Table 2. Baseline Comparison between the Vasopressin and Norepinephrine Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Norepinephrine Group (n = 11)</th>
<th>Vasopressin Group (n = 13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>68 [58, 75]</td>
<td>68 [58, 70]</td>
<td>0.89</td>
</tr>
<tr>
<td>% Female</td>
<td>27</td>
<td>23</td>
<td>0.81</td>
</tr>
<tr>
<td>APACHE II</td>
<td>24 [19, 30]</td>
<td>22 [20, 27]</td>
<td>0.75</td>
</tr>
<tr>
<td>Norepinephrine at baseline (μg/min)</td>
<td>20.0 [19.0, 26.4]</td>
<td>25.0 [20.0, 37.3]</td>
<td>0.35</td>
</tr>
<tr>
<td>Dopamine at baseline (μg · kg⁻¹ · min⁻¹)</td>
<td>2.7 [1, 3.5]</td>
<td>2.5 [0, 5.3]</td>
<td>0.91</td>
</tr>
<tr>
<td>Gram-positive cultures (%)</td>
<td>64</td>
<td>46</td>
<td>0.39</td>
</tr>
<tr>
<td>Gram-negative cultures (%)</td>
<td>36</td>
<td>38</td>
<td>0.92</td>
</tr>
<tr>
<td>Site of infection (%)</td>
<td>Lung</td>
<td>55</td>
<td>0.97</td>
</tr>
<tr>
<td>Abdomen</td>
<td>18</td>
<td>31</td>
<td>0.48</td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>13</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Values are median [25th percentile, 75th percentile], unless otherwise stated. P value refers to difference between the norepinephrine and vasopressin groups.

An initial set of measurements was taken. Patients were then randomized, using a computer-based procedure, to receive an infusion of either vasopressin or norepinephrine in a double-blind fashion for 4 h. During the initial 60 min of this 4-h infusion protocol, the study drug was titrated (infusion increased by 7 ml/h every 5–10 min), and the prestudy vasopressor agent (in all cases this was norepinephrine) was titrated down to maintain mean arterial pressure constant at a level determined by the attending intensive care physician. All other medications were held constant, dobutamine infusions were not adjusted, and mechanical ventilator settings and positive end-expiratory pressure were not changed. If the patient deteriorated while on the study drug, then unblinding of the study drug infusion was allowed at any time. However, as this never occurred, no patients were unblinded during the 4-h study period. At the end of the 4-h study drug infusion period, a second set of measurements was obtained to complete the study.

The concentrations of vasopressin and norepinephrine in the study drug infusions were chosen so that the starting volume of the randomized drug infusion was 7 ml/h. This corresponded to a vasopressin infusion of 0.01 units/min or a norepinephrine infusion of 2 μg/min. The maximum rate of infusion allowed in this study protocol was 56 ml/h of blinded study drug, which corresponded to a vasopressin infusion rate of 0.08 units/min or a norepinephrine infusion rate of 16 μg/min.

Statistical Analysis

A number of measured variables, including the primary outcome of norepinephrine dose, demonstrated skewed distributions. Therefore, we used a nonparametric statistical analysis. We tested for differences in baseline characteristics between experimental groups using a Mann-Whitney test for continuous variables and a chi-square test for proportions. We tested for changes from baseline to 4 h in outcome variables between the two study groups using a Kruskal-Wallis analysis of variance. All data are reported as median with 25th and 75th percentiles in parentheses in the text and tables. A threshold of 0.05 was used to assign statistical significance. This analysis was repeated using corresponding parametric tests (t test for baseline characteristics, analysis of variance for changes from baseline to 4 h for each variable) and identified exactly the same significant differences.

Results

Patient groups were well matched such that there was no significant difference between the norepinephrine and vasopressin groups at the prestudy baseline (table 2). Titration of the study drug (either norepinephrine or vasopressin) was accomplished within 1 h without difficulty while maintaining hemodynamic stability. Mean arterial pressure and cardiac index were unchanged after titrating prestudy norepinephrine down and the blinded vasopressin or norepinephrine infusion up in the two groups (table 3). Similarly, there was no change in heart rate, pulmonary artery occlusion pressure, systemic vascular resistance index, or pulmonary vascular resistance in either the norepinephrine or vasopressin group (table 3). In the norepinephrine group, the median prestudy norepinephrine infusion rate was 20.0 μg/min (25th percentile, 19.0 μg/min; 75th percentile, 26.4 μg/min) and, after titrating the prestudy norepinephrine down and the blinded norepinephrine infusion up, total norepinephrine infusion rate was 17.0 μg/min (12.0, 29.9 μg/min; fig. 1). The concordance of prestudy and 4-h norepinephrine infusion rate in the norepinephrine group further demonstrates constant hemodynamic support and status during titration of study drugs and titration down of prestudy norepinephrine.

In the vasopressin study group, the norepinephrine infusion decreased from 25.0 μg/min (20.0, 37.3 μg/min) prestudy to 5.3 μg/min (0, 8.0 μg/min; P < 0.001) at 4 h while maintaining mean arterial pressure (table 3). The median vasopressin infusion rate in this group was 0.06 units/min (0.05, 0.06 units/min). Thus, a vasopressin infusion significantly reduced the requirement for norepinephrine in these patients with severe septic shock.

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Vasopressin infusion doubled urine output ($P < 0.05$) from baseline to 4 h (fig. 2). In contrast, urine output did not change from baseline to 4 h in the norepinephrine group. The vasopressin-induced increase in urine output was associated with a significantly increased creatinine clearance in the vasopressin group ($P < 0.05$; fig. 3) with no change in fractional excretion of sodium (table 4).

Thus, vasopressin improved some aspects of renal function.

Vasopressin did not appear to have deleterious effects on other organ perfusion and function. Specifically, gastric–arterial PCO$_2$ gradient did not change significantly in the norepinephrine group from baseline (8.0 mmHg [3.2, 9.5 mmHg]) to 4 h (6.9 mmHg [5.4, 10.7 mmHg]) or in the vasopressin group from baseline (5.2 mmHg [4.0, 8.0 mmHg]) to 4 h (7.0 mmHg [4.0, 16.2 mmHg]). Similarly, vasopressin infusion did not alter the position of ST segments on the monitor electrocardiogram in the vasopressin group (ST position change of 0.0 mm [0.0, 0.0 mm]) or in the norepinephrine group (ST position change of 0.0 mm [0.0, 0.1 mm]), did not result in arrhythmias and did not change heart rate or the rate-pressure product (table 3). Thus, there was no evidence of coronary hypoperfusion.

Vasopressin, also called antidiuretic hormone, had no effect on sodium or osmolality in blood or urine during the short time course of this study in patients with septic shock (table 4). Baseline vasopressin concentration in the blood was no different between the two groups and was very low (1.3 ± 0.9 pg/ml) for the degree of hypotension of these patients. Vasopressin infusion significantly increased blood vasopressin concentration to 17.1 ± 3.9 pg/ml ($P < 0.001$), while norepinephrine did not alter vasopressin concentration (0.7 ± 0.5 pg/ml).

**Discussion**

The principal finding of this study is that vasopressin infusion spared conventional catecholamine use. Compared with a hemodynamically equivalent dose of nor-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Norepinephrine</th>
<th>Vasopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>97 (89, 110)</td>
<td>92 (83, 100)</td>
</tr>
<tr>
<td><strong>Mean arterial pressure (mmHg)</strong></td>
<td>68 (65, 70)</td>
<td>67 (61, 70)</td>
</tr>
<tr>
<td><strong>Cardiac index (l · min$^{-1}$ · m$^{-2}$)</strong></td>
<td>5.0 (3.8, 5.6)</td>
<td>4.0 (3.2, 5.1)</td>
</tr>
<tr>
<td><strong>Pulmonary artery occlusion pressure (cm H$_2$O)</strong></td>
<td>15 (14, 19)</td>
<td>19 (13, 22)</td>
</tr>
<tr>
<td><strong>Systemic vascular resistance index (dyn · cm$^{-5}$ · s · m$^2$)</strong></td>
<td>750 (681, 1173)</td>
<td>781 (662, 1263)</td>
</tr>
<tr>
<td><strong>Pulmonary vascular resistance index (dyn · cm$^{-5}$ · s · m$^2$)</strong></td>
<td>185 (116, 195)</td>
<td>163 (121, 188)</td>
</tr>
</tbody>
</table>

Values are median (25th percentile, 75th percentile). No statistically significant differences were observed in any of these variables between groups or over time.

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**Fig. 1.** Mean norepinephrine infusion rate of all patients at the prestudy baseline and after 4 h of study drug infusion is shown for both the norepinephrine and vasopressin groups. Titrating on the blinded control drug (norepinephrine) allowed an expected decrease in the unblinded clinical norepinephrine infusion so that the total (blinded plus unblinded) norepinephrine infusion did not change significantly. In contrast, vasopressin infusion had a marked sparing effect on norepinephrine use ($P < 0.001$). Error bars indicate the range from the 25th to 75th percentile.

**Fig. 2.** Mean urine output per hour for all patients in the 4 h before study and in the 4 h during study drug infusion is shown. Not surprisingly, urine output in the norepinephrine group did not change because prestudy norepinephrine was replaced with almost the same dose of blinded vasopressin infusion during the 4-h study. In contrast, urine output during a vasopressin infusion, which resulted in an equivalent hemodynamic state, more than doubled urine output ($P < 0.001$). Error bars indicate the range from the 25th to 75th percentile.
epinephrine, vasopressin infusion significantly increased
urine output and creatinine clearance. Vasopressin in-
fusion had no measurable adverse impact on the heart and
the gastric–arterial \( P_{CO2} \) gradient, while maintaining
mean arterial pressure and cardiac output in patients
with severe septic shock.

Cardiovascular dysfunction contributes importantly
to the high mortality rate (40–70%) of septic shock. Vasopressors play a critical role in the cardiovascular
management of sepsis, first, by increasing venous tone,
which increases venous return and, second, by increasing
arterial tone, which increases mean arterial pressure. 
\( \alpha \)-Adrenergic agonists have been the primary vasopres-
sors used in septic shock to maintain venous tone and
mean arterial pressure. However, \( \alpha \)-adrenergic agonists
have important potential problems. Little is known
about alternative vasopressors, such as vasopressin, in
managing clinical septic shock.

Vasopressin is a potentially interesting alternative
agent that has recently been used in septic and distrib-
utive shock. Vasopressin is an endogenous hormone secreted by the posterior pituitary. Activation of \( V_1a \) receptors on vascular smooth muscle is responsible for
vasoconstriction and increased systemic vascular resis-
tance. Increased vasopressin concentrations activate
baroreceptor reflexes, which reduce heart rate and car-
diac output, so that vasopressin has little effect on
arterial pressure at physiologic concentrations during
normal conditions. However, during hypotension and
ehypovolemia, vasopressin concentrations are
increased significantly, and vasopressin maintains arterial
blood pressure by acting as a potent vasoconstric-
tor. When baroreceptor reflexes are impaired, as they are during septic shock, the pressor activity of vasopressin is greatly enhanced. The lack of
change in heart rate in response to vasopressin infusion
that we and other investigators observed is consistent
with the hypothesis that impaired baroreceptor reflex activity may be the cause of enhanced sensitivity
to infused vasopressin.

Our study is currently the only randomized controlled
clinical trial comparing vasopressin to norepinephrine in severe
septic shock. There are only three previously reported
clinical studies of vasopressin in septic shock that
evaluated a total of 34 patients. One was a case series (n = 5), one was a case-control study (n = 19), and one was a randomized controlled trial (n = 10) using a placebo control group. These studies suggested that
vasopressin spared norepinephrine use, but none compared vasopressin versus norepinephrine directly. We chose to compare vasopressin to norepinephrine, rather
than compare vasopressin to placebo, because it is already
known that vasopressin has vasopressor properties in patients with septic shock, yet it is not
known whether vasopressin has significant beneficial
effects compared with conventional norepinephrine
therapy. Furthermore, comparison to norepinephrine
allowed us to use a double-blind study design, which we
believe is an important strength.

We observed low baseline serum vasopressin concen-
trations in these patients who had severe septic shock,
which is similar to results reported by Landry et al. These
investigators concluded that septic shock is associated
with vasopressin deficiency compared with similar
degrees of hypotension during cardiogenic shock, because
vasopressin concentrations were dramatically increased in patients who had cardiogenic shock. Decreased vasopressin concentrations observed during septic
shock could be a result of depletion of vasopressin
stores in the posterior pituitary, inhibition of

Table 4. Measures Related to Free Water and Sodium Handling

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Vasopressin</th>
<th>4 h</th>
<th>Vasopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeNa (%)</td>
<td>1.5 (0.3, 4.7)</td>
<td>2.1 (0.2, 5.2)</td>
<td>2.1 (0.2, 4.9)</td>
<td>2.8 (0.5, 7.2)</td>
</tr>
<tr>
<td>Serum sodium concentration (mm)</td>
<td>136 (135, 139)</td>
<td>135 (134, 138)</td>
<td>136 (133, 142)</td>
<td>137 (133, 140)</td>
</tr>
<tr>
<td>Urine sodium concentration (mm)</td>
<td>37 (12, 47)</td>
<td>32 (19, 52)</td>
<td>32 (19, 85)</td>
<td>40 (32, 88)</td>
</tr>
<tr>
<td>Plasma osmolality (mm)</td>
<td>297 (295, 310)</td>
<td>297 (292, 307)</td>
<td>306 (291, 314)</td>
<td>305 (292, 315)</td>
</tr>
<tr>
<td>Urine osmolality (mm)</td>
<td>333 (301, 359)</td>
<td>343 (309, 392)</td>
<td>360 (311, 378)</td>
<td>357 (318, 388)</td>
</tr>
</tbody>
</table>

Values are median (25th percentile, 75th percentile). No statistically significant differences were observed in any of these variables between groups or over time.
Vasopressin production (e.g., by increased nitric oxide production), or increased clearance of vasopressin. Increased clearance of vasopressin in septic shock is unlikely because a relatively low-dose infusion of vasopressin increased vasopressin concentrations in our patients and in other studies. The vasopressin infusion we used restored vasopressin concentrations to those observed in other types of hypotension. Thus, we consider low-dose vasopressin infusion during septic shock to be similar to hormonal replacement therapy as opposed to pharmacotherapy using catecholamines titrated to a blood pressure endpoint.

Vasopressin infusion allowed us to reduce norepinephrine infusion rates while maintaining blood pressure and cardiac output. The bedside critical care nurses were able to titrate on vasopressin and titrate down norepinephrine, while maintaining hemodynamic stability, without difficulty. The resulting cardiac output and pulmonary capillary occlusion pressure (as a measure of left ventricular preload) were unchanged. Lack of a difference in preload, afterload, and cardiac output indicate that there was no difference between the effect of vasopressin and norepinephrine on cardiac function.

The most striking additional finding of this study is that infusion of vasopressin, at a dose that did not alter mean arterial pressure or cardiac output while decreasing norepinephrine infusion, increased urine output and creatinine clearance. Previous studies of the physiology of vasopressin and norepinephrine suggest a plausible explanation. Norepinephrine increases resistance in both the afferent and efferent glomerular arterioles, which can contribute to decreased glomerular filtration rate, creatinine clearance, and urine output. In contrast, vasopressin increases resistance in efferent glomerular arterioles but has virtually no effect on afferent glomerular arterioles. Hence, for similar systemic hemodynamics, replacement of norepinephrine with vasopressin may result in increased glomerular perfusion pressure and flow and, hence, an elevated glomerular filtration rate because of beneficial vasoconstriction of efferent arterioles and relative vasodilation of afferent arterioles.

Vasopressin did not alter gastric–arterial PCO₂ gradients or ST segments on the monitor electrocardiogram. These observations suggest that vasopressin, in the low doses used here, did not result in overt gastric ischemia or coronary perfusion as a result of excessive arterial vasoconstriction. However, gastric–arterial PCO₂ gradients do not fully reflect splanchic blood flow, so that it is appropriate to interpret these results cautiously—particularly because vasopressin has been used for many years as a splanchic vasocostructor. Although the main vascular effect of vasopressin is vasocostriction, in low doses, vasopressin induces vasodilation in a number of vascular beds via oxytocin receptor stimulation, which results in endothelial nitric oxide release. The vasopressin-induced vasodilatory effects modulate the vasopressin vasoconstrictor effects so that low-dose vasopressin has less pronounced vasoconstrictor effects, particularly in coronary and cerebral arteries.

This study has a number of limitations. First, the study duration was brief, which we chose to focus on indices of hemodynamic stability and measures of organ function. Thus, these data do not address the issue of whether vasopressin increases survival of septic shock compared with conventional catecholamine therapy. However, the current randomized controlled trial demonstrates that it is feasible to institute low-dose vasopressin therapy, and vasopressin has potentially important physiologic benefits compared with norepinephrine. These results are a necessary starting point for a survival outcome randomized controlled trial. A further potential concern is that our sample size was limited to 24 patients. We chose this sample size to adequately address the current physiologic hypotheses. A much larger sample size will be required to demonstrate a survival benefit. Although the sample size is relatively small, this is the only randomized controlled trial of vasopressin versus norepinephrine, the largest randomized controlled trial of any type using vasopressin versus another agent in septic shock, and our patients were well matched at baseline. Finally, our entry criterion of a pulmonary artery wedge pressure greater than 12 mmHg may be regarded as somewhat low, although the median wedge pressure for the group was higher (table 3). Thus, the initial vasopressor requirement may have been lower if these patients had received more fluid.

In summary, vasopressin spares conventional vasopressor use in patients with severe septic shock and improves aspects of renal function when compared with norepinephrine. One interpretation of the beneficial effects of vasopressin may be that it reduced the norepinephrine dose and therefore reduced the detrimental effects of high-dose norepinephrine. The results of this very preliminary clinical study are promising, but a larger more definitive study is needed to determine whether vasopressin is safe and effective in terms of meaningful clinical outcomes.

References