In this article, I examine the role of exogenous arginine vasopressin in catecholamine-refractory septic shock. I review normal physiological mechanisms of endogenous vasopressin, describe clinical benefits and adverse reactions associated with use of exogenous arginine vasopressin, and provide recommendations for nursing care of patients who require the exogenous form.

Clinical Scenario
A 54-year-old man with staphylococcal septicemia is admitted to the intensive care unit for mechanical ventilation, hemodynamic support, and invasive monitoring. Despite antibiotic therapy, multiple fluid boluses, and the continuous administration of norepinephrine at 5 μg/min, his mean arterial pressure (MAP) remains less than 60 mm/Hg. After consultation with the interdisciplinary team, the decision is made to start an intravenous infusion of arginine vasopressin at a rate of 0.04 units/min.

The Challenge of Sepsis
Sepsis is a clinical syndrome characterized by a systemic inflammatory response to a focus of infection.1 In the United States, the annual cost of the treatment of sepsis is tens of billions of dollars,2 because sepsis is associated with an increase in hospital length of stay and higher rates of mortality.

* This article has been designated for CE credit. A closed-book, multiple-choice examination follows this article, which tests your knowledge of the following objectives:
1. Identify the pathophysiological changes associated with the systemic inflammatory response and sepsis
2. Describe the role of arginine vasopressin in catecholamine refractory septic shock
3. Discuss the management of septic shock according to the Surviving Sepsis Campaign Guidelines

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stay and hospital charges. Septic shock is characterized by hypotension and decreased organ perfusion that remain unresponsive to fluid replacement. Altered systemic vascular resistance in septic shock results in a redistribution of blood flow that leads to hypoperfusion, decreased oxygen delivery, and end-organ dysfunction. Despite advances in the understanding of the pathogenesis and treatment of sepsis, the worldwide incidence is increasing, and the mortality rate in patients with septic shock and organ dysfunction remains approximately 50%.

Refractory Septic Shock
Refractory septic shock is manifested by a decrease in vascular reactivity to both endogenous and exogenous catecholamines that results in vasodilatation and relative hypovolemia. Decreases in systemic vascular resistance and MAP associated with septic shock are initially managed with volume replacement and intravenous infusion of vasopressors such as the catecholamines norepinephrine and dopamine. This combination of therapy contributes to temporary increases in both systemic vascular resistance and MAP.

Advanced vasodilatory septic shock, however, is often refractory to both volume replacement and high doses of catecholamines. Patients with vasodilatory septic shock that remains unresponsive to aggressive fluid replacement and increases in catecholamine therapy continue to have an extremely high mortality rate (close to 100%). High doses of catecholamines are associated with several adverse effects and do not significantly improve outcome measures in refractory septic shock. The use of exogenous arginine vasopressin may be effective in stabilizing cardiovascular function in patients with refractory septic shock.

Endocrine Function of Endogenous Vasopressin
Endogenous arginine vasopressin maintains cardiovascular homeostasis by regulating serum osmolality and is thought to be a potent catecholamine-independent vasoconstrictor in states of physiological shock. Vasopressin is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and stored in granules within the posterior lobe of the pituitary gland. Endogenous arginine vasopressin is released into the circulation in response to various stimuli, most commonly in response to either an increase in serum osmolality or hypotension related to a severe decrease in blood volume.

Osmoreceptors, located centrally, in the periphery, and in specialized cells within the hypothalamus, are sensitive to hypertonic conditions and stimulate release of arginine vasopressin. Release of vasopressin is also regulated via impulses from baroreceptors located in the cardiac chambers, the aortic arch, and the carotid sinuses. Impulses from the carotid sinus and aortic arch reflect decreased arterial blood pressure and stimulate release of arginine vasopressin.

Additional endogenous substances that stimulate the expression of arginine vasopressin include acetylcholine, histamine, dopamine, angiotensin II, and prostaglandins. Expression of endogenous arginine vasopressin is inhibited by opioids, nitric oxide, atrial natriuretic peptide, and γ-aminobutyric acid.

Increased plasma levels of arginine vasopressin have been detected in patients with early-stage sepsis. In response to a stimulus, approximately 20% of stored arginine vasopressin is immediately released into the circulation, accounting for an initial surge. Subsequent release occurs at a reduced rate, reflecting the mechanism of synthesis, transport, and storage of the molecule, which take up to 2 hours. In patients with septic shock, however, the release of endogenous arginine vasopressin is inhibited by the production of nitric oxide, leading to a relative or absolute deficiency. In addition, circulatory cytokines produced as part of the inflammatory cascade downregulate receptors for arginine vasopressin on target organs, severely limiting the action of circulating arginine vasopressin.

The effects of circulating arginine vasopressin occur throughout the body (Table 1). Vasopressin is a direct constrictor of vascular smooth muscle via V1 receptors, but only at high

Table 1 Vasopressin receptors and actions

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Site</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>Vascular smooth muscle</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>V2</td>
<td>Distal nephrons</td>
<td>Water retention</td>
</tr>
<tr>
<td></td>
<td>Endothelium</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>V3</td>
<td>Pituitary gland</td>
<td>Release of corticotropin</td>
</tr>
</tbody>
</table>
plasma levels. Unlike catecholamines, arginine vasopressin induces both a negative chronotropic effect and a negative inotropic effect by indirectly enhancing parasympathetic and decreasing sympathetic tone. Vasopressin enhances the vasoconstrictive action of catecholamine vasopressors by enhancing the sensitivity of vascular smooth muscle to sympathetic stimulation. In addition, at normal plasma levels, arginine vasopressin causes less vasoconstriction in the coronary, cerebral, and mesenteric vasculature than the endogenous catecholamines epinephrine and norepinephrine do.

Vasopressin regulates both water retention and urine concentration by increasing the membrane permeability of renal collecting ducts, via activation of V2 receptors. In addition, arginine vasopressin selectively reduces blood flow in the inner medulla, leading to maximally concentrated urine. This property is reflected in the alternative nomenclature for arginine vasopressin: antidiuretic hormone.

Adrenal insufficiency has been detected in patients with sepsis and contributes to refractory shock. Vasopressin increases release of both cortisol and corticotropin via the V3 receptor. Vasopressin deficiency may then contribute to adrenal insufficiency in septic shock, and restoration of normal levels of arginine vasopressin may facilitate expression of endogenous adrenal hormones.

Clinical Guidelines for Management of Sepsis

In 2003, guidelines for the management of severe sepsis and septic shock were created under the auspices of the Surviving Sepsis Campaign. Although controversy exists regarding many aspects of management of patients with septic shock, control of the source of infection, volume replacement, and restoration of arterial blood pressure remain essential. Patients’ outcomes are influenced by appropriate and timely therapy within the first hours of development of the syndrome.

Currently, the catecholamines dopamine and norepinephrine are listed as first-line vasopressors to correct hypotension related to septic shock. Adverse reactions, such as tachycardia and splanchic hypoperfusion, can occur when epinephrine is used to treat hypotension related to septic shock.

Exogenous Vasopressin in Clinical Trials

During the past 9 years, the use of arginine vasopressin in patients with refractory septic shock has been evaluated in several clinical trials (Table 2). Exogenous arginine vasopressin has been administered to patients in vasodilatory septic shock to restore serum concentrations of arginine vasopressin, increase MAP, and decrease requirements for exogenous catecholamines. Early studies on the use of arginine vasopressin in the treatment of refractory septic shock were designed to evaluate baseline hemodynamic and metabolic effects. As the understanding of both the pathogenesis of sepsis and the cardiocirculatory effects of arginine vasopressin evolved, the focus of clinical trials included not only hemodynamics but also end-organ perfusion.
Hemodynamic Outcomes

In 4 studies,9,13,14,20 use of arginine vasopressin resulted in an increase in MAP without significant changes in cardiac index or heart rate. Conversely, in 3 studies4,18,19 cardiac index decreased significantly and MAP increased. In the largest published study21 to date of arginine vasopressin

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Type of study</th>
<th>Sample and treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landry et al22</td>
<td>1997</td>
<td>Case control</td>
<td>5 patients with septic shock Arginine vasopressin (AVP) at 0.04 units/min</td>
<td>Increase in arterial blood pressure Decrease or discontinuation of catecholamines Increase in urine output None</td>
</tr>
<tr>
<td>Landry et al22</td>
<td>1997</td>
<td>Matched cohort</td>
<td>19 patients with septic shock AVP at 0.04 units/min</td>
<td>Increase in arterial blood pressure Decrease or discontinuation of catecholamines Decrease in cardiac output</td>
</tr>
<tr>
<td>Malay et al9</td>
<td>1999</td>
<td>Randomized controlled trial with isotonic sodium chloride solution</td>
<td>10 patients with septic shock AVP at 0.04 units/min</td>
<td>Increase in arterial blood pressure Decrease or discontinuation of catecholamines None</td>
</tr>
<tr>
<td>Tsuneyoshi et al13</td>
<td>2001</td>
<td>Case control</td>
<td>16 patients with septic shock AVP at 0.04 units/min</td>
<td>Increase in arterial blood pressure Increase in urine output None</td>
</tr>
<tr>
<td>Patel et al8</td>
<td>2002</td>
<td>Double-blind, randomized controlled trial with norepinephrine</td>
<td>24 patients with septic shock AVP at 0.01-0.08 units/min</td>
<td>Increase in arterial blood pressure Decrease or discontinuation of catecholamines None</td>
</tr>
<tr>
<td>Dünser et al12</td>
<td>2003</td>
<td>Randomized controlled trial with norepinephrine</td>
<td>48 patients with vasodilatory shock AVP at 4 units/h</td>
<td>Increase in arterial blood pressure Decrease in end-organ perfusion, hepatic</td>
</tr>
<tr>
<td>van Haren et al14</td>
<td>2003</td>
<td>Case control</td>
<td>11 patients with septic shock AVP at 0.04 units/min</td>
<td>Increase in arterial blood pressure Decrease in end-organ perfusion, gastrointestinal mucosal</td>
</tr>
<tr>
<td>Klinzing et al18</td>
<td>2003</td>
<td>Case control</td>
<td>12 patients with septic shock AVP, with dose adjusted until patient weaned off of norepinephrine</td>
<td>Increase in end-organ perfusion, hepatosplanchnic Decrease in cardiac output Decrease in end-organ perfusion, gastrointestinal mucosal Bradycardia</td>
</tr>
<tr>
<td>Morelli et al4</td>
<td>2004</td>
<td>Case control</td>
<td>15 patients with septic shock 1-mg bolus of AVP analog (terlipressin)</td>
<td>Increase in arterial blood pressure Decrease or discontinuation of catecholamines Increase in urine output Increase in end-organ perfusion, gastrointestinal mucosal</td>
</tr>
<tr>
<td>Obritsch et al21</td>
<td>2004</td>
<td>Retrospective</td>
<td>102 patients with septic shock AVP at 0.11-0.17 units/min</td>
<td>Increase in arterial blood pressure Decrease or discontinuation of catecholamines Decrease in cardiac output Bradycardia</td>
</tr>
<tr>
<td>Albanèse et al20</td>
<td>2005</td>
<td>Randomized controlled trial with norepinephrine</td>
<td>20 patients with septic shock Boluses of AVP analog (terlipressin) vs norepinephrine</td>
<td>Increase in arterial blood pressure Increase in urine output Decrease in cardiac output Decrease in oxygen delivery</td>
</tr>
</tbody>
</table>
in the management of patients with septic shock, infusion of the vasopressin resulted in a rapid decrease in heart rate and an increase in MAP. In one study, higher cardiac index was associated with the use of arginine vasopressin in addition to high doses of norepinephrine in patients with vasodilatory shock. Several investigators who evaluated the use of arginine vasopressin in addition to norepinephrine infusions noted a decrease in norepinephrine requirements when vasopressin was given concomitantly. Overall, significantly enhanced MAP was noted by all investigators who evaluated the addition of low-dose arginine vasopressin in catecholamine-refractory septic shock.

In a study of hemodynamics in which norepinephrine was replaced with an escalating dose of arginine vasopressin, significant decreases in heart rate, cardiac index, and oxygen delivery occurred. In patients with catecholamine-refractory septic shock, intravenous bolus administration of a long-acting vasopressin analog (terlipressin) resulted in a decrease in catecholamine requirements and an increase in MAP, but significant decreases in cardiac index occurred.

**End-Organ Perfusion**

Several investigators evaluated end-organ perfusion as an outcome end point for use of arginine vasopressin. In 3 studies in which ST-segment analysis and detection of dysrhythmias were used to evaluate myocardial perfusion, no cardiovascular complications were detected. Significant increases in urine output occurred with the use of arginine vasopressin in several studies, but no changes in plasma levels of sodium or creatinine, base deficit, or osmolality have been detected. Most recently, no significant change in urine output was detected when arginine vasopressin was used in addition to other catecholamines in the treatment of septic shock.

The effects of arginine vasopressin on gastric and hepatosplanchnic blood flow have been inconsistent. Several studies included the measurement of gastric mucosal carbon dioxide gradient to indicate gastrointestinal perfusion. In the studies in which arginine vasopressin was used in addition to norepinephrine, gastrointestinal perfusion did not change significantly in one, was improved in one, and was significantly decreased in one. When adjusted doses of vasopressin were used to replace treatment with norepinephrine in patients with septic shock, hepatic blood flow increased, but gastrointestinal perfusion decreased. These findings most likely reflect an increase in blood flow to the viscera, but not necessarily to the hepatosplanchnic mucosal vasculature.

Dünser et al were the first to describe decreased perfusion to the hepatic microvasculature, as indicated by a significant increase in total bilirubin levels, with use of arginine vasopressin. Insignificant increases in serum lactate levels have also been detected during attempts to adjust doses of arginine vasopressin to replace norepinephrine, confirming microvascular hypoperfusion. Significant decreases or no change in arterial lactate levels also occurred when low-dose arginine vasopressin was infused along with norepinephrine.

In addition, platelet aggregation and thrombocytopenia have been detected when arginine vasopressin was added to norepinephrine in the management of septic shock; however, overall coagulation with the combination did not differ significantly from that associated with use of norepinephrine alone.

**Recommendations for Practice: Exogenous Arginine Vasopressin Clinical Benefits**

Until now, the recommendation to use arginine vasopressin in patients who have refractory septic shock despite adequate fluid volume replacement and high-dose vasopressor therapy has been based on case studies, expert opinion, and uncontrolled trials. The current recommendation is based on the premise that levels of endogenous arginine vasopressin are elevated in the early stages of septic shock and that plasma concentrations decrease to the normal range within 24 to 48 hours, leading to a relative deficiency of arginine vasopressin.

In the 3 clinical studies in which levels of endogenous arginine vasopressin were measured before therapy, all patients with septic shock had abnormally low levels, indicating an absolute deficiency of endogenous arginine vasopressin. A subsequent evaluation of plasma levels of vasopressin revealed that almost all patients in the early stages of septic shock have elevated levels of endogenous arginine vasopressin and that in the late stages, the levels have decreased to a relative deficiency in one third of patients. Additional evidence exists that downregulation of vasopressin receptors influences the effects of endogenous circulatory arginine vasopressin.
The results of 2 small double-blinded, randomized, controlled studies; several small prospective, case-controlled studies; and 1 large retrospective study have indicated that the use of low-dose arginine vasopressin restores MAP and decreases other catecholamine requirements when added to norepinephrine in the treatment of refractory septic shock. In another study of patients with vasodilatory shock, both with and without sepsis, adding arginine vasopressin to norepinephrine treatment had beneficial overall hemodynamic effects.

Exogenous arginine vasopressin as a continuous infusion at rates up to 0.04 units/min should be considered in patients with septic shock that remains refractory to fluid replacement and continuous administration of catecholamines. Increases in MAP and the catecholamine-sparing effects of arginine vasopressin should be detectable within 1 hour of administration.

Adverse Effects

Serious adverse reactions to the use of arginine vasopressin in septic shock have been described. In particular, replacement of first-line vasopressor agents with arginine vasopressin and continuous infusions of arginine vasopressin in excess of 0.04 units/min maintain cardiocirculatory homeostasis at the cost of decreased tissue perfusion and end-organ dysfunction. Although exogenous catecholamine requirements often decrease with the use of arginine vasopressin, no evidence exists that arginine vasopressin should replace a catecholamine as a first-line agent in the treatment of refractory septic shock or should be infused at rates greater than 0.04 units/min. An ongoing study (the VASST trial) comparing use of arginine vasopressin with use of norepinephrine in the initial maintenance of homeostasis in septic shock may reveal new data. However, whether the hemodynamic improvements in septic shock are a result of a synergistic effect of arginine vasopressin plus catecholamines or of arginine vasopressin alone has not yet been established.

Patients who require arginine vasopressin for maintenance of MAP in septic shock are doubly vulnerable to hypoperfusion and must be monitored for alterations in tissue perfusion and end-organ dysfunction.

Arginine vasopressin should be used with caution in patients with low cardiac output or cardiac dysfunction, because the negative inotropic and chronotropic effects of the agent can be marked. Because patients in septic shock often have increased cardiac output and heart rate, the clinical importance of decreases in cardiac output and heart rate warrants further study. Recent myocardial ischemia and chronic heart failure are exclusion criteria in the VASST trial, and researchers recommend that arginine vasopressin be used with caution in patients with a cardiac index less than 2.5 to 3.0. Patients with cardiac dysfunction who require arginine vasopressin for management of septic shock should be monitored for acute signs and symptoms of decreased cardiac output.

Unlike the effects of catecholamines, the effects of arginine vasopressin on microvascular perfusion are not well described. In studies in which measurement of the gastric mucosal carbon dioxide gradient was used as an indication of splanchnic perfusion, results were inconsistent. Increases in total bilirubin levels and elevated serum lactate levels have been detected in patients who required arginine vasopressin for vasodilatory shock. Furthermore, ischemic skin lesions, myocardial ischemia, and decreased myocardial ischemia are exclusion criteria in the VASST trial, and researchers recommend that arginine vasopressin be used with caution in patients with a cardiac index less than 2.5 to 3.0. Patients with cardiac dysfunction who require arginine vasopressin for management of septic shock should be monitored for acute signs and symptoms of decreased cardiac output.

Distinguishing between the clinical use of exogenous catecholamines and the clinical use of arginine vasopressin in the management of septic shock is vital. Furthermore, the appropriate dose of exogenous arginine vasopressin for management of catecholamine-refractory septic shock is not the same as the recommended dose for the treatment of cardiac arrest. Simply put, in patients with catecholamine-refractory septic
symptoms of decreased cardiac output, vasopressin, particularly patients who require exogenous arginine vasopressin and end-organ perfusion. Patients Adverse reactions associated with use of vasopressin in the treatment of septic shock should be limited to continuous infusions of no more than 0.04 units/min and should be confined to patients with catecholamine-refractory septic shock. Adverse reactions associated with the use of arginine vasopressin include decreases in cardiac index, heart rate, and end-organ perfusion. Patients who require exogenous arginine vasopressin, particularly patients with cardiac dysfunction, require vigilant monitoring for signs and symptoms of decreased cardiac output and alterations in tissue perfusion.

References
CE Test  Test ID C066: Role of Exogenous Arginine Vasopressin in the Management of Catecholamine-Refractory Septic Shock

Learning objectives: 1. Identify the pathophysiological changes associated with the systemic inflammatory response and sepsis. 2. Describe the role of arginine vasopressin in catecholamine refractory septic shock. 3. Discuss the management of septic shock according to the Surviving Sepsis Campaign Guidelines.

1. Which one of the following is not a consequence of altered systemic vascular resistance in septic shock?
   a. Hypoperfusion  
   b. Decreased oxygen delivery  
   c. Decreased cardiac output  
   d. End-organ dysfunction

2. Which of the following is the best way to initially manage decreased systemic vascular resistance and mean arterial pressure associated with septic shock?
   a. Intravenous (IV) infusion of epinephrine and corticosteroids  
   b. IV infusion of norepinephrine and dopamine  
   c. Volume replacement and IV infusion of epinephrine  
   d. Volume replacement and IV infusion of norepinephrine and dopamine

3. What is the approximate mortality rate of patients with vasodilatory septic shock that remains unresponsive to aggressive fluid replacement and increases in catecholamine therapy?
   a. 45%  
   b. 76%  
   c. 94%  
   d. 100%

4. Which one of the following statements best describes the action of arginine vasopressin?
   a. Acts on cells to maintain cell permeability  
   b. Acts on the kidney tubules to reabsorb water  
   c. Maintains cardiovascular homeostasis by regulating serum osmolality  
   d. Maintains glycemic state

5. Arginine vasopressin is released into the circulation in response to which stimuli?
   a. Increased serum osmolality and hypotension  
   b. Tachycardia and hypotension  
   c. Decreased renal blood flow and hypotension  
   d. Serum osmolality and tachycardia

6. Which one of following endogenous substances does not stimulate the expression of arginine vasopressin?
   a. Histamine  
   b. Nitric oxide  
   c. Atrial natriuretic peptide  
   d. Prostaglandins

7. Which one of the following substances inhibits the release of arginine vasopressin?
   a. Histamine  
   b. Dopamine  
   c. Atrial natriuretic peptide  
   d. Prostaglandins

8. What percentage of the stored arginine vasopressin is immediately released in response to stimulus like early stage sepsis?
   a. 5%  
   b. 20%  
   c. 39%  
   d. 80%

9. Which one of the following statements best describes vasopressin action on catecholamine vasopressors?
   a. Vasopressin enhances the release of cortisol.  
   b. Vasopressin reduces the release of thyroid hormone to assist with increased metabolic activity.  
   c. Vasopressin enhances the sensitivity of vascular smooth muscle to sympathetic stimulation.  
   d. Vasopressin enhances the release of atrial natriuretic peptides.

10. Which one of the following is not a recommendation of the Surviving Sepsis Campaign guidelines for the treatment of severe sepsis and septic shock?
    a. Control the source of infection  
    b. Volume replacement  
    c. Restoration of arterial blood pressure  
    d. Thyroid hormone replacement

11. Which one of the following is not a consequence of high doses of vasopressors?
    a. Refractory hypertension  
    b. Increased pulmonary vascular resistance  
    c. Increased tissue oxygen demand  
    d. Dysrhythmias

12. What is the recommended dose of vasopressin according to the Surviving Sepsis Campaign guidelines?
    a. >0.04 units/min  
    b. 0.4 units/min  
    c. ≤0.04 units/min  
    d. 4.0 units/min

13. Which one of the following is not an adverse reaction associated with arginine vasopressin?
    a. Increased cardiac output  
    b. Decreased heart rate  
    c. Decreased end-organ perfusion  
    d. Decreased cardiac index

Test answers: Mark only one box for your answer to each question. You may photocopy this form.

1. [ ] a [ ] b [ ] c [ ] d
2. [ ] a [ ] b [ ] c [ ] d
3. [ ] a [ ] b [ ] c [ ] d
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9. [ ] a [ ] b [ ] c [ ] d
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11. [ ] a [ ] b [ ] c [ ] d
12. [ ] a [ ] b [ ] c [ ] d
13. [ ] a [ ] b [ ] c [ ] d

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Role of Exogenous Arginine Vasopressin in the Management of Catecholamine-Refractory Septic Shock
Christopher S. Lee

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