Vasopressin in the Cardiac Surgery Intensive Care Unit
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The care of patients who have undergone cardiac surgery is often complicated by profound hypotension (mean arterial pressure [MAP] ≤ 70 mm Hg). Often, shock after cardiotomy is associated with low cardiac output syndrome (also termed low-output heart failure). These patients are best treated with volume resuscitation, afterload reduction, and inotropic support. However, some patients remain hypotensive because of systemic vasodilation. Recent clinical data suggest that a physiological deficiency in levels of the hormone vasopressin, also known as antidiuretic hormone, may be the cause of vasodilatory shock after cardiotomy.\(^1\) Thus, vasopressin replacement is an intuitively attractive therapy for hypotension that occurs after cardiopulmonary bypass. In this review, we outline the pathophysiology of vasodilatory hypotension in postoperative cardiac surgery patients, discuss the physiological role of endogenous vasopressin, explore the clinical basis for vasopressin replacement, and review pharmacological and administration guidelines.

Pathophysiology of Vasodilatory Shock After Cardiopulmonary Bypass

Exposure of blood to abnormal surfaces and conditions that exist during cardiopulmonary bypass initiates a systemic inflammatory response. Kirklin\(^2\) describes a “whole body inflammatory response” involving humoral amplification of the coagulation cascade, the kalikrein system, the fibrinolytic system, and the complement cascade. It is hypothesized that the deleterious effects of cardiopulmonary bypass are related to the activation of these proinflammatory pathways. Adverse effects of bypass include pulmonary insufficiency, extracellular accumulation of fluid (third spacing), renal dysfunction, hyperthermia, coagulopathy, and vasomotor dysfunction.\(^3\)
In a recent study, Argenziano et al\textsuperscript{4} found that nearly 10\% of cardiac surgery patients experience vasodilatory hypotension after bypass that is not associated with primary cardiogenic shock or sepsis. Vasodilatory shock is a central component in the systemic inflammatory response.\textsuperscript{5} The hallmarks of vasodilatory shock include decreased MAP, organ hypoperfusion, and lactic acidosis.\textsuperscript{6} A substantial decrease in systemic vascular resistance (SVR) leads to a generalized maldistribution of blood flow and ultimately to end-stage organ failure.\textsuperscript{7} Interestingly, in instances of prolonged hypotension after bypass, vascular smooth muscle becomes poorly responsive to circulating catecholamines. This decreased response may be due to the down-regulation of adrenergic receptors.\textsuperscript{5,8}

**Physiological Role of Endogenous Vasopressin**

Vasopressin, also termed antidiuretic hormone or arginine vasopressin, is a peptide hormone produced in the hypothalamus and stored in the posterior lobe of the pituitary gland. Vasopressin affects numerous organ systems, including the brain, where it acts as a neurotransmitter mediating thermoregulation, nociception, and release of adrenocorticotropic hormone.\textsuperscript{9,10} In the pulmonary vasculature, moderate doses of vasopressin cause vasodilatation, whereas higher doses stimulate vasoconstriction.\textsuperscript{11} Vasopressin also has several effects on thrombosis and hemostasis, including promotion of platelet aggregation and release of both factor VIIIa and von Willebrand factor from the vascular endothelium.\textsuperscript{12,13} In the distal tubule and collecting duct of the kidney, vasopressin stimulates water resorption so that concentrated urine is produced.\textsuperscript{14} High concentrations of vasopressin stimulate smooth muscle contraction in both the uterus and the gastrointestinal tract and promote hepatic glycogenolysis.\textsuperscript{15,16} High concentrations of vasopressin also have a profound effect on vascular smooth muscle cells, resulting in vasoconstriction.\textsuperscript{17}

Crucial in the regulation of fluid balance, vasopressin is released in response to a decrease in blood volume or an increase in osmolarity.\textsuperscript{5} The principal end-organ effects are mediated by 2 distinct receptor subtypes. The V\textsubscript{1} receptor is present on vascular smooth muscle cells throughout the body, particularly in skin, skeletal muscle, and thyroid gland vasculature.\textsuperscript{18} The direct vasopressor effects are a result of V\textsubscript{1}-mediated intracellular signal transduction. G protein-coupled activation of phospholipase C results in the release of calcium from the sarcoplasmic reticulum and a subsequent increase in peripheral resistance.\textsuperscript{19} Of note, the majority of end-organ effects are mediated by the V\textsubscript{1} receptor. A second receptor, the V\textsubscript{2} receptor, is present in the distal and collecting tubules of the glomeruli and promotes water resorption. These effects are mediated by an increase in intracellular levels of cyclic adenosine monophosphate and ultimately by activation of protein kinase A.\textsuperscript{14} By increasing water channel-containing vesicles to the apical membrane, protein kinase A increases membrane permeability and eventually extracellular fluid volume.\textsuperscript{19} A third receptor, the V\textsubscript{3} receptor, is localized in the posterior lobe of the pituitary gland. Although signal transduction involves both activation of G proteins and increases in the levels of cyclic adenosine monophosphate, its physiological role is unknown.\textsuperscript{20}

Under normal physiological conditions, concentrations of endogenous vasopressin are below the vasoactive range. Although low-dose exogenous vasopressin has little pressor effect in subjects with normal hemodynamic status, high-dose vasopressin replacement markedly increases MAP when the cardiac baroreflex is impaired, as occurs in septic shock or autonomic insufficiency.\textsuperscript{20} High-dose vasopressin directly stimulates contraction of vascular smooth muscle, causing vasoconstriction of capillaries and small arterioles. When antidiuresis is advantageous, as in diabetes insipidus, exogenous vasopressin can lead to conservation of up to 90\% of the water that might otherwise be excreted in the urine. Importantly, the doses used for antidiuresis are markedly lower than those needed for pressor support. Antidiuresis can be accomplished with single doses of 5 to 10 U, whereas the vasoconstrictive effects require up to 0.5 U every 5 minutes by continuous intravenous infusion.

**Clinical Basis for Vasopressin Replacement**

Recently, Landry et al\textsuperscript{20} made an interesting observation in patients with sepsis. These investigators found that plasma vasopressin levels were inappropriately low in patients with refractory hypotension. In that study, exogenous vasopressin replacement markedly increased arterial pressure (systolic/diastolic) and SVR. Landry et al concluded that when pretreatment levels are inappropriately low, a vasopressin deficiency may contribute to refractory hypotension in septic shock.

Argenziano et al\textsuperscript{1} randomized 10 patients who met eligibility requirements for a diagnosis of shock after cardiopulmonary bypass: an MAP of 70 mm Hg or less despite norepinephrine infusion in excess of 8 \(\mu\)g/min and a cardiac index (calculated as cardiac output in liters per minute divided by body surface area in square meters) of 2.5 with a left ventricular assist device (LVAD) in place. Patients were randomized 5
minutes after cardiopulmonary bypass was discontinued to receive either vasopressin at 0.1 U/min (n = 5) or a placebo of isotonic sodium chloride solution (n = 5). Additionally, plasma samples were taken at the time of randomization to measure the level of endogenous vasopressin. After 15 minutes, subjects receiving the placebo had no significant change in arterial pressure, SVR, or catecholamine dose. Three subjects who initially received placebo were subsequently treated with vasopressin. In the 8 patients who received vasopressin, MAP increased from 61.3 to 87.4 mm Hg, and SVR increased from 845 to 1284 dyne sec cm⁻⁵. All patients given vasopressin were successfully weaned off catecholamines. Of the 8 subjects who received vasopressin therapy, 5 had endogenous levels of vasopressin less than 20 pg/mL, far less than the expected range for after cardiopulmonary bypass (100-200 pg/mL). No vasopressin-related complications were reported.

Chart review at Columbia-Presbyterian Medical Center in New York yielded 50 patients undergoing LVAD placement who had had vasopressin administered in the operating room or the intensive care unit within 24 hours of implantation. All patients had an MAP less than 60 mm Hg and a depressed SVR despite catecholamine support. Administration of vasopressin at a rate of 0.09 U/min increased MAP from 58 to 75 mm Hg, increased SVR from 920 to 1200 dyne sec cm⁻⁵, and decreased norepinephrine administration by 32%. No change in LVAD flow was noted, and no complications were reported.

In a more recent study, Argenziano et al examined use of vasopressin in the management of vasodilatory hypotension after orthotopic heart transplantation. Of 175 patients who underwent orthotopic heart transplantation, 20 met the criteria for hypotension after cardiopulmonary bypass. Infusion of vasopressin at a rate of 0.1 U/min significantly increased MAP (from 60 to 86 mm Hg) and decreased norepinephrine requirements. No complications were linked to vasopressin therapy directly, although 1 patient died on postoperative day 21 of hemorrhagic shock and multiple organ failure.

Finally, in a third study, Argenziano et al prospectively studied several preoperative variables in a group of 145 patients that included both patients undergoing orthotopic heart transplantation and patients having an LVAD implanted. The authors noted that low ejection fraction and preoperative use of an ACE inhibitor were independent risk factors for hypotension after cardiopulmonary bypass. They also found that vasodilatory shock after bypass was associated with inappropriately low serum concentrations of vasopressin (12.0 pg/mL). Retrospectively, 40 of the 145 patients met the standard criteria for vasodilatory shock. Patients treated with low-dose vasopressin infusions (0.1 U/min) had a significant increase in MAP and a decrease in norepinephrine requirements. Similar findings in children have been reported.

### Clinical Perspectives

Collectively, clinical evidence suggests that vasopressin therapy may be a valuable alternative or adjunct for patients with refractory vasodilatory shock after cardiopulmonary bypass. However, these data must be interpreted cautiously. Large, randomized, double-blind trials that compare vasopressin with catecholamines have yet to be done. Central to the issue of refractory hypertension after cardiopulmonary bypass is the concept of vasopressin deficiency. Vasopressin levels in healthy hydrated humans are normally less than 4 pg/mL, whereas water deprivation stimulates an increase to about 10 pg/mL. Plasma levels of vasopressin in patients after bypass are in the range of 100 to 200 pg/mL, whereas hemorrhagic shock promotes levels as high as 1000 pg/mL. Several investigators reported inappropriately low vasopressin levels in different populations of patients. Although this deficiency was initially described in patients with septic shock, similar indices (<20 pg/mL) were noted in several recent studies in patients after cardiopulmonary bypass. Exogenous replacement consistently resulted in hemodynamic stability in both groups of patients. However, Argenziano et al also found a response to exogenous vasopressin in patients with moderately elevated plasma levels of vasopressin before treatment. This finding suggests a direct pressor effect in patients with normal function of the posterior lobe of the pituitary gland. Thus, vasopressin may provide hemodynamic support in patients with appropriate levels as well as in patients with a deficiency. Aside from the low number of patients in each study, the heterogeneity of these populations of patients poses a problem for interpreting the data. Furthermore, are patients with chronic congestive heart failure resulting in LVAD placement pathologically similar to patients who receive a more routine coronary artery bypass graft or heart valve replacement? Finally, although the dose of vasopressin remained essentially uniform in each study, the length of treatment varied and was confounded by concurrent administration of catecholamine.

### Pharmacology and Dosing Guidelines

Vasopressin has been used clinically to treat a variety of disorders, both as an antidiuretic and as a
vasoconstrictor (Table 1). Interestingly, in outlining the new Advanced Cardiac Life Support standards, the American Heart Association adopted vasopressin as its first-line drug in the treatment of ventricular tachycardia/fibrillation refractory to initial defibrillation. With its use in advanced life support and in vasodilatory shock, vasopressin is gaining popularity for use in treating critically ill patients. Critical care nurses must gain a basic understanding of the pharmacology of vasopressin and its clinical indications.

**Pharmacokinetics**

Vasopressin is distributed throughout the extracellular space. With a half-life of 10 to 35 minutes, the pressor effects after a single dose last about 30 to 60 minutes.28 When the goal is to maintain continuous hemodynamic support, vasopressin must be given by continuous intravenous infusion. Vasopressin is inactivated and metabolized by the kidney and liver; 5% to 15% is excreted in the urine.29

**Compatibility, Dosing, and Current Indications**

Approved uses for vasopressin by either intravenous or intramuscular injection include diabetes insipidus, abdominal distention, gastrointestinal bleeding, and refractory ventricular fibrillation. Desmopressin is a synthetic, longer-acting analog of vasopressin. It has minimal vasopressor activity with an antidiuretic-to-vasopressor ratio 4000 times that of vasopressin.30 Clinically, desmopressin is used to treat nocturnal enuresis, hemophilia A, and von Willebrand disease. Furthermore, it is useful for treating bleeding due to platelet dysfunction associated with uremia and cardiopulmonary bypass. These hemostatic effects are related to increased release of von Willebrand factor from vascular endothelial cells, thus promoting more effective platelet adhesion.12

Vasopressin can be diluted to a concentration of 100 to 1000 U/L in 5% dextrose in water or isotonic sodium chloride solution.31 The normal infusion mixture is 100 U per 250 mL. Infusion with vasopressin is often used as adjunctive therapy to treatment with catecholamines and phosphodiesterase inhibitors. No incompatibilities have been reported, and these drugs can conveniently be infused through the same central catheter.

Because treatment of vasodilatory shock is currently not an approved use of vasopressin, dosing guidelines for such use have not been firmly established. Research to date indicates that a dosing range of 0.01 up to 0.1 U/min is most effective in patients with vasodilatory shock without causing any adverse effects. Patients in the studies reported here received a continuous infusion for up to 24 hours. Vasopressin results in a decrease in splanchnic blood flow and has been used to treat gastrointestinal bleeding. Continuous infusion to treat variceal bleeding and other types of upper gastrointestinal hemorrhage, which are uses approved by the Food and Drug Administration, start at a rate of 0.2 U/min and may be increased each hour by 0.2 U/min. The optimal upper limit dose is 1 U/min, but up to 2 U/min may be tolerated. Infusion continues up to 12 hours after bleeding is controlled. The dosage is then cut in half for an additional 12 to 24 hours before cessation.12 By comparison, doses used to treat variceal bleeding (up to 2 U/min) are much higher than the doses used to treat hypotension that occurs after cardiopulmonary bypass. Conversely, doses used to treat vasodilatory shock are markedly higher (up to 0.1 U/min) than those used for other conditions. For example, primary nocturnal enuresis requires only 20 µg given intranasally. Similarly, hemophilia A and von Willebrand disease require only 300 µg per dose.

**Precautions and Contraindications**

While ongoing investigation continues to characterize the appropriate dosing regimen for patients who have had cardiothoracic surgery, caution must be used when administering this drug. Contraindications include anaphylaxis or hypersensitivity to vasopressin and chronic nephritis with nitrogen retention. Because
of the antidiuretic effect of vasopressin, patients with heart failure, asthma, epilepsy, and migraine must be followed up closely. The most serious adverse effects include myocardial ischemia and ventricular dysrhythmias (Table 2). Vasopressin should be infused through a central catheter because peripheral extravasation could cause tissue necrosis and gangrene. Although the doses of vasopressin currently being used are not sufficient to have deleterious effects on a fetus, vasopressin should be used in pregnancy only when clearly indicated.29

Table 2 Possible adverse effects of therapeutic vasopressin

<table>
<thead>
<tr>
<th>Effect</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Decreased cardiac output</td>
<td>Vertigo</td>
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<tr>
<td>Angina</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>Abdominal cramps</td>
</tr>
<tr>
<td>Ventricular dysrhythmia</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Bronchial constriction</td>
<td>Gastric infarction</td>
</tr>
<tr>
<td>Tremor</td>
<td>Water intoxication</td>
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<tr>
<td>Facial pallor</td>
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Summary

Although approximately 10% of patients undergoing cardiopulmonary bypass have profound vasodilatory hypotension, a subset of these patients is refractory to traditional therapies of fluid replacement and administration of catecholamine vasopressors. This lack of response may be due in part to an endogenous vasopressin deficiency related to depletion in patients with chronic heart failure. Alternatively, baroreflex-mediated secretion may be impaired. Clinical studies to date suggest that an infusion of vasopressin at a rate of 0.01 to 0.1 U/min significantly improves MAP and SVR without toxic effects. Because additional research must be done before vasopressin administration can be safely recommended in patients with vasodilatory shock after cardiopulmonary bypass, patients undergoing treatment must be closely followed up and monitored for potential adverse effects. Familiarity with the physiology of endogenous vasopressin and the pharmacology of replacement therapy will help critical care providers meet this challenge.

REFERENCES


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**CE Test Form**

**Vasopressin in the Cardiac Surgery Intensive Care Unit**

**Objectives**
1. Describe the pathophysiology of vasodilatory shock following cardiopulmonary bypass
2. Recognize traditional treatment modalities utilized for low cardiac output syndrome following cardiopulmonary bypass
3. Understand the role of vasopressin in the treatment of refractive vasodilatory shock after cardiopulmonary bypass, including dosage and administration guidelines

Mark your answers clearly in the appropriate box. There is only one correct answer. You may photocopy this form.

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CE Test Questions
Vasopressin in the Cardiac Surgery Intensive Care Unit

1. Which of the following are not utilized in the initial treatment of low cardiac output syndrome following cardiac surgery?
   a. Afterload reduction
   b. Inotropic support
   c. Beta blockade
   d. Volume resuscitation

2. A deficiency of which of the following hormones may be present in vasodilatory shock after cardiectomy?
   a. Antidiuretic hormone
   b. Thyroid stimulating hormone
   c. Vasopressin
   d. Both a and c

3. During cardiopulmonary bypass, which of the following physiologic responses is initiated?
   a. Systemic inflammatory response
   b. Humoral amplification of the coagulation cascade
   c. Humoral amplification of the complement cascade
   d. All of the above

4. Which of the following is not an adverse effect of cardiopulmonary bypass?
   a. Extracellular accumulation of fluid
   b. Renal dysfunction
   c. Hepatocellular dysfunction
   d. Hyperthermia

5. Which of the following is a hallmark of vasodilatory shock?
   a. Organ hypoperfusion
   b. Decreased mean arterial pressure
   c. Decreased systemic vascular resistance
   d. All of the above

6. Where is the hormone vasopressin endogenously produced?
   a. Hypothalamus
   b. Posterior pituitary
   c. Anterior pituitary
   d. Parathyroid

7. Which of the following is an indication for the use of vasopressin in addition to the treatment of vasodilatory shock?
   a. Diabetes mellitus
   b. Gastrointestinal bleeding
   c. Acute cerebral vascular accident
   d. Acute tubular necrosis

8. Which of the following best describes dosing recommendations given by the authors for the use of vasopressin in vasodilatory shock?
   a. 0.2 to 0.9 U/min continuous IV infusion
   b. 20 micrograms intranasally
   c. 0.01 to 0.1 U/min continuous IV infusion
   d. 5 to 10 U intramuscularly

9. Which of the following is not an adverse effect of vasopressin administration?
   a. Decreased cardiac output
   b. Metabolic alkalosis
   c. Myocardial ischemia
   d. Cardiac arrhythmias

10. Which of the following statements is true regarding vasopressin?
    a. Its half-life is 45 to 60 minutes
    b. It is metabolized by the kidneys and liver
    c. 50% is excreted in the urine
    d. Normal infusion mixture is 100 to 200 U/L
CORRECTIONS

In the article titled “Celebrating the 100th Birthday of the Electrocardiogram: Lessons Learned From Research in Cardiac Monitoring” (July 2002;11:378-386), on page 382, 2nd column, 3rd paragraph, 10th line, it reads, “Of interest, ST-segment elevation is present in lead aVR with less elevation than in V1 . . . .” The word “than” was inadvertently added during our internal editorial process and should be deleted because it imparts just the opposite meaning than the author intended. The criterion that has been recently described in the literature to indicate a left main coronary artery stenosis is as follows: If, during a transient myocardial ischemic event involving ST-segment depression, there is ST-segment elevation in lead aVR that is greater than the ST-segment elevation normally seen in lead V1, a left main coronary artery stenosis is likely. This criterion is illustrated in the electrocardiogram shown in Figure 4B (p384).

In Figure 4 (p384) of this article, the last two sentences of the legend belong in the Figure 3 legend. These sentences describe how the ST trend is displayed, with time represented on the x axis, and millimeters of ST-segment deviation on the y axis.

In the article titled “Vasopressin in the Cardiac Surgery Intensive Care Unit” (July 2002;11:326-332), on page 327, 2nd column, last sentence of the first true paragraph, the wrong dosing regimen is given. The sentence should read as follows: “Antidiuresis can be accomplished with single doses of 5 to 10 U, whereas the vasoconstrictive effects require up to 0.5 U every 5 minutes.” Additionally, Table 1 (p329) incorrectly lists the continuous infusion rate for vasodilatory shock after cardiopulmonary bypass as 0.01 to 1.0 U/min. This should be 0.01 to 0.1 U/min. In the continuing education test (p332) for this article, choice C in question 8 should read as follows: 0.01 to 0.1 U/min continuous IV infusion.