Use of Vasopressors in Septic Shock

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Abstract

- **Objective:** To review the latest findings on the use of vasopressor agents in septic shock.
- **Methods:** Review of the literature.
- **Results:** The Surviving Sepsis Campaign guidelines recommend norepinephrine or dopamine as first-line vasopressor therapy for patients with septic shock. However, recent publications have demonstrated that dopamine has a less desirable side-effect profile than norepinephrine, especially in patients at increased risk of cardiovascular events. Therefore, dopamine should no longer be considered a first-line vasopressor, especially in patients with a history of cardiovascular disease. Currently, the role of vasopressin is adjunctive therapy to other vasopressors like norepinephrine and dopamine. Epinephrine and phenylephrine should be reserved for those patients requiring multiple vasopressors, unless patient-specific parameters preclude the use of first-line agents. When patients require multiple vasopressors to maintain mean arterial pressure goals, selection of a second vasopressor agent should be based on individual hemodynamic parameters and patient-specific comorbidities.
- **Conclusion:** As new research is conducted, the role of each vasopressor in septic shock will be more clearly defined.

Sepsis is a complicated infectious process that propagates the release of inflammatory mediators, resulting in hemodynamic decompensation [1]. The hemodynamic goal in the treatment of septic shock is to maintain mean arterial pressure (MAP) and cardiac output to achieve adequate tissue perfusion. When initial fluid resuscitation fails to meet MAP goals, vasopressors are initiated to maintain perfusion to vital organs. Vasopressors are endogenous or synthetic catecholamines that produce their effects through stimulation of various receptors, predominantly α and β [2]. Current practice guidelines recommend the use of norepinephrine or dopamine as first-line agents to correct hypotension in septic shock [3]. However, new research suggests that reexamination of these guidelines is necessary. In this article, we review the physiologic and theoretical differences between individual vasopressors and the implications of these in the clinical management of patients with septic shock, focusing on Level I evidence (evidence from high-quality randomized controlled trials).

**Basic Physiology**

Catecholamines, mediated through adrenergic nervous system receptors, are responsible for the regulation of smooth muscle and vascular tone as well as myocardial contractility [2]. Catecholamine-mediated cardiac stimulation occurs through the adrenergic receptors α1, β1, and β2. α1-adrenergic receptors are found on arterial vascular smooth muscle. Upon stimulation, the Gq protein is activated, signaling a cascade of events that leads to increased cytosolic calcium concentrations, which consequently leads to peripheral vasoconstriction [4]. β1-adrenergic receptors, found on cardiac myocytes, augment cardiac output through increased production of cyclic adenosine monophosphate (cAMP), resulting in increased activation of voltage-gated calcium channels [5]. β2-adrenergic receptors are found in various smooth muscle including vascular and bronchial tissues. Stimulation of these receptors mediates relaxation and subsequently vasodilation. Dopamine receptors (D1, D2) are stimulated when dopamine doses are between 1 to 3 mcg/kg/min [4,6]. These receptors are found in the kidney, cerebral bed, splanchic and mesenteric circulation, and systemic vasculature. Upon stimulation, dopamine receptors promote vasodilation and increased blood flow to these areas. In addition, a recent review by Levy and colleagues demonstrated the effects of vasopressors on mitochondrial activity in terms of cellular pathways and which vasopressors are effective at attempting to reverse these effects in patients with septic shock [7].

Preload, afterload, and contractility are important concepts to understand when managing hemodynamic parameters. Preload reflects the venous filling pressure in the left atrium, before contraction has started, at the end of diastole, whereas afterload reflects the systolic load on the left ventricle after it has started to contract. Myocardial contractility is the intrinsic ability of the heart to contract independent of preload and afterload. Current vasoactive therapy affects...
Dopamine is an endogenous catecholamine which stimulates receptors to varying degrees depending on the dose. At low doses (1–3 mcg/kg/min), dopamine stimulates D₁ and D₂ receptors. This dosing, formally referred to as “renally-dosed dopamine,” is no longer common practice. To date, no discernable increase in glomerular filtration rate has been demonstrated in critically ill patients and renal protective effects have not been proven at this dose [9]. At intermediate doses (3–10 mcg/kg/min), β₁ receptors are stimulated, increasing norepinephrine release and myocardial contractility. At higher infusion rates (10–20 mcg/kg/min), stimulated α₁ receptors mediate peripheral vasoconstriction (Figure). Doses higher than 20 mcg/kg/min are not recommended due to the increased incidence of cardiac arrhythmias. Common adverse effects of dopamine infusions include tachycardia, cardiac arrhythmias, hyperprolactinemia, and potential for vascular injury if extravasated [12] (Table).

The Surviving Sepsis Campaign recommends dopamine, along with norepinephrine, as first-line agents for treatment of hypotension in septic shock [3]. An observational study of patients receiving dopamine versus norepinephrine for shock found higher intensive care unit (ICU) and overall hospital mortality in the patients receiving dopamine [10]. The results of this observational study prompted further investigation. The first trial to compare dopamine versus norepinephrine for the treatment of all types of shock was a multicenter, randomized trial with a primary endpoint that was 80% powered to show a 15% relative difference in the rate of mortality at 28 days [11]. This trial of 1679 patients showed no difference in death at 28 days after randomization (odds ratio [OR], 1.17 [95% confidence interval {CI}, 0.97–1.42]; P = 0.1); however, the rate of death was significantly higher in a pre-defined subgroup of patients with cardiogenic shock treated with dopamine compared with those treated with norepinephrine (P = 0.03). There was also a statistically significant difference in the number of patients having to discontinue therapy due to arrhythmias in the dopamine group (6.1% vs. 1.6%; P < 0.001).

A single-center, randomized controlled study comparing dopamine and norepinephrine in 252 medical intensive care unit patients with septic shock showed similar results in the primary endpoint as the De Backer trial (relative risk [RR], 1.16 [95% CI, 0.886–1.51]; P = 0.282). This study had an 80% power to detect a 20% difference in 28-day mortality. It also showed a significant increase in sinus tachycardia as well as arrhythmias with dopamine therapy compared with norepinephrine (RR, 3.21 [95% CI, 1.88–5.49]; P < 0.001) [12]. It can be concluded from the results of these studies that the higher selectivity of dopamine for β-adrenergic receptors results in higher probability of excitation on myocardium. In light of these recent clinical trials showing no mortality benefit with increased incidence of adverse effects, dopamine has fallen out of favor as first-line therapy for treatment of septic shock, especially those patients with a predisposition to arrhythmias or history of cardiovascular disease.

Norepinephrine
Norepinephrine is an endogenous catecholamine that stimulates both β-adrenergic and α-adrenergic receptors to varying degrees. Norepinephrine increases SVR and cardiac contractility through α- and β-adrenergic stimulation, respectively (Figure). Common adverse affects of norepinephrine infusions include tachycardia, cardiac arrhythmias, and potential for vascular injury if extravasated [2] (Table).

Norepinephrine is considered first-line therapy for the treatment of septic shock and has been the most extensively studied vasopressor. In recent years it has been compared to dopamine, vasopressin, and epinephrine and has consistently been shown to be equally efficacious as compared with epinephrine or dopamine. In a multicenter, randomized controlled trial, 330 septic shock patients were randomly assigned to receive epinephrine alone or norepinephrine with or without dobutamine [13]. This study was powered to show an absolute reduction of 20% in the mortality rate at day 28 with 95% probability. Overall, there was no significant difference in all-cause mortality between the

Figure. Selectivity and hemodynamic parameters of vasopressors. DA = dopamine; EP = epinephrine; HR = heart rate; NE = norepinephrine; PE = phenylephrine; SVR = systemic vascular resistance.
The epinephrine group and the norepinephrine ± dobutamine group at 28 days (RR, 0.86 [95% CI, 0.65–1.14]; P = 0.31) or 90 days (RR, 0.96 [95% CI, 0.78–1.19]; P = 0.73). The study also found the rate of adverse effects to be similar between the 2 groups. The epinephrine group had higher initial serum concentrations of lactate (P < 0.001); however, this difference did not persist throughout the study duration. There was no significant difference in the rate of arrhythmias between the 2 groups; however, the additional pure β-adrenergic stimulation of dobutamine may have confounded the rate of arrhythmias in the norepinephrine group [13].

Norepinephrine was also compared with vasopressin for the treatment of septic shock in a prospective, randomized, multicenter, double-blind controlled trial of 778 patients. This study, which was 80% powered to show a 10% absolute difference in mortality, also found no difference in the primary outcome of 28-day mortality between the 2 treatment groups (RR, 0.9 [95% CI, 0.75–1.08 CI]; P = 0.26). Unlike previous studies, the norepinephrine group showed a higher incidence in cardiac arrest; however, this was not statistically significant (P = 0.14). There was also a trend toward digital ischemia in the vasopressin group (P = 0.11) [14].

A third trial comparing norepinephrine and epinephrine was a randomized controlled trial of 280 patients with all types of shock [15]. With an 80% power to detect an absolute reduction of 15% in response to either drug, there was no difference in the primary endpoint of time to achievement of MAP goals for more than 24 hours without vasopressors between the 2 groups (hazard ratio [HR], 0.88 [95% CI, 0.69–1.12]; P = 0.26) or in overall mortality (HR, 0.86 [95% CI, 0.57–1.31]; P = 48). Epinephrine was associated with lactic acidosis (P < 0.001) and tachycardia (P = 0.04) within the first 24 hours of study treatment. Withdrawal from the study due to adverse effect was higher in the epinephrine group compared to the norepinephrine group [15].

While no study has demonstrated mortality benefits with norepinephrine compared to other vasopressors, it has a favorable adverse effect profile, making it a more appropriate first-line agent in septic shock treatment.

**Table.** Vasopressors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Site of Activity</th>
<th>Dose</th>
<th>Adverse Effects</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>DA</td>
<td>β₁</td>
<td>β₂</td>
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<tr>
<td>Dopamine</td>
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<td></td>
<td></td>
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<tr>
<td>1–3 mcg/kg/min</td>
<td>++++</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>3–10 mcg/kg/min</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>&gt; 10 mcg/kg/min</td>
<td>–</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>–</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.01–0.05 mcg/kg/min</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>&gt; 0.05 mcg/kg/min</td>
<td>–</td>
<td>+++</td>
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<tr>
<td>Phenylephrine</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Vasopressin</td>
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</tbody>
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*Organ ischemia: coronary, cerebral, mesenteric, hepatic, renal.
**VASOPRESSORS**

Epinephrine
Epinephrine is a potent $\alpha$- and $\beta$-adrenergic receptor agonist that increases MAP through peripheral vasoconstriction and augments cardiac contractility (Figure). The use of epinephrine has fallen out of initial resuscitation efforts due to the potential adverse effects. As stated above, a trial comparing norepinephrine to epinephrine found patients treated with epinephrine had higher lactate levels, though this did not correlate to any defined clinical outcome [14]. As with other vaspressors, epinephrine has the potential to cause arrhythmias. Epinephrine has also been shown to decrease splanchnic circulation, which leads to decreased oxygen perfusion to vital organs [16,17] (Table).

Phenylephrine
Phenylephrine is a selective $\alpha$-adrenergic receptor agonist that increases SVR through peripheral vasoconstriction (Figure). Phenylephrine lacks any $\beta$-adrenergic stimulation; therefore, these characteristics may be desirable for patients who previously experienced tachyarrhythmias due to vasopressor agents with $\beta$ stimulation. This agent should be used with caution in patients with a significant cardiovascular history such as congestive heart failure or coronary artery disease [18]. Due to its selectivity for $\alpha$-adrenergic receptors, phenylephrine can decrease splanchnic and renal perfusion; however, the clinical significance of these properties is controversial [17,19]. In a small study of only 32 patients randomized to receive phenylephrine or norepinephrine for septic shock, no difference was detected in the primary outcome of global or regional hemodynamics or renal function. This study was 80% powered to detect a 30% difference in 1 of the 2 hemodynamic parameters measured [20].

Vasopressin
Vasopressin is a hormone synthesized in the hypothalamus that acts on various vasopressin receptors throughout the body. V1$_a$ receptors are located in the cardiac myocytes and vascular smooth muscle. When stimulated these receptors are responsible for vascular smooth muscle constriction, which increases blood pressure [21]. V1$_b$ receptors have central effects, such as increasing adenocorticotropic hormone (ACTH) [22]. Vasopressin is also thought to act as an adjunct therapy to other vasopressors by improving the responsiveness of the vasculature to catecholamines [22]. Vasopressin may also increase blood pressure by inhibition of nitric oxide and K-ATP channels in vascular smooth muscle [23]. V$_2$ receptors, found in the renal collecting duct, when stimulated promote water reabsorption by increasing permeability [24]. Vasopressin also augments cardiac contractility through its binding to purinergic receptors, specifically P2Y$_R$, causing a large increase in cytosolic calcium in cardiac myocytes [25].

Patients in septic shock have been found to have abnormally low levels of endogenous vasopressin [26]. Therefore, dosing of vasopressin is usually standardized from 0.01 to 0.03 units/min as adjunctive therapy to restore vascular tone and blood pressure, reducing the need for the use of exogenous catecholamines [13].

**Selection of Therapy**

Though there is still much research to be done in the area of determining the optimal vaspressor therapy, there are preferred agents for specific subgroups of patients. In general, norepinephrine can be considered the primary vaspressor given that its adverse effects do not restrict its use in specific subgroups of patients. Through its balanced stimulation of $\alpha$ and $\beta$ receptors, it is a reliable agent for increasing SVR and cardiac contractility. Dopamine can be considered as an option for initial vaspressor therapy; however, as stated above, it should be limited to patients without a history of cardiovascular disease due to its proarrhythmic effects [10,12].

When patients require multiple vaspressors to maintain MAP goals, selection of a second vaspressor agent should be based on individual hemodynamic parameters and patient-specific comorbidities. $\beta$-receptor stimulation has the potential to evoke tachycardia, which may limit the titration of the initial vaspressor. In this situation, phenylephrine’s $\alpha$ selectivity is beneficial in that it increases SVR; therefore, it can be added to the initial vaspressor to maintain MAP goals. Vasopressin, like norepinephrine, is not limited by its adverse effects, unless doses above 0.03 units/min are utilized [3]. Though it is not recommended as monotherapy, its augmentation of blood pressure without stimulation of $\alpha$- and $\beta$-receptors makes it an ideal adjunctive agent. Although not discussed in this article, dobutamine and milrinone are used to augment cardiac output in heart failure patients through their selective stimulation of $\beta$-receptors.

**Summary**

Hemodynamic goals in septic shock are achieved through the use of adequate fluid resuscitation and use of vaspressors. The Surviving Sepsis Campaign guidelines recommend norepinephrine or dopamine as first-line vaspressor therapy for patients with septic shock [3]. However, recent publications have demonstrated that dopamine has a less desirable side effect profile than norepinephrine, especially in patients at an increased risk of cardiovascular events. Therefore, dopamine should no longer be considered a first-line vaspressor, especially in patients with a history of cardiovascular disease. Currently, the role of vasopressin is adjunctive therapy to other vaspressors like norepinephrine and dopamine. Epinephrine and phenylephrine are
effective at raising blood pressure, but in clinical trials have demonstrated adverse effects leading to discontinuation of therapy. Their use should be reserved for those patients requiring multiple vasopressors, unless patient-specific parameters preclude the use of first-line agents. As new research is conducted, the role of each vasopressor in septic shock will be more clearly defined.

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References