# Vasopressors and Inotropes in Sepsis

Leeanne Stratton, MD[a], David A. Berlin, MD[b], John E. Arbo, MD[a,b,*]

**KEYWORDS**

- Vasopressors • Inotropes • Sepsis • Septic shock • Cardiac contractility
- Norepinephrine • Epinephrine • Dopamine

**KEY POINTS**

- Vasopressors and inotropes are beneficial in shock states when they increase the systemic arterial pressure to allow autoregulation, increase venous return, augment abnormal cardiac contractility, or increase the coronary perfusion gradient.
- Norepinephrine should be administered within 6 hours in patients with sepsis-associated hypotension that does not correct with an initial 30 mL/kg crystalloid fluid bolus.
- Dobutamine should be considered in septic patients with evidence of myocardial dysfunction or signs of hypoperfusion despite restoration of adequate intravascular volume and mean arterial pressure with fluid and vasopressor therapy.

## INTRODUCTION

The British physician George Oliver was among the first to investigate the vasoactive properties of the adrenal gland. In 1893, using his son as a research subject, Dr Oliver observed that ingestion of sheep adrenal extract produced narrowing of the radial artery diameter.[1] Over the next 2 years, Dr Oliver, working with the physiologist Edward A. Schäfer from the University of London, described both the lethal effects of large amounts of the substance and the ability of lower doses to increase arteriolar blood pressure in animal models.[2] Efforts to isolate a pure form of the active constituent of the adrenal gland extract, generically referred to as 'epinephrine,' would not be achieved until 1901, when the Japanese chemist Jokichi Takamine successfully marketed the substance under the proprietary name *adrenalin*.[2] George Crile, the cardiovascular surgeon and Cleveland Clinic cofounder, would be among the first to

demonstrate the clinical applications of synthetic adrenaline and its power to restore arterial blood pressure in surgical patients with various forms of shock.[3] He would go on to describe adrenaline's resuscitative effects in dogs with induced cardiac arrest. There would not, however, be a definitive thesis of the adrenoreceptor mechanism until Raymond Ahlquist published his seminal paper in 1948 proposing the existence of alpha- and beta-receptors.[4]

## PHYSIOLOGIC RATIONALE FOR VASOACTIVE MEDICATIONS IN PATIENTS WITH SEVERE SEPSIS

Vasopressor and inotrope medications are vasoactive agents used in shock states to assist in the restoration of impaired perfusion. The physiologic effects these agents in sepsis-associated hypoperfusion are diverse and, often, overlap (Table 1). Before reviewing the clinical application of individual vasoactive medications, it is useful to consider the primary therapeutic effects of each agent on the arterial, venous, and cardiac systems of patients in shock.

### Effect of Vasopressors and Inotropes on the Systemic Arterial System

In general, vasopressors induce vasoconstriction within the arterial system, whereas inotropes increase cardiac contractility. In reality, most vasoactive agents produce both effects. The most commonly used vasopressor and inotrope medications are synthetic catecholamines that stimulate alpha, beta, and dopaminergic receptors in the arteries and arterioles. Typically, the alpha effects predominate in these vessels, especially at standard doses. Specifically, stimulation of alpha-1 receptors on vascular smooth muscle cells leads to an increase in intracellular calcium, and, consequently, intense vasoconstriction and increased systemic blood pressure.[4,5]

The small arterioles supply most of the resistance in the high-pressure systemic arterial circulation. This is essential for autoregulation, the process by which tissues control their own blood flow. Tissues that require increased perfusion can dilate their arterioles and admit additional blood flow into their capillary beds. Autoregulation, therefore, improves the distribution of blood flow within the arterial system. Importantly, autoregulation requires that the pressure in systemic arteries exceed a minimum threshold.[6] If systemic arterial blood pressure falls below this minimum threshold, there can be an insufficient pressure gradient for perfusion.[7] Agents with vasoconstrictive activity can therefore help to increase the resistance and pressure in the systemic arteries and arterioles above the threshold required to enable autoregulation, restoring critical perfusion to regional vascular beds.

### Effect of Vasopressors and Inotropes on the Systemic Venous System

Normally, the compliant systemic venous system contains two-thirds of the total blood volume. Smooth muscle in the walls of systemic veins constrict in response to activation of alpha and vasopressin (a noncatecholamine vasoconstrictor) receptors.[8–10] This feature allows the systemic veins to serve as an adjustable blood reservoir that is under autonomic control. The venous reservoir has an average pressure that is independent of the pressure generated by the heart's pumping, and is determined by both the circulating volume of blood and the intrinsic stiffness of the vessel walls. This pressure, called the mean systemic filling pressure (MSFP), is normally around 7 mm Hg. For blood to return to the heart, the MSFP must be greater than the right atrial pressure, which is normally 0 mm Hg in early diastole. The rate of venous return to the heart depends on the pressure gradient between the MSFP and the right atrium. Endogenous vasopressors play an essential role in regulating venous return through

**Table 1**
**Summary of vasopressor and inotropic agents**

| Agent | Indication | Activity in Sepsis and Septic Shock | Receptor Binding | | Typical Dose | Adverse Effects |
|---|---|---|---|---|---|---|
| Norepinephrine | Shock (septic, cardiogenic) | Inoconstriction, mobilizes unstressed venous blood volume; provides some direct inotropic support | Heart $\beta_1$: +++ | Vasculature $\alpha_1$: +++++ $\beta_2$: ++ | 0.02–0.3 µg/kg/min | Tachyarrhythmias, cardiac myocyte apoptosis, limb ischemia |
| Epinephrine | Shock (septic, cardiogenic), cardiac arrest, symptomatic bradycardia, anaphylaxis | Inoconstriction, mostly $\beta_1$ effects at doses up to 0.1 µg/kg/min; $\alpha_1$ effects predominate at higher doses | Heart $\beta_1$: ++++ | Vasculature $\alpha_1$: +++++ $\beta_2$: +++ | 0.01–0.20 µg/kg/min | Ventricular arrhythmias, severe hypertension leading to cerebrovascular events, limb ischemia, metabolic acidemia, and lactic acidosis |
| Vasopressin | Shock (septic, vasoplegic), ± cardiac arrest | Vasoconstriction of the pulmonary and systemic vasculature, adjunctive | Vasculature $V_1$: vascular smooth muscle $V_2$: renal collecting ducts | | 0.01–0.04 U/min | Tachyarrhythmias, digital ischemia |
| Dopamine | Symptomatic bradycardia, shock (septic, cardiogenic) | Inoconstriction, vasodilatory via DA receptors at doses <2 µg/kg/min; $\beta_1$ effects from 2–5 µg/kg/min; $\alpha_1$ predominate at higher doses | Heart $\beta_1$: ++++ | Vasculature $\alpha_1$: +++ $\beta_2$: ++ DA: +++++ | 2–20 µg/kg/min | Tachyarrhythmias, cardiac ischemia, severe hypertension |

**Table 1**
**(continued)**

| Agent | Indication | Activity in Sepsis and Septic Shock | Receptor Binding | | Typical Dose | Adverse Effects |
|---|---|---|---|---|---|---|
| Phenylephrine | Acute hypotension (vagal, medication related), aortic stenosis w/hypotension, HCM with LVOT gradient | Vasoconstriction, adjunctive | Heart $\beta_1$: 0 | Vasculature $\alpha_1$: +++++ $\beta_2$: 0 | 100–180 μg/min initial, 40–60 μg/min maintenance; boluses 50–200 μg q20 min | Worsening cardiac function, baroreflex bradycardia |
| Dobutamine | Shock (cardiogenic, septic cardiomyopathy), ADHF/low CO states | Inodilatation, mostly $\beta_1$ and $\beta_2$ effects <15 μg/kg/min; mild $\alpha_1$ at higher doses but offset by $\beta_2$ | Heart $\beta_1$: +++++ | Vasculature $\alpha_1$: + $\beta_2$: +++ | 5–15 μg/kg/min | Ventricular arrhythmias, cardiac ischemia, hypotension as a known $\beta_2$ effect |
| Milrinone | Low CO states refractory to dobutamine and/or in chronically β-blocked patients, or in RV failure with pHTN | Inodilatation, decreases pulmonary vascular resistance | Heart Blocks PDE3 degradation of cAMP, equivalent to $\beta_1$: +++++ | Vasculature Blocks PDE3 degradation of cAMP, equivalent to $\beta_2$: ++++ | 0.25–0.75 μg/kg/min | Profound vasodilatory effects mediated through PDE3 inhibition, torsades and other ventricular arrhythmias |

Abbreviations: ADHF, acute decompensated heart failure; CO, cardiac output; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; MAPs, mean arterial pressures; PDE3, phosphodiesterase 3; pHTN, pulmonary hypertension; RV, right ventricle.

their ability to increase MSFP, increase this pressure gradient, and drive blood into the heart. A normal heart responds to increased venous return by increasing its output by the Frank–Starling mechanism and autonomic reflexes.[11,12] Importantly, this mechanism of increasing cardiac output occurs independent of direct cardiac stimulation, and is similar to the effect of a fluid bolus.[13–16]

### Effect of Vasopressors and Inotropes on the Heart

Vasoactive agents that stimulate beta-receptors, specifically beta-1 receptors, increase cardiac myocyte contractility; an effect mediated by an increase in intracellular cyclic adenosine monophosphate (cAMP) and intracellular calcium. The enhanced contractility that results can increase stroke volume and reduce ventricular end-diastolic volume and filling pressures.[17] Beta agonists, however, typically cause only a modest increase in cardiac output because the unstimulated heart is normally able to eject almost all of the blood that has returned to it. Significant increases in cardiac output will only occur if the end-diastolic volume is abnormally increased, as occurs in the setting of myocardial dysfunction. Beta agonists may also improve cardiac performance through increased chronotropy (beta-1) and enhanced lusitropy (beta-2).[18] Activation of beta-2 receptors also results in relaxation of vascular smooth muscle and, consequently, peripheral arterial vasodilation. In certain clinical scenarios, this can offset the work imposed on the heart by the vasculature and improve cardiac performance.

Vasopressors also improve cardiac performance by augmenting coronary artery perfusion. The coronary arteries carry nutrient blood flow from the aorta to the myocardium. During systole, the high pressure generated by ventricular contraction compresses the coronary arteries within the walls of the myocardium, resulting in both anterograde and retrograde flow. The relative proportion of anterograde and retrograde flow depends on the pressure gradient between the aorta and the ventricles. Coronary perfusion to either ventricle can decrease precipitously if intraventricular pressures increase at the same time systemic arterial pressure decreases. A vicious and potentially rapidly fatal cycle of low cardiac output reducing coronary perfusion ensues, which further reduces cardiac performance. This can occur in multiple clinical scenarios (**Box 1**). In these settings, vasopressors can serve to increase vascular tone, restore systemic arterial pressure, and preserve the coronary perfusion gradient, thereby minimizing myocardial ischemia. This approach has been shown to be effective in experimental models of pulmonary embolism, tamponade, and cardiogenic shock from left ventricular ischemia.[19–22]

---

**Box 1**
**Conditions in which vasopressors may improve coronary perfusion**

- Cardiac tamponade
- Aortic stenosis
- Hypertrophic obstructive cardiomyopathy
- Pulmonary embolism
- Pulmonary hypertension
- Systolic heart failure
- Cardiopulmonary resuscitation

Vasopressors and inotropes have multiple effects on cardiac performance and perfusion in shock states. The net effect will vary depending on the clinical situation. In general, benefit will be realized when use of vasoactive agents (1) increases the systemic arterial pressure to greater than the threshold to allow autoregulation, (2) increases venous return, (3) augments abnormal cardiac contractility, or (4) increases the coronary perfusion gradient.

### Other Physiologic Effects of Vasopressors and Inotropes

Vasoactive agents exert a multitude of other significant physiologic effects. Select agents result in pulmonary artery constriction and increased pulmonary vascular resistance.[23] However, the right ventricular strain this effect can produce is typically offset by a simultaneous improvement in both cardiac contractility and the coronary perfusion gradient.[24] Vasoactive agents also have important metabolic effects.[25] Beta agonists, particularly epinephrine, can increase blood glucose and lactate concentrations. Both epinephrine and norepinephrine increase kaliuresis and urine output independent of their effect on blood pressure and cardiac output.[26]

## INITIATING VASOPRESSOR THERAPY IN SEVERE SEPSIS

The Surviving Sepsis Campaign (SSC) recommends vasopressor therapy in patients with severe sepsis within 6 hours if hypotension, defined as a mean arterial blood pressure (MAP) of less than 65 mm Hg, persists after a 30 mL/kg crystalloid fluid bolus. In practice, many patients whose hemodynamics and physical examination findings improve with appropriate initial volume resuscitation will, nevertheless, receive additional volume before vasopressor therapy is started. Accurate estimation of intravascular volume status is challenging in an emergency department setting. What is considered 'adequate' volume resuscitation is often determined at the point of volume unresponsiveness, or the failure of additional fluid boluses to further augment indices of cardiac output. This approach, however, can lead to overresuscitation with large volumes of crystalloid and the sequelae of acute renal insufficiency, cardiac insufficiency, pulmonary edema, and prolonged ventilator dependency.[24,27]

Time to initiation of vasopressors may prove to be an independent predictor of mortality. A recent retrospective cohort study in patients with septic shock found that mortality rates increased with increasing time to norepinephrine initiation; this was true even when vasopressors were begun within the SSC's recommended 6-hour window.[28] Patients who received norepinephrine within 2 hours of onset of septic shock had significantly lower 28-day mortality rates compared with patients who received vasopressors after 2 hours of shock (30% vs 43%). In this study, mortality rates increased by 5.3% for every hour delay in vasopressor initiation once shock was recognized. Earlier administration of norepinephrine also led to shorter duration of vasopressor use and lower total doses of the drug administered. Patients in whom norepinephrine was started after 2 hours also took significantly longer to achieve goal MAPs than patients in the early initiation group (6.1 vs 4.6 hours; *P*<.001). Importantly, both groups received similar volumes of fluid within the first 6 hours, and there were no differences in time to antibiotic initiation or corticosteroid use.

Vasopressor use typically requires a central venous catheter. The time and effort required for catheter insertion, as well as the known complications of the procedure, may contribute to provider delay in initiating vasopressor therapy. Central venous catheter placement and use is associated with infectious, thrombotic, and mechanical complications.[29] The safety of peripherally administered vasopressors, however, remains a subject of debate, with tissue necrosis, gangrene, or limb ischemia resulting

from vasopressor extravasation being primary concerns. The first randomized controlled trial comparing mechanical, infectious, and thrombotic complication rates in patients in the intensive care unit (ICU) receiving vasopressor therapy via peripheral or central venous catheters demonstrated a trend toward increased complications in the peripheral catheter group.[30] The majority of complications were attributed to difficulty with peripheral catheter insertion, insertion-site erythema, and subcutaneous extravasation with subsequent blistering, or local tissue necrosis. There were no differences in mortality between the central and peripheral catheter groups; however, more than one-half of the peripheral catheter group eventually required central venous catheter placement because of increasing vasopressor requirements or because peripheral access could not be obtained.

A more recent single-arm study in 734 ICU patients who received peripheral norepinephrine, dopamine, or phenylephrine for a median of 49 hours demonstrated the safety of administering these agents peripherally when local phentolamine and nitroglycerin paste were used in combination to treat incidences of peripheral extravasation.[31] No cases of tissue injury resulted. Importantly, the study protocol mandated the use of at least 20-G catheters placed in vessels with diameters of greater than 4 mm, as determined on bedside ultrasonography. Importantly, the integrity of the catheters was assessed every 2 hours by nursing staff.

A recent systematic review composed of mostly case reviews and case studies concluded that the peripheral administration of vasopressors is safe for short durations (<2 hours) via larger bore catheters that are placed proximal to the antecubital and popliteal fossae.[32] This review recommended the use of peripherally administered vasopressors only as a temporizing measure while central access is obtained.

When using vasopressors, it is important to remember that local derangements of the microcirculation (ie, perfusion of regional capillary beds) may persist despite optimization of surrogate macrocirculatory variables. Boerma and Ince[33] cite in vitro studies demonstrating that capillary hematocrits vary dynamically, from 6.8% to 38%, despite a systemic hematocrit of 50%, depending on whether there is upstream vasoconstriction or dilatation of the contributing arterioles. Vasoconstriction also increases the diffusion distance of oxygen, which is inversely proportional to oxygen delivery at the cellular level. Various imaging and detection modalities have been used to capture the state of the microcirculation in severe sepsis and have underscored the heterogeneity of flow to different microvascular beds despite optimization of macrocirculatory variables.[33] Although it is clear that a functioning microcirculation requires a minimum MAP, it is not always the case that meeting threshold MAPs will be sufficient to normalize flow to these low-pressure vascular beds.

## Norepinephrine

Norepinephrine is the first-line vasopressor in patients with sepsis or septic shock. It is a hydroxylated derivative of dopamine and stimulates both alpha and beta receptors. Its alpha-1 effects predominate at therapeutic doses. As noted, the venous effects of norepinephrine (augmentation of MSFP) act similarly to a fluid bolus, and can provide preload support during simultaneous fluid resuscitation. Norepinephrine also provides moderate inotropic support via its beta-1 activity.

At therapeutic doses, norepinephrine carries a lesser risk of serious adverse events than dopamine in the treatment of septic shock, with an absolute risk reduction of 11% in mortality compared with dopamine in a recent systematic review.[34] Dopamine also doubled the risk of cardiac arrhythmias in this analysis and in an earlier metaanalysis by De Backer and colleagues,[35] who reported a relative risk of arrhythmias of 2.34 when dopamine was used instead of norepinephrine in patients with septic shock.

Prolonged use of norepinephrine, however, can be directly toxic to cardiac myocytes and may result in reflex bradycardia, cardiac arrhythmia, and tissue ischemia as a result of profound vasoconstriction.

### Epinephrine

Epinephrine is a potent nonselective alpha and beta agonist recommended by the SSC for use in sepsis-associated hypotension as either a first alternative or in addition to norepinephrine when norepinephrine fails to achieve hemodynamic goals. It is also the first-line vasopressor in cardiac arrest and, like dopamine, is recommended for use in symptomatic bradycardia that does not respond to atropine.

Epinephrine is typically administered at doses of 0.01 to 0.20 µg/kg/min. Its beta effects predominate at lower doses, up to 0.1 µg/kg/min, and it has powerful effects on cardiac contractility and heart rate in this range.[36] At higher doses, epinephrine's alpha-1–mediated vasoconstrictive effects predominate, and its inoconstricting properties begin to approximate those of combined norepinephrine and dobutamine. A multicenter, randomized, controlled, double-blind study of 330 patients with septic shock showed no differences in the duration of vasopressor dependency, ICU or hospital duration of stay, or 28- and 90-day mortality when vasopressor therapy with epinephrine plus placebo was compared with combined norepinephrine and dobutamine.[37] There was no increase in adverse events in the epinephrine group; however, the epinephrine group did have significantly lower arterial pH values over the first 4 days, with significantly higher arterial lactate values on day one. Although these findings had no effect on the primary outcomes of interest, epinephrine's acid–base and metabolic effects are well-documented, and may reflect local ischemia from alpha-1–mediated vasoconstriction,[38] although it is increasingly believed that these effects result from the beta-2–mediated activation of the aerobic glycolytic pathway.[39]

### Vasopressin

Vasopressin is an endogenous peptide hormone that produces contraction of vascular smooth muscle via $V_1$ receptors, which are ubiquitous in the systemic circulation, especially the skin and splanchnic vessels.[40] It is considered a nonadrenergic vasopressor adjunct in the treatment of sepsis-associated hypotension. Under normal physiologic conditions, vasopressin is primarily responsible for free water homeostasis. In healthy subjects, it is associated with only moderate vasoconstriction in the pulmonary and renal arterial systems and, at very low doses, can actually lead to pulmonary vasodilatation via release of endothelial nitric oxide.[41] The latter effect may be helpful in specific instances of acute right ventricular failure.[42] Vasopressin's effects on arterial tone becomes more significant in instances of acute hypotension, when it is released from the neurohypophysis in concentrations that are tens to hundreds of times greater than basal levels.[43] Endogenous vasopressin stores can become depleted within hours of shock onset. In this setting, normalization of circulating concentrations with exogenous administration can result in marked peripheral vasoconstriction and increased systolic and diastolic pressures.[44]

At the standard therapeutic dose, vasopressin is considered a "catecholamine-sparing" agent in severe sepsis, and is used most often in conjunction with norepinephrine. The SSC does not recommended its use as a single agent. The VASST (Vasopressin and Septic Shock Trial) study was a multicenter, randomized controlled, double-blind study of 778 septic patients who were dependent on vasopressor therapy to maintain goal MAPs. The study was designed to evaluate the use of the combination of vasopressin and norepinephrine compared with norepinephrine alone. Patients were stratified by disease severity based on their vasopressor requirements

1 hour before randomization; patients requiring 5 to 14 μg/min and greater than or equal to 15 μg/min of norepinephrine (or the equivalent) were considered to have less and more severe forms of septic shock, respectively. The use of low-dose vasopressin (0.03 U/min) significantly decreased the requirement for norepinephrine over the first 4 days of treatment, although this did not result in fewer adverse events. The study authors did report a trend toward improved 28- and 90-day mortality among patients with less severe shock in the combined therapy group, although the vasopressin group also demonstrated a trend toward higher incidence of digit ischemia ($P$ = .11). Importantly, the study was neither powered to detect a mortality difference between combination vasopressin and norepinephrine therapy and single-agent norepinephrine, nor was it a study of vasopressor-refractory shock.[45]

### Dopamine

Dopamine is no longer considered first-line treatment for hypotension in sepsis or septic shock. Its recommended use in sepsis is limited to a subset of patients at low risk for tachyarrhythmias or with bradycardia.[46] In the 2013 American Heart Association guidelines, dopamine was also no longer recommended as the first-line vasoactive medication in cardiogenic shock.[47] Dopamine remains an important component of the Advanced Cardiac Life Support protocol for the treatment of symptomatic bradycardia.

At low doses, dopamine acts primarily through presynaptic and postsynaptic dopaminergic DA2 and DA1 receptors, respectively. These receptors are scattered throughout the coronary, cerebral, renal, and splanchnic vascular beds. In healthy subjects, dopamine has been shown to directly increase effective renal plasma flow and natriuresis in a dose-dependent fashion, via a noncatecholaminergic pathway and independent of any changes in cardiac output.[48,49] For this reason, 'renal dose' dopamine was once thought to restore renal perfusion and protect septic patients from risk of acute kidney injury. However, one of the first randomized controlled trials on the subject demonstrated no benefit for progression to severe kidney injury or need for renal replacement therapy when low-dose dopamine was compared with placebo.[50] Similarly, Marik and Iglesias[51] showed no difference in progression to acute renal failure, the need for renal replacement therapy, or 28-day survival when low-dose dopamine, high-dose dopamine, and no dopamine strategies were compared in 395 oliguric patients with septic shock. The study authors postulated that renal afferent arteriolar dilatation is already maximized under septic conditions, thus limiting low-dose dopamine's potential renovascular protective effects.[52] In another prospective, double-blind, randomized controlled study of 40 ICU patients, low-dose dopamine resulted in decreased renal vascular resistance in patients with preserved renal function; the same doses, however, worsened resistive indices and renal perfusion in patients greater than 55 years of age with preexisting renal insufficiency.[53] The physiologic basis for this finding is not clear, but the study authors suggest that increased levels of endogenous dopamine in older patients with underlying renal insufficiency may predispose to higher tissue-specific concentrations of dopamine when the drug is administered exogenously. As a result of these and other studies, the use of low-dose dopamine for renal protection in sepsis is no longer recommended.

At doses of 2 to 10 μg/kg/min, dopamine's beta-1 effects become more apparent, and its effects on inotropy, dromotropy, and chronotropy predominate.[54] In chronically beta-blocked patients, however, dopamine's DA1- and DA2-mediated effects may continue to have significant effect even at these doses, and vasodilatation of the renal and splanchnic vasculature can precipitate worsening hypotension.[55]

At doses between 10 and 20 µg/kg/min, dopamine's alpha-1 effects predominate, increasing peripheral vascular resistance and MAP. Administration of doses of greater than 20 µg/kg/min can result in profound vasoconstriction, lead to limb ischemia, and worsen end-organ perfusion. Doses in this range are not recommended.

In a predefined subgroup analysis of the SOAP (Sepsis Occurrence in Acutely Ill Patients) II trial, a 2010 randomized controlled trial comparing dopamine and norepinephrine use in all forms of shock, there were no apparent differences in 28-day mortality in patients with septic shock; dopamine use was, however, associated with worse survival curves in patients with cardiogenic shock.[55] The reason for the increased mortality risk in these patients is unclear, but study investigators surmised that dopamine-mediated increases in heart rate were contributory. Notably, the median dopamine doses for all patients over the first 7 days fell within the medium to high dose range, but did not exceed 17 µg/kg/min.[55]

### Phenylephrine

Phenylephrine is a pure alpha-1 agonist whose use in sepsis is not recommended except in very circumscribed conditions that include when norepinephrine use leads to or can be expected to exacerbate serious cardiac arrhythmias, when cardiac output is known to be high despite persistent hypotension, or as a vasopressor adjunct in refractory hypotension. Its use is more ideally suited to the purpose of rapidly correcting vasodilatory hypotension (eg, medication related or vagally mediated). Phenylephrine increases both arterial and venous tone at therapeutic doses and leads to rapid changes in MAP and a baroreflex-mediated bradycardia.

Randomized, controlled trials comparing the use of phenylephrine with norepinephrine in septic shock have explicitly excluded patients with underlying cardiac dysfunction,[56,57] or only included patients with baseline normal-to-high cardiac indices.[58] These studies failed to demonstrate any worsening of cardiac output when phenylephrine was used for hemodynamic support in septic shock. A study using animal models of septic shock with sepsis-induced cardiomyopathy, however, demonstrated worsening ventricular performance when phenylephrine was used.[59] A study of 18 nonseptic patients with underlying cardiac insufficiency demonstrated that single dose phenylephrine, in boluses of 50 to 200 µg, increased the MAP within 20 to 40 seconds of the infusion, with a concurrent and predictable worsening of cardiac output.[60] Negative effects on cardiac output were greatest in the patients with the poorest baseline cardiac function. Given the prevalence of sepsis-associated cardiomyopathy[61,62] and the challenges of appreciating the full complexity of an acutely ill patient's medical history in an emergency department setting, phenylephrine should be used rarely and with extreme caution.

## INITIATING INOTROPIC THERAPY IN SEPSIS

Septic shock is a hyperdynamic process characterized by increased cardiac output and low systemic vascular resistance. Prolonged peripheral vasodilation and increased cardiac indices in sepsis can lead to high-output failure, or may mask an underlying myocardial depression.[63] Myocardial dysfunction is, in fact, common in sepsis and is thought to be explained by to a nonischemic phenomenon of myocardial depression and, possibly, even a self-protective 'hibernation' of the myocardium.[64] Although coronary artery blood flow has been shown to increase in sepsis, the measured difference between coronary artery and coronary sinus oxygen tensions is smaller than expected.[27] This finding suggests that a combination of altered cellular metabolism and autoregulatory changes in the microvasculature of the heart underlie the observed impairment in cardiac contractility in sepsis.

The use of inotropes in sepsis should be considered when there is evidence of myocardial dysfunction, as suggested by low cardiac output, increased filling pressures, or ongoing signs of hypoperfusion despite the restoration of adequate intravascular volume and adequate MAP with fluid and vasopressor therapy. Depending on the presence or absence of fixed valvular insufficiency, diastolic dysfunction, impaired venous return, or increased systemic vascular resistance, selective inotropy may have variable effects on intraventricular filling pressures. Ideally, the use of inotrope therapy augments cardiac contractility while offsetting increases in myocardial oxygen demand (owing to increased contractility and heart rate) with lower filling pressures.[65] Concurrent vasopressor use is often required to achieve this goal.

### Dobutamine

Dobutamine is a dehydroxylated derivative of isoproterenol, with predominantly beta-1 and, to a lesser extent, beta-2 agonism.[66] Dobutamine is also a mild alpha-1 agonist, which is apparent at doses of greater than 15 μg/kg/min, but is more likely to lower systemic vascular resistance via its beta-2 effect at more clinically relevant doses of 5 to 15 μg/kg/min. Dobutamine is the SSCs first-line recommendation for inotropic support in septic patients with high filling pressures or other evidence of impaired cardiac output.

Dobutamine's inotropic effects are more prominent than its chronotropic effects; nevertheless, even at low doses it may increase myocardial oxygen demand and can precipitate malignant arrhythmias. In a 2007 multicenter, randomized controlled trial of 330 ICU patients in septic shock, the combination of dobutamine and norepinephrine had similar efficacy when compared with monotherapy epinephrine.[37] The 2 treatment groups also demonstrated similar side effect profiles and comparable frequencies of adverse events. The majority of adverse events in both the dobutamine plus norepinephrine and monotherapy epinephrine groups were supraventricular tachycardias (13% vs 12%, respectively) and ventricular arrhythmias (5% vs 7%, respectively). Lower frequencies of coronary events, central nervous system bleeding, ischemic strokes, and limb ischemia occurred in both groups (0.9%–2% overall). Vasopressor requirements were also comparable in the groups, and the median daily requirements for dobutamine did not exceed 6 μg/kg/min.

### Milrinone

Milrinone is a nonadrenergic inodilator that exerts its effects via the inhibition of phosphodiesterase 3 and augmentation of cAMP. Cyclic AMP is a critical second messenger in cardiac cell signaling, and is degraded by phosphodiesterase 3. Cyclic AMP triggers the release of calcium from the sarcoplasmic reticulum, and increased cytosolic concentrations of calcium augment cardiac contractility. In the periphery, cAMP inhibits myosin light chain kinase, which binds and activates smooth muscle myosin. Milrinone's potentiation of cAMP's activity in the peripheral vasculature accounts for its vasodilatory effects. These effects may be welcome in cases of cardiogenic shock owing to right ventricular failure, because milrinone also decreases pulmonary vascular resistance. Administration of milrinone for its inotropic properties, however, frequently necessitates the concurrent use of a vasopressor if the phosphodiesterase 3 inhibitor's vasodilatory effects predominate. Milrinone, and inotropes in general, should be used very cautiously, if at all, in patients who are intravascularly volume depleted.

Because milrinone does not exert its effects through the catecholaminergic pathway, its use is specifically recommended in chronically beta-blocked patients, as well as in patients with longstanding heart failure who demonstrate downregulated

expression and desensitization of adrenergic receptors.[66] Importantly, milrinone has a notably long half-life (2–4 hours) when compared with dobutamine (2 minutes), and is further prolonged in patients with renal failure. It is also significantly more expensive than dobutamine, and the 2 drugs have demonstrated similar clinical efficacy and mortality outcomes in patients with decompensated heart failure.[67]

### Levosimendan

Levosimendan is currently not approved for use in the United States, but is used throughout Europe to provide inotropic support in acute decompensated heart failure. Levosimendan is a cardiac myofilament calcium-sensitizing inodilator. Its vasodilatory effects, which are active in the pulmonary, coronary, and peripheral vasculature, are thought to be mediated through various potassium channels in the smooth muscle. Levosimendan is believed to produce its inotropic effects through stabilization and prolongation of the binding of intracellular calcium to cardiac troponin C, thereby augmenting myofilament contractile forces without increasing the amplitude of intracellular calcium transit (ie, the rapid inward current of calcium that occurs during an action potential).[68] Cardiac dysfunction and electrical instability in patients with heart failure reflect, in part, a pattern of abnormal calcium cycling in and out of the cell and sarcoplasmic reticulum. This abnormal calcium cycling ultimately leads to cytoplasmic calcium overload, which is proarrhythmogenic[69]; in these circumstances, the desire for an inotropic agent that avoids beta-adrenergic stimulation is understandable.

Cardiac myocyte calcium homeostasis may, however, become altered in sepsis for a variety of reasons. Animal studies investigating calcium homeostasis in cardiac myocytes in the setting of endotoxemia have reported conflicting findings on the effects of lipopolysaccharide (an endotoxin) exposure, both in terms of myocyte calcium cycling and the myofilament force–calcium relationship.[70,71] It is clear that cardiac myocytes exposed to lipopolysaccharide demonstrate worsening contractility; it is less clear whether this phenomenon reflects abnormally rapid calcium cycling (which increases myocardial oxygen demand) and decreased myofilament sensitivity to calcium (with subsequent worsening of the myofilament force–calcium relationship) or, simply, sluggish intracellular calcium cycling. Pending the outcome of further investigation, future recommendations for inotropic support in sepsis may favor calcium-sensitizing agents over currently used inotropic agents, all of which increase cytoplasmic calcium concentrations.

## VASOPRESSOR AND INOTROPE THERAPY IN PATIENTS WITH BASELINE HYPERTENSION

Higher MAP targets may be warranted in septic patients who have a history of chronic hypertension, and whose autoregulatory thresholds for end-organ perfusion are shifted rightward. The 2014 SEPSISPAM (Sepsis and Mean Arterial Pressure) study, although not adequately powered to detect a mortality benefit, showed no increased incidence of serious adverse events when higher MAPs of 80 to 85 mm Hg were targeted in septic patients with a history of hypertension.[72] The study was pragmatic in nature and allowed for provider discretion; the low target group ultimately achieved average MAPs of 70 to 75 mm Hg, compared with average MAPs of 85 to 90 mm Hg in the high target group. Among the significant subgroup of patients with chronic hypertension the high target group had a significantly lesser incidence of acute renal insufficiency (38.9% compared with 52.0%; $P = .02$), and a significantly decreased need for renal replacement within the first week (31.7% vs 42.2%; $P = .046$). Importantly, the time delay to achieving a minimum MAP of 65 mm Hg may be an independent predictor of mortality in chronically hypertensive patients.[73] Targeting MAPs of

greater than 75 mm Hg in this patient population reflects a reasonable balance of the known risks and benefits.

## SUMMARY

Evidence suggests that, once reasonable fluid resuscitation goals have been achieved, if hypotension persists, providers should promptly initiate vasopressor support with norepinephrine. If, after achieving adequate intravascular volume and adequate MAPs with fluid and vasopressor therapy, there is evidence of myocardial dysfunction or ongoing hypoperfusion, inotropic support with dobutamine should be considered. Vasopressor and inotrope therapy has complex effects that are often difficult to predict, and providers should consider both the physiology of these agents and clinical trial data when contemplating their use. As with any such intervention, it is essential to continually reevaluate the patient to determine if the selected treatment is having the intended result.

## REFERENCES

1. Zarychanski R, Ariano RE, Paunovic B, et al. Historical perspectives in critical care medicine: blood transfusion, intravenous fluids, inotropes/vasopressors, and antibiotics. Crit Care Clin 2009;25:201–20.
2. Davenport HW. Epinephrin(e). Physiologist 1982;25(2):76–82. Available at: http://www.the-aps.org/mm/Publications/Journals/Physiologist/1980-1989/1982/April.pdf. Accessed February 22, 2016.
3. Hoffman BF. Adrenaline zips from bench to bedside. In: Hoffman BF, editor. Adrenaline. Cambridge (MA): Harvard University Press; 2013.
4. Ahlquist RP. A study of the adrenotropic receptors. Am J Physiol 1948;153:586–600.
5. Glick G, Epstein SE, Wechsler AS, et al. Physiological differences between the effects of neuronally released and bloodborne norepinephrine on beta adrenergic receptors in the arterial bed of the dog. Circ Res 1967;21:217–27.
6. Shepherd AP, Granger HJ, Smith EE, et al. Local control of tissue oxygen delivery and its contribution to the regulation of cardiac output. Am J Physiol 1973;225:747–55.
7. Guyton AC, Jones CE, Coleman TG. Cardiac output and its regulation. 2nd edition. Philadelphia: Saunders; 1973.
8. Guimaraes S, Osswald W. Adrenergic receptors in the veins of the dog. Eur J Pharmacol 1969;5:133–40.
9. Medina P, Acuna A, Martinez-Leon JB, et al. Arginine vasopressin enhances sympathetic constriction through the V1 vasopressin receptor in human saphenous vein. Circulation 1998;97:865–70.
10. Kaiser GA, Ross J Jr, Braunwald E. Alpha and beta adrenergic receptor mechanisms in the systemic venous bed. J Pharmacol Exp Ther 1964;144:156–62.
11. Guyton AC, Lindsey AW, Abernathy B, et al. Mechanism of the increased venous return and cardiac output caused by epinephrine. Am J Physiol 1957;192:126–30.
12. Cannesson M, Jian Z, Chen G, et al. Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank-Starling relationship. J Appl Physiol (1985) 2012;113:281–9.

13. Maas J, Pinsky MR, de Wilde RB, et al. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. Crit Care Med 2013;41:143–50.
14. Persichini R, Silva S, Teboul JL, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. Crit Care Med 2012;40:3146–53.
15. Cecconi M, Aya HD, Geisen M, et al. Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. Intensive Care Med 2013;39:1299–305.
16. Berlin DA, Bakker J. Understanding venous return. Intensive Care Med 2014;40: 1564–6.
17. Goldberg LI, Bloodwell RD, Braunwald E, et al. The direct effects of norepinephrine, epinephrine, and methoxamine on myocardial contractile force in man. Circulation 1960;22:1125–32.
18. Zausig YA, Geilfus D, Missler G, et al. Direct cardiac effects of dobutamine, dopamine, epinephrine, and levosimendan in isolated septic rat hearts. Shock 2010; 34:269–74.
19. Binion JT, Morgan WJ, Welch GH, et al. Effect of sympathomimetic drugs in acute experimental cardiac tamponade. Circ Res 1956;4:705–9.
20. Mueller H, Ayres SM, Gregory JJ, et al. Hemodynamics, coronary blood flow, and myocardial metabolism in coronary shock; response of 1-norepinephrine and isoproterenol. J Clin Invest 1970;49:1885–902.
21. Guyton AC, Lindsey AW, Gilluly JJ. The limits of right ventricular compensation following acute increase in pulmonary circulatory resistance. Circ Res 1954;2: 326–32.
22. Gould KL. Why angina pectoris in aortic stenosis. Circulation 1997;95:790–2.
23. Aviado DM Jr, Schmidt CF. Effects of sympathomimetic drugs on pulmonary circulation: with special reference to a new pulmonary vasodilator. J Pharmacol Exp Ther 1957;120:512–27.
24. Micek ST, McEvoy C, McKenzie M, et al. Fluid balance and cardiac function in septic shock as predictors of hospital mortality. Crit Care 2013;17:R246.
25. Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. Br J Pharmacol 2012;165:2015–33.
26. Langston JB, Guyton AC. Effect of epinephrine on the rate of urine formation. Am J Physiol 1958;192:131–4.
27. Hunter JD, Doddi M. Sepsis and the heart. Br J Anaesth 2010;104(1):3–11.
28. Bai X, Yu W, Ji W. Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care 2014;18:532. Available at: http://www.ncbi. nlm.nih.gov/pmc/articles/PMC4194405/. Accessed February 10, 2016.
29. McGee DC, Gould MK. Preventing complications of central venous catheterization. N Engl J Med 2003;348:1123–33.
30. Ricard JD, Salomon L, Boyer A, et al. Central or peripheral catheters for initial venous access of ICU patients: a randomized controlled trial. Crit Care Med 2013;41(9):2108–15.
31. Cardenas-Garcia J, Schaub K, Belchikov Y, et al. Safety of peripheral administration of vasoactive medication. J Hosp Med 2015;10(9):581–5.
32. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care 2015;30(3):653.e9-17.
33. Boerma EC, Ince C. The role of vasoactive agents in the resuscitation of microvascular perfusion and tissue oxygenation in critically ill patients. Intensive Care Med 2010;36:2004–18.

34. Avni T, Lador A, Lev S, et al. Vasopressors for the treatment of septic shock: systematic review and meta-analysis. PLoS One 2015;10(8):e0129305. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4523170/?report=reader.        Accessed March 10, 2016.
35. De Backer D, Aldecoa C, Nijmi H, et al. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. Crit Care Med 2012;40(3):725–30.
36. Jentzer JC, Coons JC, Link CB, et al. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. J Cardiovasc Pharmacol Ther 2015;20(3):249–60.
37. Annane D, Vignon P, Renault A, et al, CATS Study Group. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 2007;370:676–84.
38. Mahmoud KM, Ammar AS. Norepinephrine supplemented with dobutamine or epinephrine for the cardiovascular support of patients with septic shock. Indian J Crit Care Med 2012;16(2):75.
39. Levy B. Lactate and shock: the metabolic view. Curr Opin Crit Care 2006;12(4): 315–21.
40. Barr JW, Lakin RC, Rosch J. Similarity of arterial and intravenous vasopressin on portal and systemic hemodynamics. Gastroenterology 1975;69:13–9.
41. Holmes CL, Landry DW, Granton JT. Science review: vasopressin and the cardiovascular system part 1–receptor physiology. Crit Care 2003;7:427–34.
42. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the intensive care unit. Ann Am Thorac Soc 2014;11(5):811–22.
43. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345(8):588–95.
44. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997;95(5):1122–5.
45. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358(9):877–87.
46. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41(2):580–637.
47. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362–425. Available at: https://www.heart.org/idc/groups/heart-public/@wcm/@mwa/documents/downloadable/ucm_453635.pdf. Accessed March 14, 2016.
48. Olsen NV. Effects of dopamine on renal haemodynamics, tubular function and sodium excretion in normal humans. Dan Med Bull 1998;45(3):282–97.
49. McDonald RH, Goldberg LI, McNay JL, et al. Effect of dopamine in man: augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. J Clin Invest 1964;43(6):1116–24.
50. Bellomo R, Chapman M, Finfer S, et al, ANZICS Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Lancet 2000;356(9248):2139–43.
51. Marik PE, Iglesias J, NORASEPT II. Low-dose dopamine does not prevent acute renal failure in patients with septic shock and oliguria. Am J Med 1999;107(4): 392–5.
52. Bersten AD, Rutten AJ. Renovascular interaction of epinephrine, dopamine and intraperitoneal sepsis. Crit Care Med 1995;23(3):537–44.

53. Lauschke A, Teichgräber UK, Frei U, et al. 'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure. Kidney Int 2006;69:1669–74.

54. Strehlow MC. Vasopressors and inotropes. In: Arbo JE, editor. Decision making in emergency critical care. Philadelphia: Wolters Kluwer; 2015.

55. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362(9):779–89. Available at: http://www.nejm.org/doi/suppl/10.1056/NEJMoa0907118/suppl_file/nejm_de_backer_779sa1.pdf. Accessed March 11, 2016.

56. Morelli A, Ertmer C, Rehberg S, et al. Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: a randomized, controlled trial. Crit Care 2008;12(6):R143. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2646303/. Accessed February 10, 2015.

57. Jain G, Singh DK. Comparison of phenylephrine and norepinephrine in the management of dopamine-resistant septic shock. Indian J Crit Care Med 2010;14(1):29–34.

58. Gregory JS, Bonfiglio MF, Dasta JF, et al. Experience with phenylephrine as a component of the pharmacologic support of septic shock. Crit Care Med 1991;19(11):1396–400.

59. Ducrocq N, Kimmoun N, Furmaniuk A, et al. Comparison of equipressor doses of norepinephrine, epinephrine, and phenylephrine on septic myocardial dysfunction. Anesthesiology 2012;116(5):1083–91.

60. Schwinn DA, Reevs JG. Time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. Anesth Analg 1989;68(5):571–8.

61. Vieillard-Baron A. Septic cardiomyopathy. Ann Intensive Care 2011;1:6. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3159902/pdf/2110-5820-1-6.pdf. Accessed March 15, 2016.

62. Romero-Bermejo FJ, Ruiz-Bailen M, Gil-Cebrian J, et al. Sepsis-induced cardiomyopathy. Curr Cardiol Rev 2011;7(3):163–83. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3263481/. Accessed March 15, 2016.

63. Merx MW, Weber C. Cardiovascular involvement in general medicine conditions: sepsis and the heart. Circulation 2007;116:793–802.

64. Levy RJ, Piel DA, Acton PD, et al. Evidence of myocardial hibernation in the septic heart. Crit Care Med 2005;33(12):2752–6.

65. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part I: inotropic infusions during hospitalization. Circulation 2003;108:367–72.

66. Overgaard CB, Džavík V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. Circulation 2008;118:1047–56.

67. Yamani MH, Haji SA, Starling HC, et al. Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: hemodynamic efficacy, clinical outcome, and economic impact. Am Heart J 2001;142(6):998–1002.

68. Papp Z, Édes I, Fruhwald S, et al. Levosimendan: molecular mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol 2012;159(2):82–7.

69. Wang Y, Goldhaber JI. Return of calcium: manipulating intracellular calcium to prevent cardiac pathologies. Proc Natl Acad Sci U S A 2004;101(16):5697–8.

70. Stamm C, Cowan DB, Friehs I, et al. Rapid endotoxin-induced alterations in myocardial calcium handling. Anesthesiology 2001;95(6):1396–405.

71. Takeuchi K, del Nido PJ, Ibrahim AE, et al. Increased myocardial calcium cycling and reduced myofilament calcium sensitivity in early endotoxemia. Surgery 1999; 126(2):231–8.
72. Asfar P, Meziani F, Hamel J, et al. High versus low blood-pressure targets in patients with septic shock. N Engl J Med 2014;370(17):1583–93.
73. Leone M, Asfar P, Radermacher P, et al. Optimizing mean arterial pressure in septic shock: a critical reappraisal of the literature. Crit Care 2015;19:101. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4355573/pdf/13054_2015_Article_794.pdf. Accessed March 8, 2016.