The Art and Science of Infusion Nursing

John M. Allen, PharmD, BCPS

Understanding Vasoactive Medications

Focus on Pharmacology and Effective Titration

ABSTRACT

In the care of the critically ill patient, the use of vasoactive substances such as vasopressors and inotropes can be a potentially lifesaving intervention. An understanding of the pathophysiology of the various types of shock and pharmacology of the pharmacological agents used in the treatment of shock is necessary for intensive care unit clinicians to make appropriate decisions regarding when vasopressors or inotropes are indicated and assess their effectiveness. This review article will provide background on the different types of shock, compare and contrast the commonly used vasoactive substances in critically ill patients, discuss titration strategies for these agents, and review management of extravasation of these agents.

Key words: critically ill, intensive care unit, inotropes. titration, vasopressors

Hemodynamic instability is a common cause of morbidity and mortality in critically ill patients. In clinical practice, hemodynamic instability is routinely defined as a systolic blood pressure ≤ 90 mm Hg.

However, when considering hemodynamic instability, clinicians should be more concerned with organ hypoperfusion, rather than a fixed blood pressure valve. Organ hypoperfusion can clinically manifest in a myriad of ways. Among the most prominent are altered mental status, decreased renal and hepatic function, decreased cardiac function, cold extremities, and shock.

Systemic blood pressure is the primary method of assessing hemodynamic instability and is determined by the interplay between systemic vascular resistance (SVR) and cardiac output (CO). As SVR and CO increase or decrease, so does systemic blood pressure.

There are multiple etiologies for hemodynamic instability, each with differing treatments.[1-5] In most patients with hemodynamic instability, administration of intravenous fluids, such as normal saline or lactated Ringer's, is initially used as an attempt to improve hemodynamics. This may not alleviate the hemodynamic instability completely in some cases, and, in these instances, the use of vasoactive medications, including vasopressors and/or inotropes, is warranted.

The choice of which vasoactive medication to use will depend on the etiology of the hemodynamic instability. Patients with hemodynamic instability resulting from distributive shock typically present with decreased SVR, leading to a decrease in blood pressure. Distributive shock is noted in patients with sepsis or those in anaphylactic shock. In these patients, pharmacological agents to increase SVR, such as vasopressors, are often used.

Unlike patients with distributive shock, those with cardiogenic shock have markedly decreased CO, resulting in hemodynamic instability. Patients with heart failure typically are most prone to developing cardiogenic shock when they decompensate. Strategies to improve hemodynamics include the use of pharmacological agents, such as inotropes, to increase cardiac contractility and CO.

Knowledge of receptors that affect SVR and CO is important when considering the differences among vasopressors and inotropes. When stimulated, alpha-1 adrenergic receptors found in the vasculature lead to vasoconstriction and, ultimately, an increase in SVR and blood pressure. Stimulation of beta-1 adrenergic receptors found in the heart leads to increased contractility and heart rate, leading to increased CO.

This review article will focus on comparing and contrasting various vasopressors and inotropes and discuss how they are used in clinical practice. In addition, it will present considerations for the infusion nurse, including

Author Affiliations: Department of Pharmacotherapeutics and Clinical Research, University of South Florida College of Pharmacy; and Department of Internal Medicine, University of South Florida Morsani College of Medicine, Tampa, FL.

John M. Allen, PharmD, BCPS, is an Assistant Professor at the University of South Florida College of Pharmacy. Dr. Allen also holds joint appointment as an assistant professor within the Department of Internal Medicine at the University of South Florida Morsani College of Medicine.

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Corresponding Author: John M. Allen, PharmD, BCPS, 12901 Bruce B. Downs Blvd., MDC 30, Tampa, FL 33612 (johnallen@health.usf.edu).

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how to effectively titrate vasopressors and inotropes and manage extravasation.

VASOPRESSORS AND INOTROPES

Critically ill patients with hemodynamic instability refractory to intravenous fluids typically require vasoactive medications. Among these, vasopressors are used to improve SVR and blood pressure. Examples of vasopressors include phenylephrine, norepinephrine, epinephrine, dopamine, and vasopressin. Each vasopressor has varying affinity for alpha and beta receptors, and these differences explain their varying effects on SVR and CO. A thorough understanding of the relative differences between the receptor profiles of vasopressors can help clinicians decide which agent is best in specific situations. Figure 1 illustrates these relative differences in receptor activity among the various vasopressors and inotropes.

Phenylephrine is a pure alpha-1 adrenergic agonist, with little to no beta-1 adrenergic activity. Phenylephrine is typically recommended only when patients require vasopressor therapy and are tachycardic. The lack of beta activity and neutral effects on myocardial oxygen demand make phenylephrine a reasonable alternative in those patients. Phenylephrine is not without limitations, however. It can cause peripheral ischemia and splanchnic vasoconstriction, which limits its widespread use as a vasopressor.

Norepinephrine has a mixed receptor profile with mainly alpha-1 adrenergic activity, making it an attractive option when attempting to increase SVR. Norepinephrine is considered the initial vasopressor of choice for most patients,[1-5] and the recently updated *Surviving Sepsis* guidelines continue to recommend norepinephrine as the initial vasopressor of choice for patients with septic shock.[4]

Epinephrine is a nonspecific alpha and beta adrenergic agonist. Clinical effects include an increase in CO and profound peripheral vasoconstriction. The use of epinephrine is limited to refractory cases of hypotension, however, because of its adverse effects, such as increasing serum lactate levels and reduced splanchnic blood flow.

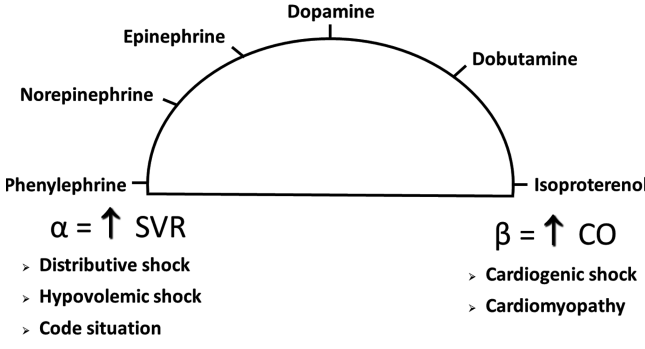

Figure 1 Comparison of relative effects of select vasopressors and inotropes.

Vasopressin is a naturally occurring hormone produced in the pituitary gland. At high doses, vasopressin can cause vasoconstriction. In response to hypotension, serum vasopressin levels typically increase, causing vasoconstriction and an increase in SVR. In the setting of sepsis, however, there is a relative deficiency in vasopressin. Previous studies evaluating vasopressin as a primary option for the management of septic shock have yielded unimpressive results when compared with norepinephrine. For this reason, the use of vasopressin in patients with septic shock is limited primarily to adjunctive therapy, usually in combination with norepinephrine for those with refractory shock.

Dopamine has a mixed-receptor profile, which has dose-dependent effects. At low doses (2-5 μg/kg/min), dopamine acts as an agonist on dopaminergic receptors. Previous literature suggested that low-dose dopamine improved renal function in critically ill patients. However, this method has not been shown to improve clinical outcomes, and it is not currently recommended.[4-6] Moderate doses of dopamine (5-10 μg/kg/min) produce beta receptor agonist activity, increasing CO. In contrast, high doses of dopamine (10-20 μg/kg/min) yield alpha-1 agonist activity, producing an increase in SVR.

Previously considered a first-line vasopressor for septic shock, dopamine is now recommended only in unique circumstances.[4,5] The downgraded recommendation for the use of dopamine was primarily based on the findings of the Sepsis Occurrence in Acutely Ill Patients–II trial, which compared norepinephrine with dopamine for the treatment of shock. No difference was noted in 28-day, all-cause mortality between the 2 agents. However dopamine was associated with a significantly increased rate of cardiac arrhythmias.[7] The use of vasopressors is not without the potential for adverse effect. A potential concern with some vasopressors is a detrimental effect on splanchnic circulation, potentially leading to bowel ischemia and perforation. This concern is most notable with the use of phenylephrine and epinephrine.[3] The risk may be reduced by ensuring adequate fluid resuscitation before starting vasopressors.

Unlike in septic shock, when increasing SVR is the therapeutic goal of vasopressors, in the setting of cardiogenic shock increasing CO is the therapeutic goal. Vasoactive medications that have positive inotropic effects, which increase CO, are known as inotropes. Examples of inotropes include dobutamine, milrinone, and isoproterenol.

Dobutamine is a beta-1 adrenergic agonist and causes increased cardiac contractility, heart rate, and oxygen delivery. Combined, these lead to an increase in CO. Milrinone has a unique mechanism of action when compared with other vasoactive medications. It acts as a phosphodiesterase-3 inhibitor, working selectively in

TABLE 1

Vasopressors and Inotropes

Drug	Mechanism of Action	Common Uses	Typical Dosing	Onset/Duration of Action	Adverse Effects
Phenylephrine	Alpha-1 adrenergic agonist	Distributive shock, hypotension with tachycardia	0.4-9.1 cg/kg/min	Onset: Immediate Duration: 15-30 minutes	Splanchnic hypoperfusion, extensive peripheral vasoconstriction (at higher doses)
Norepinephrine	Mixed alpha-1 and beta-1 adrenergic agonist	Distributive shock	0.05-0.5 mcg/kg/min	Onset: Immediate Duration: 1-2 minutes	Arrhythmias, peripheral vasoconstriction
Epinephrine	Mixed alpha-1 and beta-1 adrenergic agonist	Distributive shock, cardiac arrest, anaphylaxis, heart block, bradycardia	0.05-0.5 mcg/kg/min	Onset: Immediate Duration: Up to 60 minutes	Splanchnic hypoperfusion, increased myocardial oxygen demand
Dopamine	Mixed dopaminergic, beta-1, alpha-1 adrenergic agonist (dose-dependent)	Distributive shock, bradycardia	Low dose: 1-3 mcg/kg/min Moderate dose: 3-10 mcg/kg/min High dose: 10-20 mcg/kg/min	Onset: 5 minutes Duration: 10 minutes	Tachycardia, cardiac arrhythmias
Vasopressin	V1 receptor agonist	Refractory septic shock, GI bleeding, diabetes insipidus	0.01-0.04 units/min	Onset: Immediate Duration: 10-30 minutes	Splanchnic hypoperfusion
Dobutamine	Beta-1 adrenergic receptor agonist	Cardiogenic shock, decompensated heart failure	2-20 mcg/kg/min	Onset: 1-10 minutes Duration: 2-10 minutes	Hypotension, increased myocardial oxygen demand
Milrinone	Phosphodiasterase-3 inhibitor	Cardiogenic shock, decompensated heart failure	LD: 50 mcg/kg over 10 minutes MD: 0.375-0.75 mcg/kg/min	Onset: 5-15 minutes Duration: 2-3 hours	Hypotension, thrombocytopenia, arrhythmias
Isoproterenol	Beta-1 and beta-2 adrenergic receptor agonist	Bradyarrhythmias, AV block	2-20 mcg/min	Onset: Immediate Duration: 10-15 minutes	Hypotension, arrhythmias

Abbreviations: AV, atrioventricular; LD, loading dose; MD, maintenance dose.

cardiac and vascular tissue, resulting in an inotropic effect in cardiac tissue and vasodilation.

When choosing between dobutamine and milrinone to increase CO, numerous considerations may come into play. Because of its mechanism of action, milrinone has the potential to cause hypotension. For this reason, milrinone loading doses should be avoided in hypotensive patients, and lower initial maintenance doses should be used, if necessary. Milrinone also requires extensive renal adjustment because of its extensive renal elimination (85%), with the half-life about 15 times longer in patients with renal failure, requiring continuous renal replacement therapy compared with patients with normal renal function.[8] A potential advantage of milrinone is its longer duration of action compared with dobutamine (2-3 hours vs 5-10 minutes), making it an attractive option for outpatient use for patients with severe heart failure, as a bridge to cardiac transplantation or implantation of a left ventricular-assist device.

Isoproterenol is a nonselective beta receptor agonist that produces an increase in CO. However, because of its poor side-effect profile, its use is limited to patients refractory to other inotropic agents and is infrequent in clinical practice. Table 1 describes commonly used vasoactive medications in critically ill patients.

TITRATION OF VASOACTIVE MEDICATIONS

Given the pharmacokinetics of vasopressors and inotropes, particularly their short half-life and duration of action, continuous infusion administration is necessary. Emergent need for the use of these potentially lifesaving medications often necessitates rapid titration to achieve hemodynamic stability. The bedside nurse has this responsibility and must strike a fine balance between maintaining hemodynamic stability and adequate perfusion, while using the minimal amount of drug necessary.

Evidence regarding effective ways to titrate vasopressors and inotropes is largely absent from the literature. Titration of vasoactive medications historically has been based primarily on clinical end points, such as maintaining mean arterial pressure (MAP) > 60 mm Hg,

TABLE 2

pH and Osmolality of Select Vasopressors and Inotropes

Drug	pH	Osmolality (mOsm/kg)[10]
Phenylephrine	3.0-6.5	*
Norepinephrine	3.0-4.5	319
Epinephrine	2.5-5.0	273-348
Dopamine	3.3-3.6	261-286
Vasopressin	2.5-4.5	*
Dobutamine	2.5-5.5	260-361
Milrinone	3.2-4.0	*
Isoproterenol	2.5-4.5	277-293

**No data available.*

urine output to > 0.5 mL/kg/h, or a cardiac index > 2.5 L/min/m^2.[1-5]

When considering the pharmacokinetics of vasoactive medications, their very short elimination half-lives allow for rapid attainment of serum drug steady-state concentration (within 10-15 minutes). This allows for rapid titration of vasoactive medications to achieve hemodynamic stability. On the basis of this concept, titration typically should not occur any faster than every 5 to 15 minutes because of the potential for drug accumulation and "overshooting" therapeutic goals, such as MAP, and causing hypertension and arrhythmias when up-titrating or causing hypotension when down-titrating vasoactive medications.

Another dilemma often faced by the bedside clinician is determining which agent to titrate first when patients are on multiple vasoactive medications. There is little evidence-based guidance for clinicians to use.

One study completed by Bauer and colleagues[9] investigated the impact of the order of discontinuation of either vasopressin or norepinephrine in 50 adult patients with septic shock. The discontinuation of norepinephrine before vasopressin led to a decreased incidence of hypotension within 24 hours (16% vs 56%, P = .008) and longer time to the first episode of hypotension (7.33 vs 1.67 hours, P = .040), respectively. No differences were noted in intensive care unit (ICU) length of stay or mortality.

These results led the authors to conclude that in adult septic patients requiring both norepinephrine and vasopressin, discontinuation of norepinephrine first was associated with decreased incidence of hypotension. Although the sample size was small (n = 50), these results suggest that the order in which vasoactive medications are discontinued can have clinically meaningful consequences. Clinical decision making regarding which vasoactive medications to discontinue should focus on adverse side effects of the respective agents involved and using the minimum doses necessary to maintain hemodynamic stability.

EXTRAVASATION OF VASOACTIVE MEDICATIONS

One consideration for the bedside clinician using any intravenously administered medication is the potential for extravasation. Vasoactive medications are no different. Vasopressors and inotropes are classified as vesicants and have the potential to cause skin necrosis, if extravasation occurs. Table 2 lists the pH and osmolality of selected vasopressors and inotropes.[10]

Much of the literature regarding the potential for extravasation and skin necrosis associated with the use of vasoactive medications is limited to case reports and series.[11-15] One of the major risk factors for extravasation appears to be prolonged administration through peripheral veins. Vasoactive medications should be administered through a central line when possible. High doses of vasoactive medications, including norepinephrine and dopamine, have also been implicated.

In some circumstances, short-term peripheral administration may be necessary, such as while a central line is being placed in a hemodynamically unstable patient. If peripheral administration is necessary, a 20 gauge or larger should be placed, and central access should be obtained as soon as possible. Clinicians should exercise caution in patients with difficulty communicating pain, as this may potentially delay recognition of extravasation.

If extravasation occurs, administration of the vasoactive medication should be discontinued. Direct local administration of 5 to 10 mg of phentolamine, an alpha adrenergic receptor antagonist, causes vasodilation, which can limit the extent of skin and tissue necrosis.[16] The role of application of heat and cold to the area is less clear. Although heat and/or cold application is commonly used in the management of chemotherapy-associated extravasation, it has limited application to extravasation of vasoactive medications.[17,18]

CONCLUSIONS

Vasoactive medications are routinely used in the care of critically ill patients. Vasopressors, such as norepinephrine, are frequently used in patients with septic shock to improve SVR, whereas inotropes are often used in patients with cardiogenic shock to improve cardiac contractility and CO.

The selection of which vasopressor or inotrope to use is based on a number of considerations, including drug-, patient-, and disease-specific factors. Because the evidence on specific methods of titrating vasoactive medications is scant, titration of these medications should be based, for the most part, on clinical response. Given the short half-life of vasoactive medications, rapid titration is possible (every 5-15 minutes). However, close monitoring should be provided to assess patient response. Although rare, extravasation of vasoactive medications can be a devastating injury resulting in skin and soft tissue destruction. This adverse effect of vasoactive medications may be mitigated by central line administration and routine IV site care.

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