Cardiovascular Pharmacotherapy Update for the Intensive Care Unit

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Pharmacologic agents including vasodilators, inotropes, and vaspressors are frequently used in the critical care setting for management of the unstable cardiac patient. These medications are used to elicit varying effects on vascular resistance, myocardial contractility, and heart rate to help achieve desired hemodynamic and clinical endpoints. Therefore, it is important for the critical care nurse to have a practical understanding and working knowledge of cardiovascular pharmacotherapy in the intensive care unit setting. This article reviews the pharmacology and clinical utility of commonly used intravenous “vasoactive” medications encountered in the intensive care unit. We also highlight innovations in pharmacotherapy for this patient population, and provide practical considerations for the most appropriate and safe use of these medications. Key words: inotrope, titration, vasodilator, vasopressor

HARMACOTHERAPEUTIC agents with varying hemodynamic effects and vasoactive properties are frequently encountered in the intensive care unit (ICU) environment for management of the unstable cardiac patient. These “vasoactive” medications may be used for their effects on heart rate (chronotropy), myocardial contractility (inotropy), and/or vascular resistance (vasoconstriction or vasodilation) to elicit changes in arterial pressure and desired hemodynamic and clinical endpoints. While some of these medications provide unique mechanisms of action, others have more nonselective pharmacologic effects. Consequently, these medications are often used concomitantly to produce an intended response without precipitating deleterious effects. In fact, the therapeutic window between safety and effectiveness is influenced by many factors, including dose and duration of therapy, acid-base status, and other clinical variables such as comorbid conditions. For these reasons, it is pertinent for the critical care nurse to have a practical understanding and working knowledge of cardiovascular pharmacotherapy in the ICU setting. This article reviews the pharmacology and clinical utility of commonly used intravenous (IV) “vasoactive” medications for the unstable cardiac patient. We also highlight innovations in pharmacotherapy for this patient population, and provide practical considerations for the most appropriate and safe use of these medications. An adult titratable drip protocol (Appendix) that was implemented at one institution to provide guidance to nurses when these agents are initially ordered and for titration to maintain a hemodynamic goal is included.

VASODILATORS

An overview of the commonly used IV vasodilators is presented with an emphasis on their role in the management of patients with acute decompensated heart failure (ADHF). Although controlled clinical trials for many of these agents are lacking, they are frequently
used for hemodynamic improvement. The Heart Failure Society of America recommends consideration of nitroglycerin (NTG), nitroprusside, or nesiritide as an addition to diuretics for prompt improvement of congestive symptoms, provided there is no symptomatic hypotension. A combination of NTG or nitroprusside with diuretics is recommended for prompt symptom relief in patients with acute pulmonary edema or severe hypertension. Finally, any of the 3 IV vasodilators may be considered in patients with ADHF and advanced heart failure with persistent severe symptoms despite aggressive therapies with diuretics and standard oral therapies.

Nesiritide

Brain-type natriuretic peptide (BNP) is an endogenous hormone produced and released by the ventricular myocardium in response to increased wall stress, hypertrophy, and volume overload. The hemodynamic effects of BNP include increased arterial and venous vasodilation, natriuresis, diuresis, and an attenuation of the renin-angiotensin-aldosterone and sympathetic nervous systems. Nesiritide (Natrecor®, Scios, Fremont, Calif) is an FDA-approved recombinant human BNP for the treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. In this setting, nesiritide has demonstrated significant reductions in pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance, systolic and mean pulmonary artery pressures, and a significant improvement in cardiac index (CI) compared with NTG and placebo. A potential advantage of nesiritide is its ability to promptly reduce PCWP, achieving 90% of its peak effect within 30 minutes. For improvement in clinical symptoms, nesiritide is comparable to NTG. Nesiritide is dosed as a 2 μg/kg IV bolus, followed by a continuous IV infusion initiated at 0.01 μg/kg per minute. It may be titrated in 0.005 μg/kg per minute increments, preceded by a 1 μg/kg bolus every 3 hours to a maximum dose of 0.03 μg/kg per minute. The duration of infusion is generally 72 hours or less, and in the largest clinical trial to date, the median duration of use was 24 hours. The main adverse effect is dose-dependent hypotension, which may persist for 2 to 7 hours. If symptomatic hypotension occurs, nesiritide should be discontinued until symptoms resolve and the systolic blood pressure (BP) is higher than 90 mm Hg. At that point, it may be restarted at a 30% lower infusion rate without a bolus dose. It should not be used as primary therapy for patients with cardiogenic shock or for patients with a systolic BP of less than 90 mm Hg. Although nesiritide has been studied in combination with diuretics, dopamine, and/or dobutamine, concomitant use with nitroprusside, NTG, and/or milrinone is limited and should be avoided to minimize hypotension. The risk of dysrhythmia is lower with nesiritide than with inotropes, including dobutamine.

Since the approval of nesiritide in 2001, clinicians have used nesiritide mainly for the management of ADHF. Among some clinicians, there was a perception that nesiritide could preserve or even improve renal function and perhaps reduce the need for loop diuretics, despite a lack of clinical data to support this role. A study by Wang et al described a lack of effect of nesiritide on diuresis, natriuresis, glomerular filtration rate, or renal plasma flow in patients with ADHF and an acute decline in renal function. Recent meta-analyses by Sackner-Bernstein et al have actually suggested an increased risk of worsening renal function and short-term mortality with nesiritide as compared with non-inotropic-based therapies for ADHF. An expert panel has since convened to review the available data surrounding the safety of nesiritide. The panel noted a dose-dependent increase in serum creatinine (>0.5 mg/dL), indicating renal dysfunction at FDA-approved doses (0.01–0.03 μg/kg per minute). The mechanism and implications of these changes were not clear. There was, however, no evidence to support an improvement in renal function. With regard to effects on mortality, the panel noted that completed trials have collectively shown a trend toward an increased
hazard at 30 days but not at 180 days with nesiritide. It is important to note that the insufficient number of events, heterogeneity of the clinical trial participants, and other confounding variables have rendered the overall findings inconclusive.

Consequently, the expert panel provided overall recommendations concerning the appropriate role of nesiritide. According to the panel, its use should be strictly limited to patients presenting to the hospital with ADHF who have dyspnea at rest, consistent with the current FDA approval. In addition, it should not be used for the following purposes: to replace diuretics, to improve renal function or enhance diuresis, or for scheduled repetitive or intermittent outpatient use.

A large clinical trial is underway to further assess the benefits and risks of nesiritide compared with standard therapy.

**Nitroglycerin**

NTG is an organic nitrate (glyceryl trinitrate) that exerts its pharmacologic effects through nitric oxide–mediated smooth muscle vasodilation. NTG primarily affects venous vasodilation, particularly at lower doses (<100–150 μg/min). As the dose is increased (>100–150 μg/min), arterial vasodilation may also be observed. The main hemodynamic effects observed are reductions in preload (PCWP, central venous pressure) and arterial BP. Therefore, NTG is an effective adjunct for the management of patients with ADHF by decreasing cardiac filling pressures and increasing cardiac output (CO). In this setting, NTG is most effective in patients with volume overload and elevated BP. It is also an effective coronary artery vasodilator, making it particularly useful as an antianginal agent in the setting of myocardial ischemia. NTG may also be used for the management of patients with hypertensive emergencies, but may be most beneficial when associated with volume overload.

NTG is administered by continuous IV infusion starting at a dose of 5 to 10 μg/min, and titrated in increments of 5 μg/min every 5 to 10 minutes for the desired hemodynamic or clinical response. The hemodynamic responses to IV NTG are rapid and short acting, allowing for rapid dose escalation. The doses required vary considerably, but generally should not exceed 300 μg/min. Uninterrupted (>24 hours) use produces nitrate tolerance, or tachyphylaxis. High dose requirements (>350 μg/min) may be the result of tachyphylaxis or drug loss via adsorption to tubing. Because NTG binds to soft plastics such as polyvinylchloride, glass bottles and specialized infusion sets are used to deliver the medication.

Potential adverse effects associated with NTG are hypotension, tachycardia, paradoxical bradycardia, headache, and hypoxemia caused by increased ventilation-perfusion mismatch. The risk of hypotension is exacerbated by hypovolemia, which can occur in the setting of right ventricular infarction. Therefore, NTG and other nitrates are best avoided in this setting. It is also important to note that NTG should not be given within 24 to 48 hours of the use of phosphodiesterase (PDE) inhibitors (ie, sildenafil) for erectile dysfunction because of the excessive risk of hypotension. Fortunately, nitrate-induced hypotension responds well to fluid replacement.

Although clinical trial data evaluating the effects of NTG are minimal, it remains a cornerstone of therapy for patients with symptomatic ischemic heart disease and ADHF. In the VMAC trial comparing NTG with nesiritide and placebo for patients with ADHF, NTG and nesiritide were comparable in improving measures of clinical symptoms (dyspnea and global clinical status). However, the use of nesiritide resulted in a greater reduction in the primary endpoint (PCWP at 3 hours) than with NTG and placebo. Further titration of NTG throughout the study resulted in similar reductions in systolic BP by 24 hours and PCWP by 36 hours compared with nesiritide.

**Nitroprusside**

Sodium nitroprusside (SNP) is a potent, direct-acting vasodilator with a mechanism of
action similar to NTG despite some unique pharmacologic differences. Like NTG, SNP is metabolized to nitric oxide. However, SNP also produces cyanide, which must then be detoxified by the liver to thiocyanate and cleared by the kidneys. SNP also produces both venous and arterial vasodilation at usual doses, unlike NTG that predominantly affects only venous capacitance except at high doses. From a hemodynamic standpoint, SNP promptly reduces preload (PCWP), afterload (systemic vascular resistance or SVR and pulmonary vascular resistance), and systemic BP while causing an increase or no change in CO. It has been effective for the management of patients with severe heart failure and hypertensive emergencies. Venous vasodilation decreases right and left ventricular filling pressures, whereas arterial vasodilation causes a reduction in peripheral resistance (afterload), resulting in enhanced systolic emptying and reduced wall stress and myocardial oxygen consumption. Invasive hemodynamic monitoring has been useful during SNP therapy.\textsuperscript{10–12}

SNP is infused either centrally or peripherally as a continuous IV infusion, starting at an initial dose of 0.1 to 0.2 $\mu$g/kg per minute. Because of the rapid onset of action and short half-life, SNP may be titrated every 5 minutes up to 5 $\mu$g/kg per minute. In some cases, higher doses have been reported (up to 10 $\mu$g/kg per minute for no more than 10 minutes). However, responses may be observed at low doses (0.5 $\mu$g/kg per minute). The solution and tubing must be protected from light to avoid deterioration of SNP. The appropriate dose and duration of therapy are also determined by the safety profile.

The main risk of using SNP is cyanide and thiocyanate toxicities. Patients with hepatic or renal insufficiency, or those patients that have received more than 2 to 3 $\mu$g/kg per minute for 72 hours or more, may accumulate cyanide or thiocyanate and must be monitored accordingly. Signs of cyanide toxicity include central nervous system dysfunction (mental status change, seizure, coma), cardiovascular instability, and increasing metabolic acidosis. Thiocyanate toxicity may manifest similarly, but may also include hyperreflexia, confusion, psychosis, miosis, and other non-specific symptoms (tinnitus, fatigue, nausea, vomiting). Recommendations to minimize these risks are not to exceed a maintenance infusion of 2 $\mu$g/kg per minute or to consider alternative or additional vasodilators to reduce or shorten the infusion. Management options for suspected cyanide toxicity after discontinuation of SNP include 100% oxygen, mechanical ventilation as needed, correction of metabolic acidosis with sodium bicarbonate, 3% sodium nitrite (4–6 mg/kg slow IV), and sodium thiosulfate (150–200 mg/kg IV over 15 minutes).\textsuperscript{13} Other adverse sequelae that have been reported include exacerbation of intrapulmonary shunting, resulting in worsening of oxygenation; hypotension; headache; nausea; vomiting; and abdominal cramps. Finally, SNP is not recommended in patients with ischemia due to the potential for evoking coronary “steal” by shunting blood away from areas of ischemia to small resistance vessels. There is also the potential for reflex tachycardia due to vasodilation.

In comparison to NTG, clinical trial data surrounding the use of SNP are also limited; however, it does have a select role for the management of patients with left ventricular failure and a high SVR. There has also been recent data that evaluated SNP in patients with ADHF (CI $\leq$ 2.2 L/min per m$^2$), severe aortic stenosis, and a mean arterial pressure (MAP) of 60 mm Hg or higher. SNP demonstrated a significant increase in CI, while also reducing MAP, PCWP, and SVR. The investigators concluded that SNP might have a role in optimizing cardiac function prior to aortic valve replacement in patients with left ventricular failure, or converting to oral vasodilator therapy in patients not undergoing surgery.\textsuperscript{14}

**INOTROPES**

An overview of the commonly used IV inotropes is presented with an emphasis on
their role in the management of patients with ADHF. As with IV vasodilators, controlled clinical trials for many of these agents are lacking. The Heart Failure Society of America de-emphasizes the role of inotropes compared with vasodilators for adjunctive management of patients with ADHF.1 Dobutamine or milrinone may be considered for relief of symptoms and to improve end-organ function in patients with advanced heart failure. These patients generally have left ventricular dilation, diminished ejection fraction, and end-organ dysfunction (low-output syndrome). Additional considerations for use of these agents include marginal systolic BP (<90 mm Hg), symptomatic hypotension despite adequate filling pressure, inadequate response to vasodilators, or evidence of worsening renal function.1

**Dobutamine**

Dobutamine is a synthetic catecholamine with potent inotropic and modest vasodilatory properties. Its pharmacologic effects are mediated primarily through β-1 (inotropy) and β-2 receptor (vasodilatory) stimulation. Dobutamine produces a dose-dependent increase in myocardial contractility and reduction in cardiac filling pressures. Despite increases in CO, BP may be reduced or unchanged because of reduction in SVR through β-2 receptor and baroreceptor-mediated vasodilation.10-12 In comparison to other inotropes such as dopamine, dobutamine produces a strong inotropic response without a significant increase in heart rate. The favorable inotropic and vasodilatory effects of dobutamine make it a preferred agent for the management of low-output states including ADHF and cardiogenic shock. However, if patients have a very low systolic BP (generally <80 mm Hg systolic) at baseline, then dopamine may be preferred initially.15 Alternatively, dobutamine and dopamine may be used in combination at lower doses.

The usual dose range of dobutamine is 5 to 20 μg/kg per minute given as a continuous IV infusion. The half-life of dobutamine is approximately 2 minutes, which provides for rapid onset and prompt dose escalation. After 72 hours of infusion, however, tachyphylaxis may develop due to β-receptor down-regulation. The inotropic and chronotropic responses vary, particularly in critically ill patients, due to variable end-organ responsiveness. In fact, elderly patients are known to have a decreased overall responsiveness to dobutamine. Therefore, hemodynamic endpoints should be targeted rather than a specific dose. A dose-response study among patients with severe heart failure showed that dobutamine used at a dose of 2.5 to 10 μg/kg per minute increased CO without precipitating significant increases in heart rate. Doses higher than 20 μg/kg per minute are generally not advised because of an increased risk for hypotension and tachycardia, which can worsen myocardial ischemia. Like all inotropes, dobutamine may induce proarrhythmias including ventricular tachycardia and fibrillation. Long-term use of dobutamine has been associated with decreased survival, mainly attributable to sudden cardiac death. In fact, the incidence of ventricular arrhythmias was found to be high (>50%) among patients receiving dobutamine or milrinone in this setting.16 In addition to BP monitoring, invasive monitoring of CI, PCWP, and SVR may also be useful to minimize unanticipated adverse effects.

Dobutamine remains a cornerstone of therapy for low-output states with elevated cardiac filling pressures including ADHF and cardiogenic shock. Although dobutamine has not been extensively studied in placebo-controlled trials for patients with ADHF, it represents a reasonable firstline option for most patients in need of inotropic support. For acute management of these patients, the clinical outcomes of dobutamine appear to be comparable to milrinone.17 Intermittent and long-term outpatient use of dobutamine as a pharmacologic bridge to transplantation has also been described in a limited number of reports. Clinical outcomes relative to milrinone
in this setting are further described in the next section.

**Milrinone**

Milrinone is a PDE type III inhibitor that shares many of the hemodynamic effects of dobutamine. PDE is an enzyme that degrades cyclic adenosine monophosphate, a second messenger necessary for intracellular calcium release. Ultimately, inhibition of this enzyme by milrinone leads to vasodilation and a positive inotropic response. In fact, some authors have referred to this class of agents as "inodilators." Unlike other catecholamines, the effects of milrinone are independent of $\beta$-adrenergic receptors, a result of bypassing the receptor complex. Therefore, tachyphylaxis due to $\beta$ receptor downregulation is not a clinical concern. In addition to the pharmacologic differences between milrinone and dobutamine, unique hemodynamic differences have also been documented. Milrinone has shown a greater vasodilatory effect than dobutamine, as demonstrated by further reductions in mean pulmonary artery pressure, PCWP, and SVR. In fact, dobutamine may need to be combined with nitroprusside to exert a similar degree of vasodilation. On the other hand, dobutamine may increase CO to a greater extent than milrinone but at the expense of greater increases in heart rate and myocardial oxygen consumption. The predominant effect of milrinone in heart failure seems to be vasodilation with more modest positive inotropic effects. Because of these effects, many investigators have used milrinone as a first-line therapy over dobutamine in patients with more severe pulmonary hypertension. The overall hemodynamic profile of milrinone lends to its use as an alternative or adjunctive agent in patients with severe heart failure and cardiogenic shock, particularly when standard therapies with catecholamines have not been effective.

Milrinone may be administered as an IV loading dose of 50 $\mu$g/kg over 10 minutes, followed by a continuous infusion of 0.25 to 0.75 $\mu$g/kg per minute. A more common regimen is 0.5 $\mu$g/kg per minute. Lower doses should be initiated for patients with renal failure due to reduced milrinone elimination in these patients. Because bolus administration may exacerbate hypotension, many clinicians have initiated milrinone without the loading dose, particularly when a rapid effect is not required. Bolus-free dosing has been shown to produce significant hemodynamic changes within 30 minutes, and by 2 to 3 hours becomes comparable to bolus dosing. The half-life of milrinone in patients without renal failure is approximately 1 to 3 hours, making dosing titration more difficult than for dobutamine. The hypotensive effects may also persist for longer periods of time with a shorter acting agent such as dobutamine. These additional pharmacokinetic considerations also render milrinone an alternative agent to dobutamine. In theory, milrinone may have a lower potential for chronotropic and arrhythmogenic effects than do catecholamines. However, use of any inotropic agents may exacerbate atrial or ventricular arrhythmias. Long-term use of milrinone has been associated with decreased survival due to sudden cardiac death, and the incidence of arrhythmias is probably comparable with dobutamine. Unlike inamrinone (formerly amrinone), a much less frequently used PDE type III inhibitor, milrinone has rarely been associated with thrombocytopenia. Other potential adverse effects of milrinone include nausea and vomiting. As with other IV vasoactive medications, hemodynamic monitoring may be needed to optimize response and minimize adverse events.

Despite the potentially more favorable hemodynamic profile of milrinone than dobutamine, clinical outcomes between the two agents have not differed. In a large retrospective comparative study of these agents for advanced heart failure, no differences in hospital mortality, disposition (discharge to home on inotrope or listing for transplantation), or hospital complications (ventricular arrhythmias, ventilator use, line sepsis, acute renal failure) were observed. The OPTIME-CHF study found that routine use of milrinone...
for patients with ADHF did not decrease days of hospitalization compared with placebo, but did result in a significant increase in adverse events related to hypotension and atrial arrhythmias. The results of this trial reinforce the role of milrinone as an alternative inotropic strategy for patients with ADHF not responding to dobutamine. An important consideration for use of milrinone over dobutamine in ADHF, however, is for patients admitted on β-blocker therapy. The use of a β agonist with a β-blocker would be largely counterproductive. In these cases, the use of milrinone during titration or maintenance of carvedilol therapy has resulted in higher β-blocker maintenance doses, improved hemodynamics, and functional capacity.

The long-term outcome of patients awaiting transplantation represents a different population where comparisons between milrinone and dobutamine have produced conflicting results. In one retrospective study, more patients were successfully bridged to transplantation with milrinone (80%) than with dobutamine (50%), whereas other data, including a prospective observational study, demonstrated similar clinical outcomes between agents. Criteria for the use of either agent in this setting vary considerably by institution. Some centers have favored dobutamine due to cost considerations, whereas others preferred milrinone because of an improved hemodynamic profile and/or perceived lower risk of arrhythmias.

VASOPRESSORS

The most commonly used vasopressors are dopamine, norepinephrine, epinephrine, and phenylephrine. Because of their chemical structure, they are often referred to as catecholamines. In the past decade, the utility of vasopressin has been explored and its role is still being defined. Four of the 5 medications (epinephrine, dopamine, norepinephrine, and vasopressin) are endogenous substances. Vasopressors may be used in the management of several disease states including anaphylaxis, cardiac arrest, hypotension following coronary artery bypass surgery, and septic shock. These agents are most frequently administered as continuous IV infusions and should be administered via a central line to minimize the risk of extravasation. Vasopressors are not used as monotherapy in the management of cardiogenic shock, and, in fact, may have deleterious effects if given in the wrong setting. These agents may be employed in combination with inotropes in selected patients with mixed disorders and severe hypotension. The major role for vaspressors and the focus of this section is on their role in septic shock.

Epinephrine

Epinephrine is a potent agonist of both α and β receptors. At low doses (0.1 μg/kg per minute), it has an affinity for β-1 receptors, and is more specific for β-2 than α receptors, which may lead to vasodilation. The hemodynamic effects of low doses are increased heart rate and CO. With larger bolus doses or continuous infusions, the effects of epinephrine on α-1 and β-1 receptors dominate, which causes peripheral vasoconstriction and an increase in inotropy and chronotropy. The typical hemodynamic effects are an increased preload (PCWP) due to vasoconstriction in the periphery, increased CO, and increased afterload (SVR).

Epinephrine should not be considered as the initial vaspressor for the management of hypotension for the patient in septic shock. Although epinephrine demonstrates the ability to improve BP in the septic shock setting, it may do so at the cost of impaired gastric blood flow and increased lactate. Use of epinephrine in this setting should be reserved for extreme cases of cardiovascular collapse if other catecholamines fail. Epinephrine is typically dosed as a continuous infusion initiated at 0.02 to 0.5 μg/kg per minute, and is then titrated to a hemodynamic goal such as an MAP of 60 mm Hg.
Dopamine

Dopamine is the precursor of norepinephrine and epinephrine. The physiologic effects of dopamine are mediated by several distinct types of receptors that vary in their affinity for dopamine. Dopamine produces dose-dependent hemodynamic effects because as concentrations increase, a broader array of receptors is impacted. At low doses, dopamine primarily stimulates the dopaminergic (D1) receptors. D1 receptors in the renal, mesenteric, and coronary beds cause vasodilation when stimulated. Hemodynamic effects of these doses may include tachycardia and hypotension, especially in patients who are intravascularly volume depleted. As the dose is increased, the $\beta$-1 and $\beta$-2 receptors are stimulated, causing positive chronotropic and inotropic effects. With $\beta$ receptor stimulation, the hemodynamic response typically includes an increased CO, decreased PCWP, and variable SVR. Dopamine has a very weak affinity for $\alpha$-1 receptors, and does not directly cause vasoconstriction. At high doses, dopamine causes the release of norepinephrine from nerve terminals, which then stimulates $\alpha$-1 receptors and causes vasoconstriction. This indirect effect and the conversion of dopamine to norepinephrine causes an increase in afterload (SVR).

The initial dose of dopamine depends on the desired action. Low doses of dopamine, sometimes referred to as “renal doses,” have been recently criticized.24–27 Low doses of dopamine do cause vasodilation, and an increase in renal blood flow in healthy volunteers, which leads to an increase in urine output. However, there are no well-designed studies, especially in critically ill patients, that demonstrate benefits such as renal protection or improved mortality. In addition, some studies have demonstrated harm, due to arrhythmias, despite this lack of benefit.24–27

Although dopamine is not typically used in the setting of advanced heart failure, it may be beneficial for a patient with systemic hypotension or cardiogenic shock in the face of elevated ventricular filling pressures to raise the central aortic pressure.28 As previously mentioned, dopamine may be combined with dobutamine in the setting of low CO and hypotension that persists despite inotropic therapy.

The Surviving Sepsis Campaign Guidelines state: “Either norepinephrine or dopamine is the first-choice vasopressor agent to correct hypotension in septic shock. Dopamine increases MAP and CO, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared to dopamine.”21 Dosing should again be based on the desired outcome. For improvements in CO, initial doses of 4 to 5 $\mu$g/kg per minute may be employed and titrated to hemodynamic goal. For severe hypotension, doses higher than 10 $\mu$g/kg per minute may be required.

Norepinephrine

Norepinephrine is a potent $\alpha$ agonist with a small amount of $\beta$-1 and $\beta$-2 agonist activities. The dominant $\alpha$ effects lead to vasoconstriction and the expected hemodynamic response of increased afterload (SVR). As previously stated, norepinephrine is considered a first-line drug in the management of hypotension related to sepsis. In a prospective, observational study, 97 adult patients with septic shock were observed for 19 clinical, biological, and hemodynamic variables in an effort to identify factors associated with outcome.29 The authors reported that 5 variables were significantly associated with outcomes. The use of norepinephrine was strongly related to a favorable outcome. Patients treated with norepinephrine had significantly lower hospital mortality rates (62% vs 82%, $P < .001$) than those who did not have norepinephrine as part of their hemodynamic support regimen. Four factors were associated with unfavorable outcomes: elevated lactate, low urine flow, pneumonia as the cause of sepsis, and an organ system failure index of 3 or higher. There are 2 theoretical
reasons to consider norepinephrine over dopamine. The first is that norepinephrine is thought to be more potent than dopamine. The second reason is that dopamine relies on the body to release norepinephrine stores (which may already be depleted) or to convert dopamine to norepinephrine, therefore it is logical to use norepinephrine instead of dopamine. However, there are no randomized controlled trials that provide evidence to choose one agent over another. Norepinephrine is typically initiated at low doses (1 μg/min) and titrated to hemodynamic goal.

**Phenylephrine**

Phenylephrine is a synthetic agent that is a selective α-1 receptor agonist that causes arterial vasoconstriction. The primary hemodynamic effect is increased SVR. CO is variable, depending on myocardial capacity and reserve. Phenylephrine may be useful in the setting of severe hypotension when β agonist activity, such as tachycardia or tachyarrhythmias, would be undesirable. Phenylephrine is typically dosed between 20 and 200 μg/min.

**Safety and monitoring of catecholamines**

Catecholamines can cause severe necrosis if extravasation occurs. Therefore, administration of continuous infusions via central line is recommended. Patients must be monitored for signs of extravasation, peripheral ischemia, and gut ischemia. Vasopressors should only be used in conjunction with appropriate fluid management, therefore fluid “I’s and O’s” must be measured. Catecholamines should be used only in settings where arterial pressure, heart rate, and rhythm can be monitored frequently or continuously. In most cases, cardiac parameters such as CO or CI, PCWP, central venous pressure, and SVR would be followed. Monitoring serum electrolytes, serum lactate, and glucose may also be required.

**Vasopressin**

Vasopressin, also known as antidiuretic hormone, has been studied for more than 50 years, although its role in the management of hypotension associated with septic shock has only been investigated in the last decade. Vasopressin is a hormone that is synthesized in the hypothalamus and released because of hyperosmolality and hypotension or hypovolemia. The physiologic effects of vasopressin are mediated by the interaction with 3 types of receptors: V1, V2, and V3. The V1 receptor is located throughout the body including vascular smooth muscle, where it mediates effects on arterial BP by causing vasoconstriction. The activity of vasopressin in the body is more complex than traditional vasopressors such as the catecholamines. In many settings, vasopressin acts as a vasoconstrictor; however, low concentrations in pulmonary vessels activate V1 receptors and cause nitric oxide release and vasodilation. On a per weight basis, vasopressin is a more potent vasoconstrictor than norepinephrine, but the administration of vasopressin to healthy volunteers will not cause significant increases in BP because its effects are counteracted by baroreceptors. The V2 receptors are found in the kidney and are responsible for the antidiuretic or water-retaining effects of vasopressin. The V3 receptors are located in the anterior hypophysis and pancreatic cells and help in insulin regulation.

A relative vasopressin deficiency has been described in the setting of septic shock. The mechanism for this deficiency is unclear and may be due to depletion of vasopressin stores, inhibition of release, or increased metabolism. Administration of exogenous vasopressin increases serum concentrations, and therefore it is unlikely that an increased metabolism is the mechanism.

The role of vasopressin in the management of hypotension-associated septic shock is supported by only case reports and case series at the present time. Low-dose continuous IV vasopressin (0.01–0.04 units/min) has been shown to improve MAP and reduce catecholamine requirements. Since the mechanism of action does not involve α-adrenergic receptors, many clinicians advocate its use in the setting of vasodilatory shock refractory to
catecholamines and/or in the setting of acidosi. The Surviving Sepsis Campaign Guidelines state: “Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors. Pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a firstline agent.”

The effect vasopressin has on outcomes such as length of stay, morbidity, and mortality is still unknown. In addition the optimal dose is still unknown. The most commonly studied dose for the management of septic shock is between 0.01 and 0.04 units/min. Vasopressin should not be titrated in the same manner as traditional catecholamines. Doses higher than 0.04 units/min are not recommended at the present time.

**Safety and monitoring of vasopressin**

As with the catecholamines, vasopressin can cause severe vasoconstriction. It is important to note that the doses that have been studied for sepsis are very low doses (0.01–0.04 units/min). Higher doses have been used in the management of variceal bleeding. These higher doses may be associated with intense vasoconstriction in the peripheral, gastrointestinal, or myocardial blood vessels. At high doses, vasopressin may cause severe ischemia, altered platelet functioning, decreases in CO, and cardiac arrest.

**SUMMARY**

The therapeutic arsenal of “vasoactive” medications for the care of cardiovascular patients in ICU continues to increase. Although many traditional agents remain a cornerstone of therapy, our knowledge of their most appropriate use continues to evolve. A variety of vasodilators, inotropes, and vasopressors are often used in combination for the management of these complex patients to optimize clinical outcomes. Accordingly, it is paramount for critical care nurses to have an understanding of the basic pharmacology, anticipated hemodynamic effects, and potential adverse effects of these agents. Practical considerations regarding agent selection, dosing, and titration are equally important for the care of these patients.

**REFERENCES**


Appendix 1

Adult Vasoactive Titratable Drip Protocol (Allegheny General Hospital)

*Purpose:* To provide a framework for the ordering, initiation, and titration of vasopressors and inotropes in critically ill adults. All orders for vasopressors and inotropes must include a starting dose for initiation and must include a clearly stated hemodynamic goal. The rate and frequency of dose titration will depend upon the patient’s individual hemodynamic parameters and clinical status.

*Requirements:*
1. Vasoactive agents will be titrated only if indicated by a physician order.
2. All orders for vasopressors and inotropes must include a starting dose for initiation. All orders for titratable drips that do not contain a starting dose must be clarified with the ordering physician and documented in the chart.
3. All vasoactive agents, both vasopressors and inotropes, ordered for titration to a given response must include a clearly stated hemodynamic endpoint as part of the order placed in the chart (e.g., titrate to mean arterial pressure of 65 mm Hg, titrate to systolic blood pressure >90 mm Hg). All orders for titratable drips that do not contain a hemodynamic goal must be clarified with the ordering physician and documented in the chart.
4. If the agent used reaches the “First Notification Value,” the physician must be notified for consideration of additional treatments or alternate agent(s). Consider volume status, arterial blood pH, vasopressin deficiency, adrenal insufficiency, or other reasons for lack of efficacy regarding vasopressors.
5. Although these agents have no absolute maximum dose, if the agent used reaches the “Second Notification Value,” the physician must be called for consideration of additional treatments or alternate agent(s) before further titration of the current agent occurs. Consider volume status, arterial blood pH, vasopressin deficiency, adrenal insufficiency, or other reasons for lack of efficacy regarding vasopressors.
6. If the dose exceeds the “Second Notification Value,” additional dose increases can only occur with a physician order.
7. The lowest effective dose that achieves the stated hemodynamic goal will be utilized when the agent is ordered in a titratable fashion.

*Clinical Pearls:*
1. Vasopressors and inotropes should be avoided in hypovolemic patients until fluid status has been corrected with crystalloids, colloids, or blood products.
2. Sodium bicarbonate should not be given through the same line as catecholamines (e.g., epinephrine, norepinephrine, dopamine, and phenylephrine), as it will cause precipitation and inactivation of both agents.
3. The concentration of each bag should be checked and verified against the concentration entered in the intravenous pump and computerized charting system.
4. Dosing weight: When calculating dosing rates for vasoactive agents, ideal body weight (IBW) should be used:
   - Male IBW (kg) = 50 + (2.3 × in over 5 ft)
   - Female IBW (kg) = 45.5 + (2.3 × in over 5 ft)
### Appendix Table 1. Adult titratable drip protocol

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Standard concentration (all drugs mixed in D5W unless ordered)</th>
<th>Initial dose</th>
<th>Typical dose range</th>
<th>Titrations increment every 5–15 min to achieve hemodynamic goal</th>
<th>Weaning increment every 5–15 min based on patient response</th>
<th>First notification value</th>
<th>Second notification value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine, μg/kg per min</td>
<td>500 mg/100 mL</td>
<td>2.5–5 μg/kg per min</td>
<td>2.5–20 μg/kg per min</td>
<td>2.5–5 μg/kg per min</td>
<td>2.5–5 μg/kg per min</td>
<td>12.5 μg/kg per min</td>
<td>20 μg/kg per min</td>
</tr>
<tr>
<td>Dopamine, μg/kg per min</td>
<td>800 mg/250 mL</td>
<td>4–10-inotrop &gt;10 vasopressor</td>
<td>2–20 μg/kg per min</td>
<td>2–5 μg/kg per min</td>
<td>1 μg/kg per min</td>
<td>12.5 μg/kg per min</td>
<td>20 μg/kg per min</td>
</tr>
<tr>
<td>Epinephrine, μg/kg per min</td>
<td>4 mg/250 mL</td>
<td>0.02–0.05 μg/kg per min</td>
<td>0.005–0.2 μg/kg per min</td>
<td>0.02–0.05 μg/kg per min</td>
<td>0.02–0.05 μg/kg per min</td>
<td>0.1 μg/kg per min</td>
<td>0.2 μg/kg per min</td>
</tr>
<tr>
<td>Milrinone, μg/kg per min</td>
<td>20 mg/100 mL</td>
<td>See loading dose below; then initiate 0.25 μg/kg per min</td>
<td>0.25–1 μg/kg per min</td>
<td>Do not increase rate without MD order</td>
<td>Can be discontinued without weaning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, μg/min</td>
<td>100 mg/250 mL</td>
<td>10 μg/min</td>
<td>5–300 μg/min</td>
<td>10–20 μg/min</td>
<td>5–10 μg/min</td>
<td>200 μg/min</td>
<td>300 μg/min</td>
</tr>
<tr>
<td>Nitroprusside, μg/kg per min</td>
<td>100 mg/250 mL</td>
<td>0.2 μg/kg per min</td>
<td>0.5–5 μg/kg per min</td>
<td>0.25–0.5 μg/kg/min</td>
<td>0.25–0.5 μg/kg/min</td>
<td>3 μg/kg per min</td>
<td>5 μg/kg per min</td>
</tr>
<tr>
<td>Norepinephrine, μg/min</td>
<td>4 mg/250 mL</td>
<td>0.5–2 μg/min</td>
<td>0.5–20 μg/min</td>
<td>1–2 μg/min</td>
<td>1 μg/min</td>
<td>8 μg/min</td>
<td>20 μg/min</td>
</tr>
<tr>
<td>Phenylephrine, μg/min</td>
<td>40 mg/250 mL</td>
<td>100–150 μg/min for 1 min</td>
<td>20–200 μg/min</td>
<td>10–40 μg/min</td>
<td>125 μg/min</td>
<td>200 μg/min</td>
<td></td>
</tr>
<tr>
<td>Vasopressin, units/min</td>
<td>100 units/250 mL</td>
<td>0.02–0.04 units/min</td>
<td>0.02–0.08 units/min</td>
<td>Do not increase rate without MD order</td>
<td>Can be discontinued without weaning</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Milrinone loading dose is typically 50 μg/kg over at least 10 minute.
### Appendix Table 2. Pharmacologic effects of vasopressors and inotropes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Heart</th>
<th>Vasculature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\beta-1)</td>
<td>(\alpha-1)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>4+</td>
<td>2+ to 4+</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0 to 4+</td>
<td>0 to 4+</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>4+ (inotrope)</td>
<td>+</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2+</td>
<td>4+</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>0</td>
<td>4+</td>
</tr>
<tr>
<td>Milrinone†</td>
<td>4+ “like”</td>
<td>0</td>
</tr>
</tbody>
</table>

*Scale: 0 equals no agonist activity; 4+ equals very potent agonist.
†Milrinone does not bind to \(\beta\) or \(\alpha\) receptors, it produces its hemodynamic effects through phosphodiesterase inhibition.

### Appendix Table 3. Hemodynamic effects of vasopressors and inotropes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hemodynamic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CO/CI</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Dopamine</td>
<td>↔↑↓</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>↑</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>↑↓</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>↑↓</td>
</tr>
<tr>
<td>Milrinone†</td>
<td>↑</td>
</tr>
</tbody>
</table>

*CO indicates cardiac output; CI, cardiac index; SVR, systemic vascular resistance; PCWP, pulmonary capillary wedge pressure; and MAP, mean arterial pressure.
†Milrinone does not bind to \(\beta\) or \(\alpha\) receptors, it produces its hemodynamic effects through phosphodiesterase inhibition.