

Pressors and Inotropes



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KEYWORDS

• Vasopressors • Inotropes • Chronotropes • Hemodynamic effect

KEY POINTS

- Although disease-specific guidelines provide a framework for vasopressor, inotrope, and chronotrope selection and usage, real-world applications demand therapy be tailored to the individual patient.
- Physiologic parameters, such as fluid status or cardiovascular reserve, may alter an individual patient's response to a particular agent.
- Patients with preexisting, poorly controlled hypertension may require higher than normal goal blood pressures to achieve treatment goals.

INTRODUCTION

To effectively treat an aging and increasingly complex patient population, emergency physicians and other acute-care providers must be comfortable with the use of vasopressors, inotropes, and chronotropes. These medicines are used to augment the cardiovascular function of critically ill patients.

Each class of medication produces a different hemodynamic effect. Vasopressors induce peripheral vasoconstriction, increasing systemic vascular resistance (SVR) and mean arterial pressure (MAP). Inotropes increase the force of cardiac contractility, increasing cardiac output and MAP. Chronotropes increase heart rate. Some agents produce only one of these actions, whereas others have multiple effects. For the emergency physician, these agents are used with the explicit goal of preserving vital organ perfusion during acute and severe illness. This article reviews the physiologic receptors targeted by such drugs, common agents used, and specific clinical indications for their use.

PHYSIOLOGY

Vasopressors, inotropes, and chronotropes act on various adrenergic receptors (**Table 1**). Ubiquitous within the smooth muscle of arterial walls, α_1 receptors induce

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Drug	Action	Common Doses	Adverse Effects
Norepinephrine	$\alpha_1 > \beta_1$	0.01–0.5 $\mu\text{g}/\text{kg}/\text{min}$	Tachyarrhythmias, increased myocardial oxygen consumption, myocardial banding necrosis with prolonged infusions
Vasopressin	α_1, V_1, V_2, V_3	0.04 U/min	Possible gastrointestinal hypoperfusion
Dopamine	$\alpha_1, \beta_1, \text{dopa } 1$	0.5–25 $\mu\text{g}/\text{kg}/\text{min}$	Tachyarrhythmias, increased myocardial oxygen consumption
Epinephrine	$\alpha_1, \beta_1, \beta_2$	0.01–0.75 $\mu\text{g}/\text{kg}/\text{min}$	Tachyarrhythmias, leukocytosis, increased myocardial oxygen consumption
Phenylephrine	α_1	0.15–0.75 $\mu\text{g}/\text{kg}/\text{min}$	Reflex bradycardia
Isoproterenol	$\beta_1 > \beta_2$	0.01–0.02 $\mu\text{g}/\text{kg}/\text{min}$	Tachyarrhythmias, flushing, increased myocardial oxygen consumption
Dobutamine	$\beta_1 > \beta_2$	2.0–20 $\mu\text{g}/\text{kg}/\text{min}$	Tachyarrhythmias, increased myocardial oxygen consumption, pharmacologic tolerance in prolonged infusions
Milrinone	Phosphodiesterase inhibition	0.3–0.8 $\mu\text{g}/\text{kg}/\text{min}$	Headache, hypotension, tachycardia
Levosimendan	Increased calcium-dependent binding of troponin C	0.05–0.2 $\mu\text{g}/\text{kg}/\text{min}$	Headache, hypotension, prolonged half-life of active metabolites

arterial vasoconstriction, increasing SVR. They are also present to a lesser extent in the heart and can increase systolic contraction without affecting chronotropy, although the clinical significance of this action is unclear.¹ β_1 receptors predominate in cardiac smooth muscle. They act on the sinoatrial node to produce positive chronotropy and on atrial and ventricular muscle to produce inotropy. Located throughout the body but notably in bronchial smooth muscle, β_2 receptors increase calcium uptake by the sarcoplasmic reticulum, resulting in mild vasodilation and, of particular importance, pulmonary bronchodilation.² They are also located in uterine muscle, and are targeted during tocolysis treatment. Dopamine receptors are located in renal, splanchnic, and coronary vasculature and the central nervous system; their actions are complicated and diverse. Vasopressin receptors are located in vascular smooth muscle, the anterior pituitary gland, and the renal collecting duct. Their activation results in vasoconstriction, adrenocorticotrophic hormone and prolactin release, and renal water reabsorption.³

Although each drug carries its own side effect profile, some adverse effects can be seen with multiple agents. All catecholamines may cause myocardial contraction band

necrosis, mostly by protein kinase A activation and increased cytosolic calcium influx,⁴ which can result in ventricular aneurysm, rupture, or irreversible impairment of cardiac function. The risk of this increases with prolonged infusions. Also, any vasopressor usage carries the risk of tissue necrosis if intravenous (IV) extravasation occurs. Vasopressors are traditionally delivered by central venous access for this reason, although evidence-based trials supporting the long-followed practice are lacking.

COMMON PHARMACOLOGIC AGENTS

Norepinephrine (Levophed) is an endogenous catecholamine with strong α_1 agonist activity and modest β_1 activity, resulting in potent vasoconstriction and less potent inotropy. The net clinical effect is an increase in systolic blood pressure (SBP), diastolic blood pressure, and pulse pressure, with minimal effect on cardiac output. Chronotropic effects are also minimal.

Vasopressin, or antidiuretic hormone, is an endogenous hormone stored in the posterior pituitary gland and released in response to increased plasma osmolality, hypotension, pain, nausea, and hypoxia. It is also synthesized by the heart in response to cardiac wall stress,⁵ and by the adrenal glands in response to increased catecholamine secretion.⁶ It acts on V_1 receptors in vascular smooth muscle to induce vasoconstriction, and V_2 receptors in the renal collecting tubules to increase collecting duct permeability and renal water reabsorption. Vasopressin increases SVR but reflexive increases in systemic vagal tone result in a minimal net effect on cardiac output. Vascular sensitivity to norepinephrine is increased when vasopressin is coadministered, thus creating a synergistic effect and decreasing the needed dose (and side effects) of norepinephrine. Some have suggested it is particularly useful in sepsis because its vasoconstrictive effects are preserved in hypoxic and acidotic conditions.⁷⁻⁹

Dopamine is a central neurotransmitter and the immediate precursor to norepinephrine in the endogenous catecholamine synthesis pathway. Traditionally, systemic effects are considered dose-dependent. At low infusion rates (0.5–3 $\mu\text{g}/\text{kg}/\text{min}$), stimulation of D_1 postsynaptic receptors in coronary, renal, mesenteric, and cerebral vascular beds, and D_2 presynaptic receptors in renal tissue, result in mild vasodilation and diuresis.¹⁰ The clinical significance of this “renal dose” of dopamine is unclear. In critically ill patients, low-dose dopamine infusions have been shown not to increase glomerular filtration rate and to confer no protection against increases in serum creatinine, progression toward oliguria, or eventual need of hemodialysis.¹¹ Similarly, the increase in splanchnic blood flow is of questionable clinical significance and does not alter other key metrics of mesenteric perfusion.¹² Intermediate doses of dopamine (3–10 $\mu\text{g}/\text{kg}/\text{min}$) activate β_1 receptors and increase endogenous norepinephrine release, increasing cardiac inotropy and SVR.¹³ At high doses (10–20 $\mu\text{g}/\text{kg}/\text{min}$), α_1 activity predominates resulting in vasoconstriction and increased SVR.¹⁴ It should be noted that these distinctions are derived generally and in clinical practice the response is patient-specific.

Epinephrine is an endogenous catecholamine with high affinity for α_1 , β_1 , and β_2 receptors resulting in vasoconstriction, positive inotropy, and bronchodilation. At high infusion rates the duration of diastole is increased and myocytes are stimulated to release local vasodilators leading to increased coronary blood flow.¹⁵ When compared with norepinephrine, dopamine, and vasopressin, a higher risk exists for dysrhythmia and splanchnic vasoconstriction.¹⁶

Phenylephrine is a synthetic α agonist that rapidly increases SVR. In addition to standard infusions, it can be bolused to correct sudden, severe hypotension. It has

no direct chronotropic effects but rapid increases in MAP can induce baroreceptor-mediated reflex bradycardia.

Isoproterenol is a synthetic nonselective β agonist and acts as a strong chronotrope and inotrope. Increased systemic vasodilation and mild pulmonary vasodilation are also seen. Stroke volume is increased, but because of its β_2 -mediated decrease in SVR, the net effect on cardiac output is neutral. It may be safely administered by peripheral IV access but caution must be taken in patients at-risk for cardiac ischemia.

Dobutamine is a synthetic catecholamine that binds β_1 and, to a lesser extent, α_1 and β_2 receptors. This results in strong inotropic and weaker chronotropic activity. A mild reduction in SVR can be seen and is a reflexive response to increased inotropy. Dobutamine's activation of α_1 and β_2 receptors is of questionable clinical significance. Similar to isoproterenol, it increases myocardial oxygen consumption (useful in pharmacologic cardiac stress testing) and is potentially harmful to patients at-risk for cardiac ischemia. Significant pharmacologic tolerance can develop after only 72 hours of continued infusion.¹⁷ It is safe to administer by peripheral IV but can induce ventricular arrhythmias at any dose.¹⁸

Milrinone is a second-generation phosphodiesterase inhibitor that improves cardiac output and reduces SVR. Through inhibition of type 3 phosphodiesterase, conversion of cAMP to AMP is blocked, increasing available cAMP and resulting in increased myocardial contractility and mild peripheral vasodilation. Pulmonary vascular resistance is decreased and diastolic relaxation is improved. Milrinone may be preferable in patients with significant pulmonary venous hypertension.¹⁹ It does not induce pharmacologic tolerance, has a relatively longer half-life (2–4 hours) than most other inotropes, and is safe for peripheral infusion.²⁰ It has largely replaced its predecessor inamrinone (Amrinone) because of fewer associated side effects, particularly the risk of thrombocytopenia.

Levosimendan, a newer “calcium sensitizer” that increases calcium-dependent binding of troponin C, enhances ventricular contractility without increasing intracellular calcium concentration or affecting diastolic relaxation. It improves cardiac output and also opens vascular smooth muscle potassium channels, which provide arteriolar and venous vasodilation.^{21,22} It may increase glomerular filtration rate in acute decompensated heart failure (ADHF)²³ and is potentially cardioprotective during periods of ischemia.^{24,25} Levosimendan is an unproved but promising treatment of heart failure.^{26,27}

SEPTIC SHOCK

In the patient with sepsis, functional intravascular hypovolemia caused by decreased oral intake, insensible losses, increased venous capacitance, reduced myocardial contractility, vascular damage, and increased peripheral vasodilation lead to hypotension and impaired end-organ perfusion. Management begins with infectious source control, timely and appropriate antimicrobials, volume assessment, and initial correction of hypovolemia. Concurrent vasopressors are often needed to maintain organ perfusion. In a noted change from previous recommendations, norepinephrine is now the pressor-of-choice in septic shock. Compared with dopamine, it is less arrhythmogenic^{28,29} and, in meta-analysis, seems to confer a mortality benefit.³⁰ The Surviving Sepsis Campaign now recommends it as the first-line agent.³¹ Infusions should be initially titrated to an MAP of 65. This target has been shown to provide adequate perfusion as measured by systemic oxygen metabolism, skin microcirculatory blood flow, urine output, and splanchnic perfusion, and no benefit has been seen with higher MAP targets.³² Importantly, MAP goals must always be individualized and

based on clinically relevant perfusion markers, such as urine output, mental status, skin perfusion, and serum lactate clearance. Initial vasopressor treatment should be concomitant with volume repletion; one should not wait for euvolemia before initiating pressors.

Fixed, low-dose vasopressin should be added to norepinephrine as the “first-line additional agent” if resuscitation goals are not met. Lower levels of endogenous anti-diuretic hormone are common in shock and contribute to systemic hypotension.³³ Low doses of vasopressin (0.04 U/min) are safe and effective,^{34,35} and are particularly beneficial when coadministered with norepinephrine.³⁶ Vasopressin is not recommended as an agent that should be titrated.

Considered less safe but still acceptable, epinephrine may be substituted as the “first-line alternative” in patients intolerant of norepinephrine. Its use may be accompanied by metabolic side effects, such as tachycardia, increased lactic acidosis, and increased insulin requirements. These side effects have been shown to be reversible on discontinuation of epinephrine infusions and of questionable effect on mortality.³⁷ Phenylephrine should be used only if tachycardia or arrhythmias make norepinephrine and epinephrine intolerable, if cardiac output is known to be high with a persistently low blood pressure, or as salvage therapy. Previous studies have shown it may decrease stroke volume and impair hepatosplanchnic perfusion,^{38,39} but more recent studies suggest it may be safer than previously thought.⁴⁰ Dopamine should only be used in patients with a low risk of tachyarrhythmia. A trial of dobutamine, in addition to a vasopressor, may be considered if myocardial dysfunction is present as inferred from elevated cardiac filling pressures and low cardiac output, or signs of ongoing hypoperfusion despite fluid repletion and vasopressor therapy. The use of inotropes to increase tissue oxygen delivery beyond physiologic levels confers no additional benefit.^{41,42}

CARDIOGENIC SHOCK FOLLOWING ACUTE MYOCARDIAL INFARCTION

Definitive treatment of shock following acute myocardial infarction is revascularization. Mechanical augmentation of cardiac function with intra-aortic balloon pumps or left ventricular assist devices is a temporizing option. The use of vasopressors and inotropes carries the risk of increasing myocardial oxygen consumption, inducing ventricular arrhythmias, contraction-band necrosis, and infarct expansion. However, hypotension also compromises myocardial perfusion. When used as a bridge to definitive treatment, the hemodynamic benefits of vasopressors and/or inotropes usually outweigh the systemic risks of severe hypotension. Agents should be kept to the lowest efficacious dose and close attention paid toward the risk of arrhythmia and infarct expansion.

There exists no clear evidence-based recommendation for choice of agents in the setting of cardiogenic shock. The best strategy seems to be norepinephrine if hypotension is severe (SBP <70), or dopamine or dobutamine (or perhaps both, coadministered at lower doses of each) if hypotension is moderate (SBP 70–100).¹³ Dopamine has traditionally been recommended over norepinephrine, but newer all-type shock studies have challenged this practice.²⁸ The 2004 American College of Cardiology/American Heart Association Guidelines recommend dobutamine if SBP is 70 to 100 without shock, dopamine if shock is present, and norepinephrine if a second agent is needed.⁴³ These recommendations are not evidence-based, and the group’s 2013 update makes no comment, except noting that dopamine can be associated with “excess hazard.”⁴⁴ Some evidence suggests dopamine and dobutamine may be coadministered in doses of 7.5 µg/kg/min each to increase MAP, maintain normal

pulmonary capillary wedge pressure, and prevent hypoxemia more effectively than either single agent dosed alone at 15 $\mu\text{g}/\text{kg}/\text{min}$.⁴⁵ Other studies suggest vasopressin may be effective at increasing MAP without decreasing cardiac index or increasing pulmonary capillary wedge pressure.⁴⁶ Regardless, patients with postinfarct shock demand prompt specialty consultation, and treatment generally should be chosen in collaboration with the cardiologist who will inherit care of the patient.

Considerable expertise in treating cardiogenic shock has been gained through the perioperative management of patients undergoing cardiac surgery. Despite the widespread use of inotropes in this setting, particularly dobutamine, there remains considerable variation in practice between surgeons and centers,⁴⁷ no clear evidence-based guidelines,^{48,49} and a growing discussion regarding the side effects of inotrope use.^{50–52}

ACUTE DECOMPENSATED HEART FAILURE (ADHF)

Treatment of ADHF often involves inotropic support to lower end-diastolic pressure; improve diuresis; and allow typical regimens of angiotensin-converting enzyme inhibitors, diuretics, and β -blockers to be reinstated gradually. Despite the presence of hypotension, patients may have elevated SVR because of renal-angiotensin-aldosterone stimulation and the release of endogenous catecholamines and vasopressin. Inotropes with peripheral vasodilatory properties are therapeutic.¹³

Dobutamine or milrinone are recommended for consideration in patients with hypotensive ADHF and signs of decreased peripheral perfusion or end-organ dysfunction, or in patients unresponsive to or intolerant of IV vasodilation. Inotropes are not recommended unless left heart filling pressures are elevated, or cardiac index is severely impaired as noted on direct measurement or inferred from clinical signs. Inotropic support should be immediately discontinued if the patient experiences worsening hypotension or tachyarrhythmia.¹⁸ Evidence-based guidelines in this area are scarce. The European Society of Cardiology gives tenuous recommendations for a trial of dopamine in ADHF without shock, or dobutamine if there exists peripheral hypoperfusion with or without pulmonary edema, in patients unresponsive to standard diuretic and vasodilator therapy. For ADHF patients in shock, the Society advises proceeding with extreme caution because vasopressors can further increase SVR to the point of threatening end-organ perfusion.⁵³ Any use of dobutamine in a patient with ADHF should be done under close watch for signs of ischemia or arrhythmia, and serum potassium should particularly be monitored.

In clinical trials, dobutamine and milrinone have shown similar outcomes. Dobutamine increases contractility with only minimal systemic vasodilation, but β receptors can become blunted in patients with ADHF. Milrinone provides pulmonary vasodilation, right ventricular afterload reduction, and causes less of an increase in cardiac oxygen consumption, but has been noted at times to worsen systemic hypotension.^{54,55} Despite earlier enthusiasm for the newer “calcium sensitizer” levosimendan, it has been shown to confer no mortality benefit over dobutamine.⁵⁶

POSTCARDIOPULMONARY ARREST CARE

In the postarrest patient, MAP goals are typically 70 to 90. Without clear evidence-based support, professional consensus statements^{57,58} and expert opinion⁵⁹ offer this recommendation based mostly on small observational reports noting that postarrest patients treated accordingly have enjoyed favorable outcomes.^{60,61} These case series are confounded by other notable interventions, such as therapeutic hypothermia and percutaneous coronary intervention. The presumption is the posts ischemic

brain loses much of its autoregulatory ability, and MAP goals of 65 may not be adequate to maintain cerebral perfusion.^{58,62-64} No clear recommendations on choice of pressor are offered. Given the risk for arrhythmia in postarrest patients, norepinephrine, as opposed to dopamine, is a reasonable first-line selection. Future areas of study include the role of vasopressin and steroids during arrest, and a short course of stress-dose steroids in the week following return of circulation.⁶⁵

NEUROGENIC SHOCK

In neurogenic shock, vasopressor support is frequently indicated to counter the vasodilation, hypotension, and bradycardia resulting from spinal cord injury and the disruption of autonomic pathways and sympathetic tone. Hypotension impairs spinal cord perfusion and leads to propagation of secondary injury.⁶⁶ MAP should be kept at 85 or above immediately postinjury and in the week following. This recommendation is based on consensus statements from The American Association of Neurologic Surgeons⁶⁷ and The Consortium for Spinal Cord Medicine,⁶⁸ expert opinion,⁶⁹⁻⁷¹ and small case reports.⁷² There are no official recommendations for choice of vasopressor. Dopamine and norepinephrine are reasonable choices to augment α_1 and β_1 activity in cervical injuries, and phenylephrine may be adequate for lower thoracic injuries.⁷³

One must balance these higher MAP goals against suspected traumatic brain injury. Impaired cerebral autoregulation often accompanies traumatic brain injury and increased intracranial pressure may exacerbate cerebral edema.⁷⁴ Additionally, cerebral perfusion pressures greater than 70 have been associated with pulmonary edema and acute respiratory distress syndrome. In the setting of traumatic brain injury, one must heed these concerns and use higher MAP goals judiciously.

Excessive IV fluids can be dangerous. Impaired respiratory mechanics and loss of mobility in a bed-bound patient can lead to pulmonary edema. Also, cardiac pacing may be indicated in patients who remain bradycardic despite pharmacologic support.^{75,76} Autonomic deregulation is common and patients must be monitored closely for abrupt changes in heart rate and blood pressure.

ANAPHYLAXIS

Anaphylaxis is a difficult clinical entity to define and there exists a general consensus that health care providers are slow to recognize and treat the disease.⁷⁷⁻⁷⁹ To satisfy the World Allergy Organization's definition, one of three criteria must be fulfilled: (1) acute-onset involvement of skin or mucosal tissue with either respiratory compromise or clinically significant hypotension; (2) two or more of the following conditions arising after exposure to a likely allergen: skin or mucosal involvement, respiratory compromise, hypotension, or persistent gastrointestinal symptoms, such as abdominal pain or vomiting; or (3) hypotension after exposure to a known allergen with SBP less than 90, or greater than 30% decrease from a patient's baseline.⁷⁹

Epinephrine is first-line treatment. It should be given immediately on suspicion of anaphylaxis as 0.01 mg/kg of 1:1000 solution, up to a maximum of 0.5 mg in adults and 0.3 mg in children, intramuscular to the lateral thigh.⁷⁹ Intramuscular injections in this location achieve therapeutic plasma concentrations rapidly and reliably. The dose may be repeated every 5 to 15 minutes if clinical response is inadequate, but providers should not delay initiation of a titratable IV infusion of 1:10,000 concentration epinephrine. This is usually dosed at 0.5 to 5 $\mu\text{g}/\text{min}$ and is titrated to clinical response and tolerated tachycardia.⁷⁸⁻⁸⁰ Feared side effects, such as tachyarrhythmia, hypertensive crisis, and pulmonary edema, are rare following intramuscular dosing and, when

seen with IV infusions, are frequently caused by erroneous administration of 1:1000 concentration.⁸⁰ Patients on β -blocking medications and unresponsive to epinephrine infusions may respond to glucagon, dosed 1 to 5 mg (0.02–0.03 mg/kg to maximum of 1 mg in children) of slow IV push over 5 minutes, then infused at 5 to 15 mg/min and titrated to clinical response.^{81,82} Adjunctive therapy, such as antihistamines and corticosteroids, may be of use but should not replace or delay first-line treatment with epinephrine. Any patient treated for anaphylaxis must undergo a period of close and meaningful observation because symptoms can recur after an initial resolution.

SUMMARY

Although disease-specific guidelines provide a framework for vasopressor, inotrope, and chronotrope selection and usage, real-world applications demand therapy be tailored to the individual patient. Physiologic parameters, such as fluid status or cardiovascular reserve, may alter an individual patient's response to a particular agent. Patients with preexisting, poorly controlled hypertension may require higher than normal goal blood pressures to achieve treatment goals. Medications should be titrated to meaningful indicators of clinical response, such as urine output, skin perfusion, and mental status. If side effects render a patient intolerant of a particular medication, an alternative agent should be tried. Treatment of the critically ill patient with vasoactive medications must always be closely monitored and individualized.

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