Journal of Cardiovascular Pharmacology and Therapeutics
2015, Vol. 20(3) 249-260

DOI: 10.1177/1074248414559838
cpt.sagepub.com
SAGE

Pharmacotherapy Update on the Use of Vasopressors and Inotropes in the Intensive Care Unit

Jacob C. Jentzer, MD[1,5], James C. Coons, PharmD[1,2,6], Christopher B. Link, MD[1], and Mark Schmidhofer, MD[3,4]

Abstract

This paper summarizes the pharmacologic properties of vasoactive medications used in the treatment of shock, including the inotropes and vasopressors. The clinical application of these therapies is discussed and recent studies describing their use and associated outcomes are also reported. Comprehension of hemodynamic principles and adrenergic and non-adrenergic receptor mechanisms are salient to the appropriate therapeutic utility of vasoactive medications for shock. Vasoactive medications can be classified based on their direct effects on vascular tone (vasoconstriction or vasodilation) and on the heart (presence or absence of positive inotropic effects). This classification highlights key similarities and differences with respect to pharmacology and hemodynamic effects. Vasopressors include pure vasoconstrictors (phenylephrine and vasopressin) and inoconstrictors (dopamine, norepinephrine, and epinephrine). Each of these medications acts as vasopressors to increase mean arterial pressure by augmenting vascular tone. Inotropes include inodilators (dobutamine and milrinone) and the aforementioned inoconstrictors. These medications act as inotropes by enhancing cardiac output through enhanced contractility. The inodilators also reduce afterload from systemic vasodilation. The relative hemodynamic effect of each agent varies depending on the dose administered, but is particularly apparent with dopamine. Recent large-scale clinical trials have evaluated vasopressors and determined that norepinephrine may be preferred as a first-line therapy for a broad range of shock states, most notably septic shock. Consequently, careful selection of vasoactive medications based on desired pharmacologic effects that are matched to the patient's underlying pathophysiology of shock may optimize hemodynamics while reducing the potential for adverse effects.

Keywords

Vasoactive medications, inotropes, vasopressors, shock

Shock represents a failure of the cardiovascular system to provide adequate tissue perfusion and oxygen delivery to maintain normal cellular metabolism.[1,2] Shock is a final common pathway of numerous disease states, culminating in multiorgan dysfunction and death. Shock complicates one-third of intensive care unit (ICU) admissions and is a strong risk factor for ICU mortality, with progressive circulatory failure accounting for approximately 20% of all ICU deaths and more than 40% of deaths in patients with shock.[3-5] Vasopressor-dependent shock carries an average 28-day mortality of approximately 35% to 50%, regardless of etiology based on recent clinical studies.[4-11] Inadequate tissue perfusion during shock results from systemic hypotension and/or low cardiac output (CO), with microvascular shunting and mitochondrial dysfunction occurring independent of global perfusion in disease states such as sepsis; preshock states may occur with tissue hypoperfusion, despite adequate systemic hemodynamics.[1]

Hemodynamics in Shock

Hypotension occurs due to low systemic vascular resistance (SVR, a proxy for arteriolar tone) and/or insufficient CO. Patients may display inadequate CO with compensatory vasoconstriction and elevated SVR (cold shock) or inadequate SVR from pathologic vasodilation with compensatory elevated CO (warm shock).[1] Fluid resuscitation may convert a patient with sepsis from cold shock to warm shock, with subsequent development of myocardial dysfunction potentially reverting the

[1] Department of Cardiology, UPMC-Presbyterian Hospital, Pittsburgh, PA, USA
[2] University of Pittsburgh School of Pharmacy
[3] Heart and Vascular Institute, UPMC-Presbyterian Hospital, Pittsburgh, PA, USA
[4] Cardiac Intensive Care Unit
[5] Department of Critical Care Medicine, UPMC-Presbyterian Hospital, Pittsburgh, PA
[6] UPMC-Presbyterian Hospital, Pittsburgh, PA

Manuscript submitted: June 20, 2014; **accepted:** September 20, 2014.

Corresponding Author:
James C. Coons, Associate Professor, University of Pittsburgh School of Pharmacy Clinical Pharmacist, Cardiology, UPMC-Presbyterian Hospital.
Email: coonsjc@upmc.edu

Table 1. Pharmacologic Effects of Vasopressors and Inotropes.[a]

Medication	Heart	Vasculature	
	β1	α1	β2
Dopamine (doses > 4 μg/kg/min)	0 to 3+	0 to 3+	0 to 2+
Dobutamine	4+	+	2+
Epinephrine	4+	2+ to 4+	+ to 3+
Milrinone[b]	4+ "like"	0	3+ "like"
Norepinephrine	2+	4+	+
Phenylephrine	0	4+	0
Vasopressin[c]	0	4+ "like"	0

[a]Scale: 0 equals no agonist activity, 4+ equals very potent agonist.
[b]Milrinone does not bind to β or α receptors; it produces its hemodynamic effects through phosphodiesterase-3 inhibition.
[c]Vasopressin does not bind to β or α receptors; it produces its hemodynamic effects through vasopressin (V1) receptor agonism.

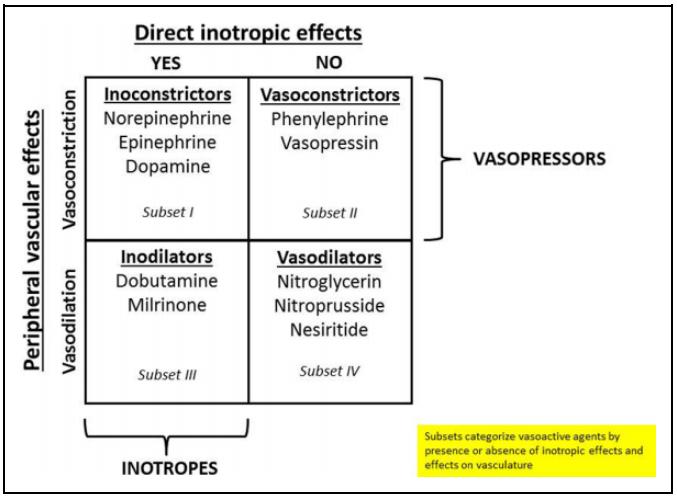

Figure 1. Proposed classification of vasoactive agents.

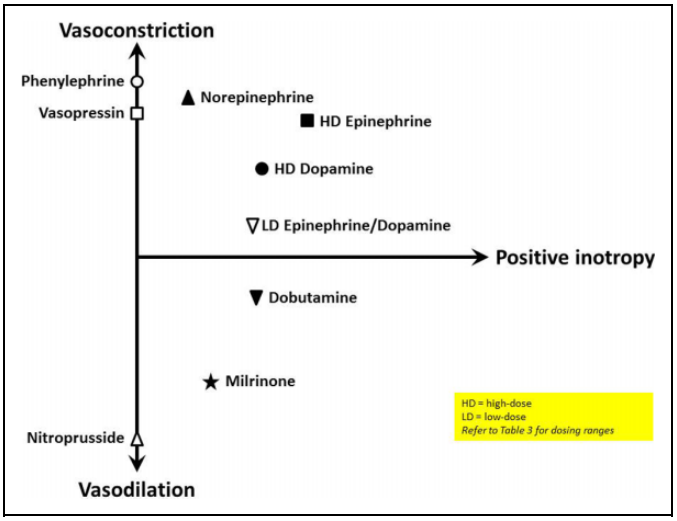

Figure 2. Vascular response to vasoactive medications.

patient back to cold shock. On examination, cold shock is characterized by cool, clammy extremities from high SVR and weak distal pulses with narrow pulse pressure from low stroke volume (SV). Low CO in cold shock primarily results from low SV due to inadequate preload (hypovolemic shock or obstructive shock) or impaired cardiac contractility (cardiogenic shock); inappropriately slow heart rate (HR) occasionally contributes. Warm (vasodilatory/distributive) shock is characterized by warm extremities from low SVR and palpable pulses due to preserved pulse pressure with normal SV. Septic shock is the most common etiology of warm shock and the most common cause of shock overall.[1,5] Pharmacologic increases in mean arterial pressure (MAP) are most often achieved via increases in SVR, and increasing CO will increase MAP only modestly when SVR is inadequate (warm shock). When low CO is the cause of hypotension (cold shock), pharmacologic increases in CO will be required to reverse hypotension. Pharmacologic increases in CO are primarily achieved by increasing SV and to a lesser extent by increasing HR because impaired diastolic filling during tachycardia can limit SV preventing further increases in CO.[2,12,13]

Adrenergic Receptors and Vasoactive Agents

Most vasoactive agents in clinical use exert their cardiovascular effects by interacting with adrenergic receptors (ARs) in the heart and vessels (Table 1).[13,14] Sympathetic activation restores MAP by increasing CO, SVR, and venous return by diverting blood from the venous and mesenteric circulation to the muscles, heart, and brain during stress and exercise.[14] Vascular α1 ARs (A1Rs) increase SVR by constricting the mesenteric, skin, and renal arterioles as well as the coronary arteries while redistributing blood volume from the mesentery and peripheral veins into the arterial circulation.[13,14] Responsiveness of vascular A1R is decreased in sepsis and warm/vasodilatory shock states, requiring higher vasopressor doses to maintain SVR when compared to patients with cold shock (especially cardiogenic shock).[13] Vascular vasopressin 1a receptors (V1aRs) mimic and augment the vasoconstrictive effects of A1R via multiple mechanisms.[13,15]

Myocardial β1 ARs (B1Rs), and to a lesser extent β2 ARs (B2Rs), increase HR (chronotropy) and cardiac contractility (inotropy) to increase SV and CO at a given preload.[13,14] Vascular B2Rs (and to a lesser extent B1Rs) oppose the vasoconstrictive effects of A1R and reduce vascular tone, especially in skeletal muscle to facilitate muscle blood flow and venous return during exercise.[14] Hepatic B2R stimulation increases glucose and lactate production to provide fuel for muscle metabolism. Patients with chronic heart failure (HF) display reduced sensitivity to B1R stimulation from chronic B1R downregulation.[14]

Vasoactive Agents and Shock

Vasopressors restore MAP by increasing SVR through arteriolar vasoconstriction (increased A1R/V1aR signaling).[2,13]

Table 2. Hemodynamic Effects of Vasopressors and Inotropes.

Medication	Hemodynamic Effects				
	CO/CI	SVR	PCWP	MAP	HR
Dopamine (doses >4 μg/kg/min)	↑	↑	↑	↑	↑↑
Dobutamine	↑↑	↔ ↓	↔ ↓	↑ ↓ ↔	↑
Epinephrine	↑↑	↑	↑	↑↑	↑↑
Milrinone	↑↑	↓↓	↓↓	↓ ↔	↑
Norepinephrine	↑ ↓	↑↑	↑	↑↑	↑
Phenylephrine	↓	↑	↑	↑	↔ ↓
Vasopressin	↓	↑	↑	↑	↔ ↓

Abbreviations: CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial pressure; HR, heart rate.

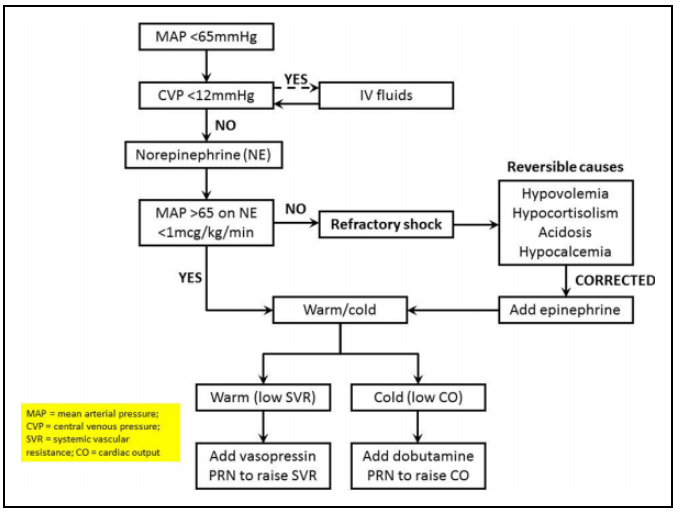

Figure 3. General approach to shock.

Inotropes increase CO and SV through improved cardiac contractility via augmented B1R/B2R signaling.[2,13] β-Adrenergic inotropes increase HR (positive chronotropic effect), which can further augment CO, although worsening tachycardia may limit further increases in CO in some patients.[2,12,13] We propose a new classification of vasoactive drugs used in shock based on their direct effects on vascular tone (vasoconstriction or vasodilation) and their direct effects on the heart (presence or absence of positive inotropic effects; Figure 1). This classification emphasizes the similarities and differences among drugs used as vasopressors (vasoconstrictors and inoconstrictors) and inotropes (inodilators and inoconstrictors; Figure 2).

Vasodilators and vasoconstrictors lack primary cardiac effects, although indirect cardiac effects occur due to sympathetic reflexes (Figure 2). Vasodilators reduce SVR without direct inotropic effects and vasoconstrictors increase SVR without direct inotropic effects. Inodilators reduce SVR and stimulate cardiac contractility, while inoconstrictors increase SVR and stimulate cardiac contractility (Figure 2). Vasodilators and inodilators tend to reduce cardiac filling pressures by reducing SVR, while vasoconstrictors and inoconstrictors tend to increase cardiac filling pressures by increasing SVR (Table 2). Vasodilators, inodilators, and inoconstrictors all can increase CO, although inodilators will tend to have the greatest effects due to combined reduction in SVR and increased contractility (Table 2). Vasoconstrictors and inoconstrictors are vasopressors and will increase MAP, with a greater effect from inoconstrictors due to the combined increases in both SVR and CO (Table 2).

The understanding of these differences is critical to the appropriate selection of vasoactive agents in various pathophysiologic states. The physiologic effects of each drug described here are only theoretical, as there can be marked interindividual variability in response to a given dose of a given drug based on underlying cardiovascular reserve, primary underlying disease pathophysiology, and intrinsic drug responsiveness. The comparative hemodynamic effects of vasoactive drugs seen in clinical studies may be confounded by other drugs the patients are receiving. Vasoactive drugs display a nonlinear dose response, whereby the incremental clinical response achieved with dose titration declines at higher doses.[16]

Goals of Resuscitation

When shock is not reversed promptly with fluid therapy to restore adequate cardiac filling pressures, vasoactive agents can increase MAP and/or CO to restore tissue perfusion (Figure 3).[1,2,13,17] Vasopressors (inoconstrictors and vasoconstrictors) are titrated to achieve an adequate systemic blood pressure (BP) that allows autoregulation of end-organ perfusion, that is, a systolic BP $\geq$90 mm Hg and/or a MAP $\geq$65 to 70 mm Hg (Table 3).[1,2,17] Titrating vasopressors to achieve MAP goals higher than 65 mm Hg does not consistently improve measures of organ function.[18] The recent Sepsis and Mean Arterial Pressure (SEPSISPAM) trial randomized 779 patients with vasopressor-dependent septic shock to a MAP goal of 65 to 70 mm Hg versus 80 to 85 mm Hg, showing no significant difference in mortality with a higher MAP goal (36.6% vs 34.0%, HR 1.07).[11] Patients with chronic hypertension randomized to the higher MAP goal had fewer renal adverse events attributed to improved renal perfusion, at the expense of more cardiac adverse events attributed to higher vasopressor doses.

Table 3. Dosing and Titration Parameters of Vasopressors and Inotropes.

Medication	Initial Dose	Typical Dose Range	Titration Increment (Every 5-15 Minutes to Achieve Hemodynamic Goal)	Weaning Increment (Every 5-15 Minutes Based on Patient Response)
Dobutamine	2.5-5 μg/kg/min	2.5-10 μg/kg/min	2.5-5 μg/kg/min; alternatively, dose increases per CO/CI or SVO_2	2.5-5 μg/kg/min
Dopamine	2-10 μg/kg/min 5-10 μg/kg/min (inotropic) > 10 μg/kg/min (vasopressor)	2-20 μg/kg/min	2-5 μg/kg/min	1 μg/kg/min
Epinephrine	0.02-0.05 μg/kg/min	0.005-0.2 μg/kg/min	0.02-0.05 μg/kg/min	0.02-0.05 μg/kg/min
Milrinone	0.25 μg/kg/min	0.25-0.75 μg/kg/min	Dose increases per CO/CI or SVO_2	Can be discontinued without weaning
Norepinephrine	0.01-0.04 μg/kg/min	0.04-1 μg/kg/min	0.02-0.04 μg/kg/min	0.02-0.04 μg/kg/min
Phenylephrine	0.1-0.3 μg/kg/min	0.1-1.5 μg/kg/min	0.2-0.4 μg/kg/min	0.2-0.4 μg/kg/min
Vasopressin	0.01-0.04 units/min	0.01-0.04 units/min	Not generally titrated	Can be discontinued without weaning

Abbreviations: CO, cardiac output; CI, cardiac index; SVO_2, mixed venous oxygen saturation.

After restoring cardiac filling pressures and MAP, increasing CO with inotropes may improve systemic oxygen delivery and tissue perfusion.[2,13] Inotropes (inodilators or low-dose inoconstrictors) can be titrated to achieve CO $\geq$5 L/min and/or cardiac index (CI, the CO divided by body surface area) $\geq$2.2 to 2.5 L/min/m^2, but markers of end-organ tissue perfusion and systemic oxygen delivery are preferred over arbitrary CO/CI goals for titration of inotropic therapy (Table 3).[2] Resuscitative measures should restore adequate end-organ perfusion, reflected by urine output >0.5 mL/kg/h with normal or declining lactate and a near-normal venous oxygen saturation.[2,17]

Inodilators

Inodilators increase SV and CO through direct stimulation of myocardial contractility coupled with reduced afterload from systemic vasodilation (reduced SVR), often with positive chronotropic effects contributing to increased CO (Table 2).[19] Dobutamine and milrinone are the inodilators most commonly used to increase critically low CO and restore tissue oxygen delivery, particularly in cardiogenic shock and low-output HF. All inodilators carry a risk of hypotension from excessive vasodilation, cardiac tachyarrhythmias from myocardial cellular calcium overload, and myocardial ischemia from oxygen supply–demand mismatch.[19] Inotrope administration is associated with increased mortality and adverse events in hospitalized patients, emphasizing the importance of restricting inodilator therapy to those patients whose CO is inadequate to maintain organ function.[20-26] Despite these important caveats, patients with critically low CO generally cannot be stabilized medically without inotropic support, and inodilator therapy appears beneficial in cardiogenic shock.[27] In the absence of severe hypotension, an inodilator is preferred over an inoconstrictor for increasing CO due to more favorable effects on afterload, cardiac filling pressures, and myocardial blood flow.[28-32]

Dobutamine

Dobutamine augments myocardial contractility via strong B1R stimulation with mild to moderate B2R agonism and mild A1R agonism, producing a strong dose-dependent increase in SV and CO with moderate increases in HR and a variable effect on MAP (Tables 1 and 2).[2] Dobutamine modestly lowers the SVR, except at high doses (>10-15 μg/kg/min) when dose-dependent A1R agonism may become more prominent.[33] The net effects of dobutamine on MAP depend on the relative changes in CO and SVR from baseline values, and uptitration of dobutamine can have unpredictable effects on MAP. Dobutamine may raise MAP when CO increases significantly and SVR declines modestly, as in cardiogenic shock when the baseline CO is very low and SVR is high.[2] Dobutamine may produce hypotension when CO increases modestly and SVR declines significantly, as in vasodilatory shock when baseline CO is relatively high and SVR is low.

Dobutamine produces a dose-dependent increase in HR, with low doses (up to 5 μg/kg/min) increasing SV via inotopic effects without significant tachycardia, but doses >10 μg/kg/min produce worsening tachycardia with minimal further increases in CO due to declining SV from decreased diastolic filling time (Table 3).[33] Comparison of dobutamine and dopamine in equal doses up to 5 to 10 μg/kg/min has shown higher CO and greater reduction in cardiac filling pressures by dobutamine and higher MAP and SVR with dopamine, despite similar overall changes in systemic hemodynamics.[28-31,34,35] Combining dopamine and dobutamine at 7.5 μg/kg/min improved hemodynamics more than either agent at 15 μg/kg/min in cardiogenic shock, suggesting a role for low-dose combination therapy in patients with hypotension requiring inotropic support.[34] After cardiac surgery, dobutamine (5 μg/kg/min) increased HR and CO to a greater extent than low-dose epinephrine (0.03 μg/kg/min).[36] Dobutamine may produce subadditive inotropic effects when combined with epinephrine, perhaps due to competition at B1R mimicking a partial agonist.[37]

Dobutamine is the preferred inotrope for acutely unstable patients in cardiogenic shock because its short half-life (less than 2 minutes) and quick onset allow prompt improvements in CO and rapid titration.[2] Dobutamine is recommended to increase CO when restoration of intravascular volume and MAP fails to normalize end-organ function in septic shock.[17] Dobutamine is recommended for support of patients with acute myocardial infarction (MI) having systolic BP <100 mm Hg and hypoperfusion without overt shock and can be added to norepinephrine to support patients with cardiogenic shock.[38-40] Meta-analysis of dobutamine compared with placebo in patients with severe HF unrelated to acute MI showed a strong trend to increased mortality with dobutamine (odds ratio [OR] 1.47, $P = .06$).[26] Prolonged use of dobutamine can lead to tachyphylaxis via B1R downregulation, requiring uptitration to maintain clinical effect.[19,41] β-Blockers (especially carvedilol) significantly impair the response to dobutamine, requiring high dobutamine doses for inotropic effects.[42,43]

Milrinone

Milrinone augments downstream B1R/B2R signaling by inhibiting phosphodiesterase 3 (PDE3), mimicking B1R/B2R activation (Table 1).[13] Milrinone produces prominent pulmonary and systemic vasodilation, significantly lowering both SVR and pulmonary vascular resistance (PVR; Table 2).[44] Patients with low CO and high SVR typically maintain their MAP after administration of milrinone, although patients with relatively low SVR or hypovolemia may become hypotensive, making milrinone suboptimal for many patients with shock.[2] Most clinical studies of milrinone have used a starting and maintenance dose of 0.5 μg/kg/min, but lower starting doses are preferred in clinical practice (Table 3). The optional loading dose of 50 μg/kg over 10 minutes often causes hypotension in unstable patients; similar hemodynamic effects are seen after approximately 2 to 3 hours of maintenance infusion without a loading dose.[2,45] The half-life of milrinone can increase from 2 to 3 hours up to 4 to 6 hours in patients with renal failure, warranting dose reduction for creatinine clearance <50 mL/min and caution in more advanced renal insufficiency due to risk of drug accumulation.[19] In hemodynamically stable patients with decompensated HF, milrinone 0.5 μg/kg/min increased rates of hypotension and tachyarrhythmias without improving any clinical outcome versus placebo, with increased mortality risk in patients with ischemic cardiomyopathy.[25,46] Milrinone retains its inotropic activity and produces sustained hemodynamic effects in patients with HF whose myocardial B1R are desensitized, downregulated, or pharmacologically blocked.[14,42,43] Combining milrinone with a direct B1R agonist may additively increase CO in patients with profoundly impaired cardiac function, with an added risk of adverse events.[24,47,48]

Dobutamine Versus Milrinone

Dobutamine and milrinone produce similar improvements in CO when titrated to full effect in patients with HF, although each individual patient may respond better to one drug or the other.[41,49-51] Dobutamine produces greater stimulation of myocardial contractility, while milrinone produces greater vasodilation and reduction in cardiac filling pressures (Table 2).[41,49,51,52] Milrinone reduces PVR more than dobutamine, making milrinone preferable in patients with significant right ventricular dysfunction.[53] Dobutamine is recommended for patients with hypotension including acute cardiogenic shock and septic shock with myocardial dysfunction as well as in patients with severe renal failure when milrinone could accumulate.[2,19,38-40] Milrinone is preferred for patients with chronic HF, especially in the presence of pulmonary hypertension, right ventricular failure, or β-blocker therapy.[2,19,42,43,53] Dobutamine produces more tachycardia, arrhythmias, hypertension, and myocardial ischemia than milrinone, while milrinone is more likely to cause hypotension.[13,41,51,54] Hospitalized patients with HF awaiting heart transplantation have similar outcomes and adverse events with dobutamine or milrinone.[55,56]

Inoconstrictors

Inoconstrictors are highly effective vasopressors that directly produce vasoconstriction and stimulate myocardial contractility to increase both CO and SVR. The endogenous catecholamine inoconstrictors (norepinephrine, epinephrine, and dopamine) all display a marked dose–response effect with variable physiologic effects across the dosing range and substantial interpatient variability in dose–response.[2,13] At low doses, these drugs stimulate myocardial B1R and increase myocardial contractility, particularly dopamine and epinephrine (Table 2). At higher doses, increasing amounts of A1R stimulation produce progressive increases in SVR and MAP (Table 2). Low-dose dopamine and epinephrine can be used for inotropic support and to therapeutically increase HR, while higher doses of all 3 drugs are used as vasopressors.[2,13,57] All inoconstrictors carry risk of tachycardia, tachyarrhythmias, myocardial ischemia, and tissue ischemia. Inoconstrictors are the first-line vasopressors for the majority of patients with shock; norepinephrine is preferred for most patients, while epinephrine and dopamine can be used when an increase in CO and/or HR is required.[1,2,13,17,58]

Norepinephrine

Norepinephrine is a potent A1R agonist and mild–moderate B1R agonist with minimal B2R activity (Table 1).[13] The hemodynamic effects of norepinephrine are dominated by A1R-mediated vasoconstriction and increased SVR, while B1R activation provides just enough inotropy to maintain CO (Table 2).[2,59,60] Increasing doses of norepinephrine may increase CO in some patients due to B1R activation, augmentation of venous return, and improved fluid responsiveness.[61-64] Norepinephrine may reduce CO like a pure vasoconstrictor in patients with cardiac dysfunction due to the strong increase in afterload, but many patients with cardiogenic shock can maintain CO during norepinephrine therapy.[60,61] As a vasopressor, norepinephrine is slightly lower in potency than epinephrine,

approximately 100-fold more potent than dopamine, and roughly 3 to 5 times more potent than phenylephrine for raising MAP.[5,7,8,59,65,66] Norepinephrine doses >0.5 to 1 μg/kg/min are considered high (Table 3), but there is no defined maximum norepinephrine dose for refractory shock.[57,67] Norepinephrine may produce reflex reductions in HR by increasing MAP, although worsening tachycardia can occur at high doses due to B1R stimulation. Norepinephrine is the first-line vasopressor for all forms of shock with severe hypotension, including undifferentiated shock, vasodilatory/septic shock, and cardiogenic shock (Figure 3).[1,2,17,40] Randomized controlled trials have not shown clear superiority of any other vasopressor over norepinephrine for clinical outcomes in patients with shock, with point estimates for mortality generally favoring norepinephrine when compared to other catecholamines.[5-9,58,68] Prior guidelines recommend dopamine for patients with acute myocardial infarction and cardiogenic shock with systolic BP >70 mm Hg, with norepinephrine recommended when systolic BP is <70 mm Hg.[38] Based on the results of the Sepsis Occurrence in Acutely Ill Patients II (SOAP-II) trial, more recent guidelines recommend the combination of norepinephrine and dobutamine for cardiogenic shock instead of dopamine.[5,39,40]

Epinephrine

Epinephrine is a potent agonist of A1R and B1R with stronger B2R activity than norepinephrine (Table 1). Epinephrine is approximately 100-fold more potent as an inotrope than dobutamine or dopamine, and low epinephrine doses of 0.01 to 0.1 μg/kg/min (2-10 μg/min) are used to therapeutically increase CO and/or HR via strong B1R and B2R stimulation (Table 2).[31,57] After cardiac surgery, low-dose epinephrine (0.03-0.04 μg/kg/min) effectively increased SV, CO, and MAP with less tachycardia than dobutamine (5 μg/kg/min).[36,37] Epinephrine is most useful as an inotrope in patients who are hypotensive and free from myocardial ischemia, especially after cardiac surgery.[2,31,32,36,37,69] In patients with septic shock and MAP <70 mm Hg despite norepinephrine (0.1 μg/kg/min), adding epinephrine (0.05-0.3 μg/kg/min) increased MAP, HR, and CI more than adding dobutamine (3-20 μg/kg/min).[69]

Higher epinephrine doses (>0.1 μg/kg/min) produce increasing A1R-mediated vasoconstriction leading to potent vasopressor and inotropic effects similar to the combination of norepinephrine plus dobutamine (Table 2).[7,70] Epinephrine increases CO when compared to norepinephrine or dopamine for vasopressor support in septic shock.[71] Epinephrine is a highly effective vasopressor that is generally second line due to metabolic effects and remains the preferred vasopressor for refractory shock (Figure 3).[2,7,8,17] Epinephrine doses >0.3 to 0.5 μg/kg/min are considered high (Table 3), but there is no defined maximum epinephrine dose for refractory shock (Table 3).[57,67]

Dopamine

Pharmacologic doses of dopamine activate dopaminergic receptors and exert AR agonist effects via direct activation of B1R and indirect increases in A1R signaling (Table 1).[13] Dopaminergic receptors produce vasodilation in the mesenteric and renal arterioles and inhibit renal tubular sodium reabsorption. The clinical effects of dopamine are strongly dose dependent with significant overlap between dose ranges (Tables 2 and 3).

Very low "renal" doses of dopamine (below 4 μg/kg/min) activate dopamine receptors, leading to splanchnic and renal vasodilation with direct natriuretic effects that increase urine output with variable and transient effects on creatinine clearance and renal blood flow (Table 3).[35,72-77] Effects of dopamine on creatinine clearance peak at dopamine doses of 4 to 7 μg/kg/min, mediated in part by increases in MAP and CO.[35,74-77] Renal effects of dopamine are blunted in acutely ill patients, and studies have failed to show any clinical benefit of "renal-dose" dopamine for preventing renal failure.[72-74] Low-dose dopamine added to diuretic therapy in HF failed to improve clinical outcomes or urine output.[78,79]

Moderate "inotropic" doses of dopamine (4-10 μg/kg/min) activate B1R, producing inotropic and chronotropic effects that increase MAP, HR, SV, and CO (Tables 2 and 3). Even "renal-dose" dopamine (2-3 μg/kg/min) can display positive inotropic and chronotropic effects.[29,35,76,77] Effects of dopamine on CO usually peak at a dose of ~4 to 6 μg/kg/min (up to 7.5-8 μg/kg/min), with increases in SVR at higher doses limiting further increases in CO and tachycardia often limiting dose titration.[28-31,34,74,77] Dopamine doses >5 to 6 μg/kg/min can increase left ventricular filling pressures and exacerbate pulmonary congestion by increasing SVR without further increasing CO.[28-31]

High "vasopressor" doses of dopamine (>10 μg/kg/min) increase A1R signaling to increase MAP by progressively increasing SVR without further increasing CO (Tables 2 and 3). Up to 60% to 69% of patients with severe shock fail to respond adequately to dopamine at the usual maximum dose of 20 to 25 μg/kg/min, and switching to norepinephrine will stabilize MAP in the majority of the cases.[80,81] Dopamine increases CO and HR to a greater extent than norepinephrine, which in turn is more effective for increasing SVR and MAP.[59,81] Dopamine is no longer recommended for vasopressor support in septic shock except in patients with relative bradycardia who are at low tachyarrhythmia risk.[17]

Comparison of Inoconstrictors

Multiple studies suggest increased mortality and/or adverse effects with dopamine as the first-line vasopressor.[4-6,58] The SOAP-II study randomized 1679 unselected patients with shock to norepinephrine (0.05-0.2 μg/kg/min) or dopamine (5-20 μg/kg/min), with open-label norepinephrine added as needed to maintain MAP.[5] There was a trend toward higher mortality at 28 days in patients receiving dopamine (48.5% vs 52.5%, OR 1.17, $P = .10$). Subgroup analysis showed significantly greater mortality ($P = .03$) in patients with cardiogenic shock receiving dopamine, with no apparent mortality difference in other subgroups. Dopamine increased the risk of tachyarrhythmias (most commonly atrial fibrillation) by a factor of 2 (24.1% vs 12.4%, $P < .001$). Patel et al randomized 252

patients with septic shock to norepinephrine (5-20 μg/min) or dopamine (5-20 μg/kg/min) with vasopressin then phenylephrine added for nonresponders, showing similar 28-day mortality (50% vs 43%, $P = .282$) and significant more cardiac arrhythmias with dopamine.[6] Meta-analysis of randomized studies comparing dopamine and norepinephrine in septic shock identified a significant excess of short-term mortality with dopamine (relative risk [RR] 1.12, $P = .035$).[58]

Randomized studies have shown similar mortality with epinephrine or norepinephrine in patients with shock.[7,8,17] The Prospective, Multicenter, Randomized, Double-Blind Study Comparing Safety and Efficacy of Norepinephrine Plus Dobutamine Versus (Epinephrine Alone in Septic Shock CATS) study randomized 330 patients with severe septic shock to norepinephrine plus dobutamine or epinephrine alone, showing similar rates of 90-day mortality (50% vs 52%, $P = .73$) and adverse events, despite more lactic acidosis with epinephrine.[7] The randomized The Catecholamine Study (CAT) study compared epinephrine to norepinephrine in 280 patients with shock, showing similar hemodynamic efficacy and 90-day mortality (30.4% vs 34.3%, $P = .43$) but a higher rate of drug withdrawal with epinephrine due to lactic acidosis and tachycardia.[8] Levy et al randomized 30 patients with cardiogenic shock to norepinephrine plus dobutamine or epinephrine alone, showing similar hemodynamic effects but more arrhythmias with epinephrine.[70]

Vasoconstrictors

The pure vasoconstrictors phenylephrine and vasopressin are second-line vasopressors for most shock states that increase SVR via isolated vasoconstriction without inotropic effects (Figure 3).[2,17] Baroreflex-mediated sympathetic withdrawal resulting in reductions in HR, SV, and CO limits the ability of vasoconstrictors to increase MAP, potentially requiring inotropic support to maintain CO (Table 2).[65,82-86] Patients with significant systolic dysfunction cannot maintain SV in the face of increased afterload from systemic vasoconstriction, leading to inadequate CO and/or elevated filling pressures with a poor MAP response.[2,61] Vasoconstrictors are reserved for vasodilatory shock states when SVR is severely low and CO is adequate (warm shock; Figure 3). Vasoconstrictors display a limited ability to raise MAP when SVR is high and/or CO is low (cold shock) and may predispose to severe tissue ischemia via further reductions in CO.[15] Vasoconstrictors are useful when inotropic stimulation is harmful, such as uncontrolled tachycardia/tachyarrhythmias or left ventricular outflow tract obstruction.[2,17] Both phenylephrine and vasopressin have longer half-lives than catecholamines, taking longer to achieve steady state effects and requiring more gradual titration.[82] When a vasoconstrictor is indicated, we typically prefer vasopressin based on its more extensive clinical trial experience, although phenylephrine is useful when short-term use or frequent dose titration is anticipated.[9,68,76,82,87]

Phenylephrine

Phenylephrine is a pure A1R agonist without B1R/B2R activity that increases arterial and venous tone (Table 1).[82] Patients with warm (vasodilatory/distributive) shock and normal baseline cardiac function usually maintain CO during treatment with phenylephrine.[65,66] Phenylephrine has a duration of action up to 20 minutes, allowing bolus administration (0.1-0.5 mg every 5-15 minutes) for abrupt-onset vasodilatory hypotension.[82] Although phenylephrine doses $\geq$5 μg/kg/min can be used, we try to limit maximum phenylephrine doses to 1.5 to 2 μg/kg/min to avoid excessive vasoconstriction and tissue ischemia (Table 3).[65,66,83] Phenylephrine is available in a lower concentration (20 μg/mL) that can be infused via peripheral intravenous line for stabilization prior to central venous access.

Cross-over studies comparing phenylephrine to norepinephrine in septic shock with high CO show similar MAP effects, despite a lower HR and CO and a higher PVR with phenylephrine.[65,66] In patients with septic shock resistant to dopamine 25 μg/kg/min, addition of phenylephrine or norepinephrine resulted in equivalent hemodynamic stabilization with a lower HR in the phenylephrine group.[83] Phenylephrine is not recommended for septic shock except when norepinephrine triggers serious arrhythmias and/or in the setting of persistent hypotension with high CO.[17]

Vasopressin

Vasopressin produces similar hemodynamic effects as phenylephrine, but V1aR activation may produce vasoconstriction even during acidemia, when A1R agonism becomes less effective.[15] Low, fixed vasopressin doses (0.03-0.04 U/min) can be used to replete the relative vasopressin deficiency that can develop in shock states with the goal of improving MAP and/or reducing catecholamine requirements in patients with shock (Table 3).[2,9,15,17,68] Higher vasopressin doses (occasionally up to 0.1 U/min) can be effective for increasing MAP but are typically reserved for salvage therapy in refractory vasodilatory shock due to risk of mesenteric ischemia and should not be used routinely.[17,88-92] Vasopressin 0.01 U/min is roughly equivalent to norepinephrine 5 μg/min for raising MAP, and studies comparing vasopressin and norepinephrine show similar effects on MAP, despite lower HR and CO with vasopressin.[2,9,84-86,91] Vasopressin may reduce PVR while increasing SVR to favorably reduce the PVR to SVR ratio, especially when combined with milrinone in postoperative cardiac surgery patients; this effect may be advantageous in patients with right ventricular failure.[85,89,92-94]

The effects of vasopressin on septic shock mortality remain controversial, with most studies suggesting no mortality reduction by adding vasopressin to catecholamine therapy.[9,17,68,87] The Vasopressin and Septic Shock Trial (VASST) randomized 778 patients with septic shock requiring vasopressors to addition of vasopressin (0.01-0.03 U/min) or norepinephrine (5-15 μg/min), essentially evaluating physiologic vasopressin

repletion as a catecholamine-sparing vasopressor strategy.[9] There was no significant difference in 90-day mortality (43.9% vs 49.6%, RR 0.88, $P = .11$) or major clinical adverse events in patients receiving vasopressin. Vasopressin reduced 90-day mortality (35.8% vs 46.1%, RR 0.78, $P = .04$) in patients with milder shock (requiring <15 μg/min norepinephrine at randomization) and in patients receiving stress-dose corticosteroids.[9,95] Two meta-analyses comparing vasopressin to catecholamines in vasodilatory or septic shock came to different conclusions, with one showing no difference in short-term mortality (RR = 0.91, $P = .21$) while the other showing a significant reduction in mortality with vasopressin (RR 0.87, p = 0.05); the majority of the patients in both meta-analyses came from VASST.[68,87] Neither meta-analysis showed an increase in serious adverse events with vasopressin, and supraventricular arrhythmias have been found more commonly with norepinephrine.[17,68,87,90] Vasopressin is not considered a first-line vasopressor but can be safely used as adjunctive therapy for patients with persistently low SVR and/or tachyarrhythmias during norepinephrine therapy, including septic shock and postoperative vasoplegia syndrome after cardiopulmonary bypass.[17,88,90,92-94]

Refractory Shock

Hypotension refractory to high doses of one or more vasopressors (ie, norepinephrine or epinephrine at >0.5-1 μg/kg/min) complicates 6% to 7% of cases with shock, with short-term mortality up to 83% to 94% and few clinical studies to guide management.[67,91,96,97] Pathologic vasodilation characterizes most cases of refractory shock, occurring via vascular hyporesponsiveness to catecholamines due to receptor desensitization, inflammatory vasodilation, systemic acidemia, ionized hypocalcemia, and relative deficiency of vasopressin and corticosteroids.[13,15,67] Exclusion of hypovolemia with an empiric fluid challenge is a reasonable first step in the management of refractory shock. Inotropic support using dobutamine or low-dose epinephrine may substantially improve MAP in patients with severely low CO. Patients not responding adequately to initial therapy with dopamine or phenylephrine may respond when these weaker vasopressors are changed to norepinephrine.[80,81] Our recommended clinical approach to refractory shock is shown in Figure 3, assuming patients are started initially on norepinephrine.

Epinephrine is the first-line vasopressor to add in patients with (septic) shock refractory to high-dose norepinephrine, especially when the HR and/or CO are inadequate.[2,17,67] Vasopressin can be added to catecholamines when HR is excessively high and/or SVR remains low with an adequate CO (warm shock), especially in the presence of significant acidemia that limits catecholamine response.[2,15,67,88-90] In refractory vasodilatory shock, vasopressin at 4 U/h (0.067 U/min) was superior to 2 U/h (0.033 U/min) for improving MAP and reducing catecholamine requirements without increasing major clinical adverse effects.[88-90] There was no difference in 28-day mortality in VASST patients with higher baseline norepinephrine requirements receiving vasopressin (44.0% vs 42.5%, RR 1.04, $P = .76$), arguing against a mortality benefit of vasopressin in refractory shock.[9] In our experience, dopamine is usually ineffective when patients fail to respond to high-dose norepinephrine and/or epinephrine. Phenylephrine may be added when other vasopressors fail to restore MAP in refractory vasodilatory shock, but its effects are usually modest.[17] Empiric hydrocortisone can be added in refractory shock based on its ability to reverse shock and reduce catecholamine requirements, despite lack of consistent mortality reduction in large-scale studies of septic shock.[17,90,97,98]

Adverse Effects

Vasopressors and inotropes can produce serious adverse effects and should be used for the shortest duration of time, at the lowest adequate dose, and only when necessary to maintain vital organ function.[13,99] Excessive A1R/V1aR stimulation produces severe vasoconstriction in the skin, mesenteric, renal, and coronary vessels leading to tissue ischemia, especially with low CO and/or hypovolemia (cold shock).[2,13,15] Clinical trials have not shown consistent differences in tissue or myocardial ischemia between vasopressor agents, despite the suggestion of increased adverse events with vasopressin doses >0.04 U/min.[5,7-9,58,68,87,91] Epinephrine may impair splanchnic perfusion when compared to dopamine or norepinephrine (with or without dobutamine) at a given MAP and CO, and some studies suggest impaired mesenteric organ perfusion with vasopressin or phenylephrine compared to norepinephrine.[15,65,71] Excessive A1R-mediated renal vasoconstriction may predispose to acute kidney injury, and changing from norepinephrine to phenylephrine in established shock may have adverse effects on renal function.[65] Vasopressin may improve urine output and/or creatinine clearance when compared to norepinephrine and adding vasopressin appeared to reduce the risk of renal dysfunction in VASST, perhaps mediated by lower norepinephrine doses.[15,84,91,100]

Excessive cardiac B1R/B2R stimulation (including PDE3 inhibition) produces tachycardia and myocardial cellular calcium overload, predisposing to atrial and ventricular arrhythmias.[13,99] Risk of tachycardia and tachyarrhythmias during inotropic therapy is lowest with milrinone, intermediate with dobutamine or epinephrine, and generally highest with dopamine (Table 2).[13,41,51,54] Norepinephrine carries a lower tachyarrhythmia risk than either dopamine or epinephrine when used for vasopressor support (Table 2).[5,6,8,70,71] Phenylephrine and vasopressin reduce HR and do not cause tachyarrhythmias but may provoke myocardial ischemia via coronary vasoconstriction.[2,65,83-86,91] All B1R agonists increase myocardial oxygen demand, but dobutamine may improve coronary blood flow when compared to epinephrine or dopamine; milrinone increases myocardial oxygen demand less than direct B1R agonists.[13,32,54,99] Vasodilatory effects of milrinone and to a lesser extent dobutamine and low-dose dopamine can exacerbate hypotension, especially in patients with hypovolemia or low SVR.[2] Activation of B1R modestly impairs insulin

sensitivity and produces hyperglycemia; B2R activation magnifies this effect and increases serum lactate levels as is prominent with epinephrine.[7,8,13,99] Pharmacologic doses of the endogenous catecholamines may have potentially harmful effects on immune function and pituitary hormone secretion; these effects appear to be greatest with dopamine and least with norepinephrine.[13,17,99] Vasopressin may reduce harmful excess cytokine levels to a greater extent than norepinephrine in septic shock.[101]

Conclusion

Vasopressor and inotropic drug support can be lifesaving in shock states when the cardiovascular system fails to maintain adequate organ perfusion for survival. Careful vasoactive drug selection matching the pharmacological effects to the underlying pathophysiology may optimize hemodynamics and reduce adverse effects. Division of vasoactive drugs into vasodilators, inodilators, inoconstrictors, and vasoconstrictors facilitates understanding of their hemodynamic and adverse effects. Inodilators and inoconstrictors act as inotropes to increase CO via enhanced contractility, while vasoconstrictors and inoconstrictors act as vasopressors to increase MAP via enhanced vascular tone. Recent large-scale clinical trials have established norepinephrine as the first-line vasopressor drug for a broad range of shock states. Further research should explore strategies for the management of refractory shock and further comparisons of commonly used vasoactive agents in larger populations using clinically relevant end points.

Author Contributions

Jacob C. Jentzer contributed to conception and design of the study, substansially contributed to data acquisition, analysis, and interpretation of the data, drafted the manuscript, and critically revised the manuscript for intellectual content. James C. Coons contributed to conception and design of the study, substansially contributed to data acquisition, analysis, and interpretation of the data, drafted the manuscript, and critically revised the manuscript for intellectual content Christopher B. Link contributed to conception and design of the study, contributed to analysis and interpretation of the data, drafted the manuscript, and critically revised the manuscript for intellectual content Mark Schmidhofer contributed to conception and design of the study, contributed to analysis and interpretation of the data, drafted the manuscript, and critically revised the manuscript for intellectual content.

Authors' Note

This manuscript was completed at UPMC Presbyterian-Shadyside Hospital, Pittsburgh, PA, USA.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med*. 2013; 369(18):1726-1734.
2. Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med*. 2011;183(7):847-855.
3. Mayr VD, Dunser MW, Greil V, et al. Causes of death and determinants of outcome in critically ill patients. *Crit Care*. 2006; 10(6):R154.
4. Sakr Y, Reinhart K, Vincent JL, et al. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. *Crit Care Med*. 2006;34(3):589-597.
5. 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):779-789.
6. Patel GP, Grahe JS, Sperry M, et al. Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. *Shock*. 2010;33(4):375-380.
7. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*. 2007;370(9588):676-684.
8. Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34(12):2226-2234.
9. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877-887.
10. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med*. 2012;367(14):1287-1296.
11. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. *N Engl J Med*. 2014;370(17):1583-1593.
12. Johnston WE, Robertie PG, Dudas LM, Kon ND, Vinten-Johansen J. Heart rate-right ventricular stroke volume relation with myocardial revascularization. *Ann Thorac Surg*. 1991;52(4): 797-804.
13. Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. *Br J Pharmacol*. 2012; 165(7):2015-2033.
14. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol*. 2009;54(19):1747-1762.
15. Russell JA. Bench-to-bedside review: vasopressin in the management of septic shock. *Crit Care*. 2011;15(4):226.
16. Sumner DJ, Elliott HL. The pressor dose-response in clinical cardiovascular pharmacology. *Br J Clin Pharmacol*. 1987;23(5): 499-503.
17. 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.
18. Bourgoin A, Leone M, Delmas A, Garnier F, Albanese J, Martin C. Increasing mean arterial pressure in patients with septic shock:

effects on oxygen variables and renal function. *Crit Care Med*. 2005;33(4):780-786.
19. Petersen JW, Felker GM. Inotropes in the management of acute heart failure. *Crit Care Med*. 2008;36(1 suppl):S106-S111.
20. Costanzo MR, Johannes RS, Pine M, et al. The safety of intravenous diuretics alone versus diuretics plus parenteral vasoactive therapies in hospitalized patients with acutely decompensated heart failure: a propensity score and instrumental variable analysis using the Acutely Decompensated Heart Failure National Registry (ADHERE) database. *Am Heart J*. 2007;154(2):267-277.
21. O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J*. 1999;138(1 pt 1):78-86.
22. Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol*. 2005;46(1):57-64.
23. Wilkman E, Kaukonen KM, Pettila V, Kuitunen A, Varpula M. Association between inotrope treatment and 90-day mortality in patients with septic shock. *Acta Anaesthesiol Scand*. 2013; 57(4):431-442.
24. Rossinen J, Harjola VP, Siirila-Waris K, et al. The use of more than one inotrope in acute heart failure is associated with increased mortality: a multi-centre observational study. *Acute Cardiac Care*. 2008;10(4):209-213.
25. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287(12):1541-1547.
26. Tacon CL, McCaffrey J, Delaney A. Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials. *Int Care Med*. 2012;38(3):359-367.
27. Pirracchio R, Parenica J, Resche Rigon M, et al. The effectiveness of inodilators in reducing short term mortality among patient with severe cardiogenic shock: a propensity-based analysis. *PloS One*. 2013;8(8):e71659.
28. Loeb HS, Bredakis J, Gunner RM. Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. *Circulation*. 1977;55(2): 375-378.
29. Francis GS, Sharma B, Hodges M. Comparative hemodynamic effects of dopamine and dobutamine in patients with acute cardiogenic circulatory collapse. *Am Heart J*. 1982;103(6):995-1000.
30. Salomon NW, Plachetka JR, Copeland JG. Comparison of dopamine and dobutamine following coronary artery bypass grafting. *Ann Thorac Surg*. 1982;33(1):48-54.
31. Sato Y, Matsuzawa H, Eguchi S. Comparative study of effects of adrenaline, dobutamine and dopamine on systemic hemodynamics and renal blood flow in patients following open heart surgery. *Jpn Circ J*. 1982;46(10):1059-1072.
32. Fowler MB, Alderman EL, Oesterle SN, et al. Dobutamine and dopamine after cardiac surgery: greater augmentation of myocardial blood flow with dobutamine. *Circulation*. 1984;70(3 pt 2): I103-I111.
33. Romson JL, Leung JM, Bellows WH, et al. Effects of dobutamine on hemodynamics and left ventricular performance after cardiopulmonary bypass in cardiac surgical patients. *Anesthesiology*. 1999;91(5):1318-1328.
34. Richard C, Ricome JL, Rimailho A, Bottineau G, Auzepy P. Combined hemodynamic effects of dopamine and dobutamine in cardiogenic shock. *Circulation*. 1983;67(3):620-626.
35. Ichai C, Soubielle J, Carles M, Giunti C, Grimaud D. Comparison of the renal effects of low to high doses of dopamine and dobutamine in critically ill patients: a single-blind randomized study. *Crit Care Med*. 2000;28(4):921-928.
36. Butterworth JFt, Prielipp RC, Royster RL, et al. Dobutamine increases heart rate more than epinephrine in patients recovering from aortocoronary bypass surgery. *J Cardiothorac Vasc Anesth*. 1992;6(5):535-541.
37. Prielipp RC, MacGregor DA, Royster RL, Kon ND, Hines MH, Butterworth JFt. Dobutamine antagonizes epinephrine's biochemical and cardiotonic effects: results of an in vitro model using human lymphocytes and a clinical study in patients recovering from cardiac surgery. *Anesthesiology*. 1998;89(1):49-57.
38. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 2004;110(9):e82-e292.
39. Task Force on the management of STseamiotESoC, Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33(20):2569-2619.
40. Werdan K, Russ M, Buerke M, et al. Cardiogenic shock due to myocardial infarction: diagnosis, monitoring and treatment: a German-Austrian S3 Guideline. *Deutsch Arztebl Int*. 2012; 109(19):343-351.
41. Mager G, Klocke RK, Kux A, Hopp HW, Hilger HH. Phosphodiesterase III inhibition or adrenoreceptor stimulation: milrinone as an alternative to dobutamine in the treatment of severe heart failure. *Am Heart J*. 1991;121(6 pt 2):1974-1983.
42. Lowes BD, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR. Milrinone versus dobutamine in heart failure subjects treated chronically with carvedilol. *Int J Cardiol*. 2001;81(2-3):141-149.
43. Metra M, Nodari S, D'Aloia A, et al. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. *J Am Coll Cardiol*. 2002;40(7):1248-1258.
44. Givertz MM, Hare JM, Loh E, Gauthier DF, Colucci WS. Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: a rapid test for reversibility of pulmonary hypertension. *J Am Coll Cardiol*. 1996;28(7):1775-1780.

45. Baruch L, Patacsil P, Hameed A, Pina I, Loh E. Pharmacodynamic effects of milrinone with and without a bolus loading infusion. *Am Heart J*. 2001;141(2):266-273.
46. Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol*. 2003;41(6):997-1003.
47. Royster RL, Butterworth JFt, Prielipp RC, et al. Combined inotropic effects of amrinone and epinephrine after cardiopulmonary bypass in humans. *Anesth Analg*. 1993;77(4):662-672.
48. Boldt J, Kling D, Moosdorf R, Hempelmann G. Enoximone treatment of impaired myocardial function during cardiac surgery: combined effects with epinephrine. *J Cardiothorac Anesth*. 1990;4(4):462-468.
49. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. *Circulation*. 1986;73(3 pt 2):III175-III183.
50. Biddle TL, Benotti JR, Creager MA, et al. Comparison of intravenous milrinone and dobutamine for congestive heart failure secondary to either ischemic or dilated cardiomyopathy. *Am J Cardiol*. 1987;59(15):1345-1350.
51. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation*. 1986;73(3 pt 2):III168-III174.
52. Karlsberg RP, DeWood MA, DeMaria AN, Berk MR, Lasher KP. Comparative efficacy of short-term intravenous infusions of milrinone and dobutamine in acute congestive heart failure following acute myocardial infarction. Milrinone-Dobutamine Study Group. *Clin Cardiol*. 1996;19(1):21-30.
53. Eichhorn EJ, Konstam MA, Weiland DS, et al. Differential effects of milrinone and dobutamine on right ventricular preload, afterload and systolic performance in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1987;60(16):1329-1333.
54. Feneck RO, Sherry KM, Withington PS, Oduro-Dominah A, European Milrinone Multicenter Trial G. Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2001;15(3):306-315.
55. Yamani MH, Haji SA, Starling RC, 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.
56. Aranda JM Jr, Schofield RS, Pauly DF, et al. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. *Am Heart J*. 2003;145(2):324-329.
57. Ecc Committee S, Task Forces of the American Heart A. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2005;112(24 suppl):IV1-IV203.
58. De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis*. *Crit Care Med*. 2012;40(3):725-730.
59. Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA*. 1994;272(17):1354-1357.
60. Rokyta R Jr, Tesarova J, Pechman V, Gajdos P, Krouzecky A. The effects of short-term norepinephrine up-titration on hemodynamics in cardiogenic shock. *Physiol Res*. 2010;59(3):373-378.
61. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. *Crit Care Med*. 2013;41(1):143-150.
62. Thooft A, Favory R, Salgado DR, et al. Effects of changes in arterial pressure on organ perfusion during septic shock. *Crit care*. 2011;15(5):R222.
63. Hamzaoui O, Georger JF, Monnet X, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. *Crit Care*. 2010;14(4):R142.
64. Monnet X, Jabot J, Maizel J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. *Crit Care Med*. 2011;39(4):689-694.
65. Morelli A, Lange M, Ertmer C, et al. Short-term effects of phenylephrine on systemic and regional hemodynamics in patients with septic shock: a crossover pilot study. *Shock*. 2008;29(4):446-451.
66. 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.
67. Bassi E, Park M, Azevedo LC. Therapeutic strategies for high-dose vasopressor-dependent shock. *Crit Care Res Pract*. 2013;2013:654708.
68. Polito A, Parisini E, Ricci Z, Picardo S, Annane D. Vasopressin for treatment of vasodilatory shock: an ESICM systematic review and meta-analysis. *Intensive Care Med*. 2012;38(1):9-19.
69. 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):75-80.
70. Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit Care Med*. 2011;39(3):450-455.
71. De Backer D, Creteur J, Silva E, Vincent JL. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Crit Care Med*. 2003;31(6):1659-1667.
72. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med*. 2005;142(7):510-524.
73. Lherm T, Troche G, Rossignol M, Bordes P, Zazzo JF. Renal effects of low-dose dopamine in patients with sepsis syndrome or septic shock treated with catecholamines. *Intensive Care Med*. 1996;22(3):213-219.

74. Ungar A, Fumagalli S, Marini M, et al. Renal, but not systemic, hemodynamic effects of dopamine are influenced by the severity of congestive heart failure. *Crit Care Med*. 2004;32(5): 1125-1129.
75. Ichai C, Passeron C, Carles M, Bouregba M, Grimaud D. Prolonged low-dose dopamine infusion induces a transient improvement in renal function in hemodynamically stable, critically ill patients: a single-blind, prospective, controlled study. *Crit Care Med*. 2000;28(5):1329-1335.
76. Juste RN, Panikkar K, Soni N. The effects of low-dose dopamine infusions on haemodynamic and renal parameters in patients with septic shock requiring treatment with noradrenaline. *Intensive Care Med*. 1998;24(6):564-568.
77. Girbes AR, Patten MT, McCloskey BV, Groeneveld AB, Hoogenberg K. The renal and neurohumoral effects of the addition of low-dose dopamine in septic critically ill patients. *Intensive Care Med*. 2000;26(11):1685-1689.
78. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA*. 2013; 310(23):2533-2543.
79. Triposkiadis FK, Butler J, Karayannis G, et al. Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion: the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial. *Int J Cardiol*. 2014;172(1): 115-121.
80. Levy B, Dusang B, Annane D, Gibot S, Bollaert PE, College Interregional des Reanimateurs du N-E. Cardiovascular response to dopamine and early prediction of outcome in septic shock: a prospective multiple-center study. *Crit Care Med*. 2005;33(10): 2172-2177.
81. Martin C, Papazian L, Perrin G, Saux P, Gouin F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest*. 1993;103(6):1826-1831.
82. Thiele RH, Nemergut EC, Lynch C III. The clinical implications of isolated alpha(1) adrenergic stimulation. *Anesth Analg*. 2011; 113(2):297-304.
83. 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.
84. Lauzier F, Levy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. *Intensive Care Medicine*. 2006;32(11):1782-1789.
85. Morelli A, Ertmer C, Rehberg S, et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. *Crit Care*. 2009;13(4):R130.
86. Gordon AC, Wang N, Walley KR, Ashby D, Russell JA. The cardiopulmonary effects of vasopressin compared with norepinephrine in septic shock. *Chest*. 2012;142(3):593-605.
87. Serpa Neto A, Nassar APJ, Cardoso SO, et al. Vasopressin and terlipressin in adult vasodilatory shock: a systematic review and meta-analysis of nine randomized controlled trials. *Crit care*. 2012;16(4):R154.
88. Torgersen C, Dunser MW, Wenzel V, et al. Comparing two different arginine vasopressin doses in advanced vasodilatory shock: a randomized, controlled, open-label trial. *Intensive Care Med*. 2010;36(1):57-65.
89. Luckner G, Mayr VD, Jochberger S, et al. Comparison of two dose regimens of arginine vasopressin in advanced vasodilatory shock. *Crit Care Med*. 2007;35(10):2280-2285.
90. Dunser MW, Mayr AJ, Ulmer H, et al. Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation*. 2003;107(18):2313-2319.
91. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. *Intensive Care Med*. 2001; 27(8):1416-1421.
92. Tayama E, Ueda T, Shojima T, et al. Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. *Interact Cardiovasc Thorac Surg*. 2007;6(6): 715-719.
93. Jeon Y, Ryu JH, Lim YJ, et al. Comparative hemodynamic effects of vasopressin and norepinephrine after milrinone-induced hypotension in off-pump coronary artery bypass surgical patients. *Eur J Cardiothorac Surg*. 2006;29(6):952-956.
94. Yimin H, Xiaoyu L, Yuping H, Weiyan L, Ning L. The effect of vasopressin on the hemodynamics in CABG patients. *J Cardiothorac Surg*. 2013;8:49.
95. Russell JA, Walley KR, Gordon AC, et al. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med*. 2009;37(3):811-818.
96. Jenkins CR, Gomersall CD, Leung P, Joynt GM. Outcome of patients receiving high dose vasopressor therapy: a retrospective cohort study. *Anaesth Intensive Care*. 2009;37(2):286-289.
97. Brown SM, Lanspa MJ, Jones JP, et al. Survival after shock requiring high-dose vasopressor therapy. *Chest*. 2013;143(3):664-671.
98. Patel GP, Balk RA. Systemic steroids in severe sepsis and septic shock. *Am J Respir Crit Care Med*. 2012;185(2):133-139.
99. Dunser MW, Hasibeder WR. Sympathetic overstimulation during critical illness: adverse effects of adrenergic stress. *J Intensive Care Med*. 2009;24(5):293-316.
100. Gordon AC, Russell JA, Walley KR, et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med*. 2010;36(1):83-91.
101. Russell JA, Fjell C, Hsu JL, et al. Vasopressin compared with norepinephrine augments the decline of plasma cytokine levels in septic shock. *Am J Respir Crit Care Med*. 2013;188(3):356-364.