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Vasopressor and Inotrope Therapy in Cardiac Critical Care

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Abstract

Patients admitted to the cardiac intensive care unit (CICU) are often in shock and require hemodynamic support. Identifying and addressing the pathophysiology mechanisms operating in an individual patient is crucial to achieving a successful outcome, while initiating circulatory support therapy to restore adequate tissue perfusion. Vasopressors and inotropes are the cornerstone of supportive medical therapy for shock, in addition to fluid resuscitation when indicated. Timely initiation of optimal vasopressor and inotrope therapy is essential for patients with shock, with the ultimate goals of restoring effective tissue perfusion in order to normalize cellular metabolism. Use of vasoactive agents for hemodynamic support of patients with shock should take both arterial pressure and tissue perfusion into account when choosing therapeutic interventions. For most patients with shock, including cardiogenic or septic shock, norepinephrine (NE) is an appropriate choice as a first-line vasopressor titrated to achieve an adequate arterial pressure due to a lower risk of adverse events than other catecholamine vasopressors. If tissue and organ perfusion remain inadequate, an inotrope such as dobutamine may be added to increase cardiac output to a sufficient level that meets tissue demand. Low doses of epinephrine or dopamine may be used for inotropic support, but high doses of these drugs carry an excessive risk of adverse events when used for vasopressor support and should be avoided. When NE alone is inadequate to achieve an adequate arterial pressure, addition of a noncatecholamine vasopressor such as vasopressin or angiotensin-II is reasonable, in addition to rescue therapies that may improve vasopressor responsiveness. In this review, we discuss the pharmacology and evidence-based use of vasopressor and inotrope drugs in critically ill patients, with a focus on the CICU population.

Keywords

shock, vasopressor, inotrope, norepinephrine, dopamine, epinephrine, CICU

Introduction

Shock occurs when failure of the cardiovascular system compromises tissue and organ perfusion and is often differentiated into hypovolemic, vasodilatory, and cardiogenic phenotypes.[1] Patients admitted to the cardiac intensive care unit (CICU) are often in shock and require hemodynamic support.[2] Cardiovascular instability has a number of potential causes, and sorting through the mechanisms operating in an individual patient is crucial to achieving a successful outcome. Before those mechanisms have been fully addressed, circulatory support therapy is often necessary to maintain adequate tissue perfusion.[3] Although identification and treatment of the underlying etiology is crucial to achieving a good outcome in shock, support of mean arterial pressure (MAP) and cardiac output (CO) is usually necessary while that is being accomplished. Prior optimization of intravascular fluid volume is crucial, but is beyond the scope of this manuscript, as are considerations of the potential role of mechanical circulatory support (MCS). Notably, randomized controlled trials have not demonstrated a clear survival benefit with MCS over medical therapy in cardiogenic shock, emphasizing the ongoing importance of vasoactive therapy in clinical practice.[4] This review focuses on circulatory support with vasoactive drugs for the most common forms of shock encountered in the modern CICU practice, including vasodilatory and cardiogenic shock.

Epidemiology and Outcomes With Vasopressor and Inotrope Use in CICU

Multicenter observational data suggest that approximately 30% of patients in general intensive care units (ICUs) are treated

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with vasopressor agents and that norepinephrine (NE) is the initial choice in over 90% of patients in contemporary studies.[5,6] It is clear that the dose, duration, and number of vasoactive agents required affect clinical outcomes in shock, even after taking into consideration confounding by indication in observational studies. Higher doses and area under the curve of both NE and epinephrine (EPI) were associated with higher mortality in a multicenter survey of ICUs.[7] Refractory shock is most reproducibly defined by high doses of vasopressor agents and has consistently been associated with poor outcomes.[8] Although vasopressors requirements are a simple measure of shock severity, associations between high catecholamine doses and poor outcomes do not prove causation.

Data confined to CICUs are more sparse, but a recent study showed that 1 in 4 CICU patients received a vasopressor or inotrope, and these patients had higher mortality.[9] Higher peak vasopressor and inotrope requirements were strongly associated with hospital mortality, and the use of NE was associated with lower mortality among patients requiring higher vasopressor doses.[9] Among patients with cardiogenic shock, EPI has been associated with worse short-term survival in multiple observational studies.[10,11] A stepwise increase in mortality risk has been observed with an increasing number of vasoactive medications in cardiogenic shock, even after institution of percutaneous MCS.[12] Cardiogenic shock remains the most prevalent form of shock in contemporary CICU practice, but vasodilatory and mixed forms of shock are common.[13,14]

Pathophysiology of Shock

The diagnosis of circulatory shock is made at the bedside by the presence of hypotension along with a combination of clinical signs indicative of poor tissue perfusion, including oliguria, clouded sensorium, and cool, mottled extremities.[1] Laboratory measures such as serum lactate levels, central or mixed venous oxygen saturation (SVO_2), and arteriovenous PCO_2 ($AVDCO_2$) gap can help in assessment of the severity of the perfusion deficits.[15]

Shock can be divided into 4 general categories: hypovolemic, cardiogenic, distributive, and obstructive.[1] Hypovolemic shock results from decreased preload and is treated by fluid repletion. Cardiogenic shock occurs when the heart is unable to deliver CO sufficient to maintain adequate perfusion.[16] Obstructive shock can be considered a form of cardiogenic shock resulting either from decreased preload, as in pericardial tamponade or tension pneumothorax, or from increased afterload, as in pulmonary embolism; treatment involves relief of the obstruction. Distributive shock differs in that CO is normal or increased, but systemic vasodilation causes hypotension. The classic form of distributive shock is sepsis, but anaphylaxis and spinal shock have similar hemodynamic presentations.

Cardiogenic shock is characterized by a downward spiral in which myocardial dysfunction reduces stroke volume (SV), CO, and MAP, which compromise myocardial perfusion, exacerbate ischemia, and further depress myocardial function, SV, and systemic perfusion.[16,17] Compensatory mechanisms include sympathetic stimulation, which increases heart rate (HR) and contractility, raising CO at the expense of increased myocardial oxygen demand. Compensatory vasoconstriction increases MAP at the expense of increased myocardial afterload, further impairing cardiac performance and increasing myocardial oxygen demand. In the face of inadequate perfusion, this increased demand can worsen ischemia and perpetuate a vicious circle that may culminate in death.[17]

Shock is not always confined to a single-classic hemodynamic presentation; such states are often termed *mixed shock*. Development of a systemic inflammatory response can produce inappropriate systemic vasodilation in cardiogenic shock that counteracts the compensatory vasoconstriction needed to maintain blood pressure.[16] Patients with cardiogenic shock may sometimes be hypovolemic at presentation, while myocardial dysfunction during other forms of shock (for instance, due to coronary hypoperfusion or direct myocardial depression) may also cause mixed shock.[16,18] Microcirculatory abnormalities may accompany macrocirculatory abnormalities in shock, including perturbations in flow as well as decreases in the proportion of perfused microvessels in patients with both septic and cardiovascular shock.[19,20] Microcirculatory abnormalities leading to regional heterogeneity in blood flow may play an important role in the pathogenesis of organ failure.

As shock progresses, common pathways leading to tissue and organ dysfunction emerge in shock, regardless of the original etiology.[1] With prolonged cellular hypoxia, adenosine triphosphate (ATP) and intracellular energy reserves are depleted, and active energy-dependent ion transport pumps eventually fail, leading to buildup of intracellular sodium, hydrogen, and calcium with consequent cell swelling due to osmosis. Changes in membrane potential can trigger release of cytochrome C into the cytoplasm, which activates caspases and can initiate apoptosis. Once a critical drop in mitochondrial transmembrane potential has occurred, mitochondrial permeability transition pores are formed, fully dissipating the transmembrane gradient and uncoupling electron transport from ATP synthesis, after which cell death is inevitable.[21]

Activation of inflammatory mechanisms is common to different forms of shock, with oxidative stress and release of inflammatory cytokines. Inflammatory cascades activated in different forms of shock may have similar effects on the microcirculation, potentially mediated by a combination of the effects of inducible nitric oxide (NO) synthase, oxidative stress, and peroxynitrite. Numerous vasodilator mechanisms govern local tissue blood flow and can produce pathologic vasodilation, including enhancement of cyclic guanosine monophosphate via NO, ischemia-driven byproducts such as adenosine.[8] Various pathophysiologic processes can open vascular ATP-sensitive potassium (K_{ATP}) channels, which can lead to refractory vasodilation in later stages of shock even if there was vasoconstriction in earlier phase.[8,22]

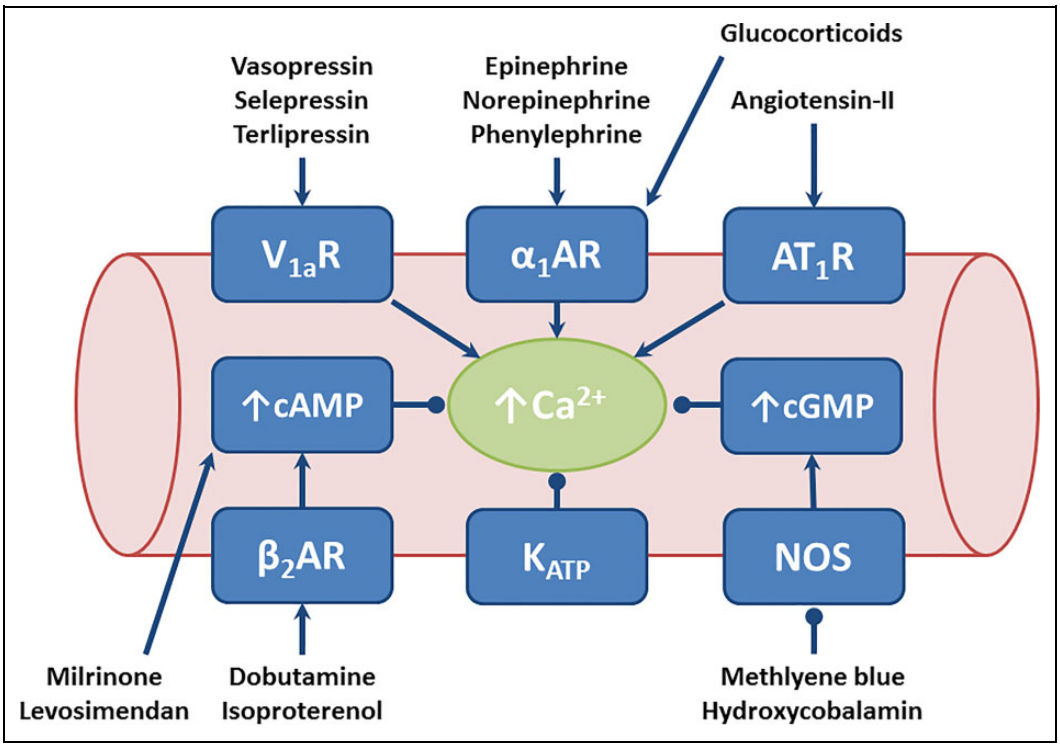

Figure 1. Simplified vascular smooth muscle cell demonstrating predominant vasoconstrictor (top) and vasodilator (bottom) mechanisms, as well as effects of vasopressor and inotrope drugs on these mechanisms.

Pharmacology of Inotropes and Vasopressors

We conceptualize vasoactive agents as vasopressors, whose aim is to increase MAP, and inotropes, whose aim is to increase CO. The most commonly used inotropes and vasopressors directly stimulate adrenergic receptors and/or enhance adrenergic postreceptor signaling pathways.[2] Although catecholamines have both vasopressor and inotropic actions, this conceptualization may help clinicians focus on the goals of vasoactive therapy and consider how to assess whether those goals are being achieved. The most important thing to remember is that the final goal in an individual patient, of course, is not attainment of a given MAP or CO, but rather achievement of adequate tissue and cellular perfusion.

Inotropic Drugs

Inotropes increase the force of myocardial contraction, increasing SV at a given preload; many inotropes increase HR, which can further augment CO.[2,23] It is typically more desirable to increase CO by increasing SV than simply by increasing HR, especially in patients with the potential for myocardial ischemia. Inotropic effects of catecholamines are mediated by the cardiac β-adrenergic receptor (βAR)-cyclic adenosine monophosphate (cAMP) pathway, which enhances cytosolic calcium availability in cardiac myocytes (Figure 1); the βAR-cAMP pathway relaxes vascular smooth muscle cells, producing vasodilation.[23] While other mechanisms, such as enhancement of myofibrillar calcium sensitivity, can produce inotropic effects, all currently available inotropes modulate this final common pathway.[23] Novel inotropic drugs are under development, which can increase myocardial contractility without increasing cytosolic calcium in cardiac myocytes, which is a major mediator of toxicity of currently available inotropes.[23] Omecamtiv mecarbil can directly activate cardiac myosin to produce inotropic effects independent of calcium signaling and has shown favorable hemodynamic effects in clinical studies of patients with heart failure (HF).[23-25] In addition, metabolic modulation may improve myocardial function without directly activating inotropic pathways.[26]

Vasopressor Drugs

Vasopressors act via multiple receptors that enhance cytosolic calcium availability in vascular myocytes, leading to peripheral vasoconstriction, increasing systemic vascular resistance (SVR), and thus MAP.[2] Catecholamines activate vascular α-1 adrenergic receptors (α_1ARs) to increase vascular calcium signaling (Figure 1), which is opposed by βAR-cAMP signaling.[2] The vasopressin-1a receptor ($V_{1a}R$) and angiotensin receptor-1 (AT_1R) activate similar postreceptor mechanisms, enhancing α_1AR signaling.[27,28] Furthermore, vascular α_1AR density can be increased by activation of corticosteroid receptors. In contrast to cardiac myocytes, elevated cAMP levels from βAR stimulation in vascular myocytes will lower intracellular calcium levels and produce vasodilation.[2]

Table 1. Clinical Pharmacology and Use of Vasopressors and Inotropes.

	Mechanism	Usual Dose Range	Inotropy	Clinical Use
Vasoconstrictors				
Phenylephrine	α_1	0.1-1 μg/kg/min	0	Tachyarrhythmias, dynamic LVOT obstruction
Vasopressin	V_{1a}	0.03-0.06 U/min	0	Tachyarrhythmias, vasoplegia
Angiotensin-II	AT_1	10-40 ng/kg/min	0	Refractory shock
Inoconstrictors				
Norepinephrine	$\alpha_1 > \beta_1$	0.01-0.3 μg/kg/min	+	First-line for all forms of shock
Epinephrine	$\beta_{1/2} > \alpha_1$	0.01-0.3 μg/kg/min	+++	Second-line vasopressor or inotrope
Dopamine	$\beta_1 > \alpha_1$	2-10 μg/kg/min	+++	Second-line inotrope or bradycardia (low dose)
Inodilators				
Dobutamine	$\beta_{1/2} > \alpha_1/\beta_2$	2-10 μg/kg/min	+++	First-line inotrope for shock
Isoproterenol	$\beta_{1/2}$	0.01-0.1 μg/kg/min	+++	Bradycardia
Milrinone	PDE_3I	0.1-0.5 μg/kg/min	++	First-line inotrope for heart failure
Levosimendan	PDE_3I[a]	0.05-2 μg/kg/min	++	Not FDA-approved for clinical use in USA

Abbreviations: FDA, Food and Drug Administration; LVOT, left ventricular outflow tract; PDE-3I, phosphodiesterase-3 inhibitor.
[a] Also sensitizes myofilaments to calcium.

Baroreflex Mechanisms

The baroreflex is a homeostatic mechanism that maintains MAP by adjusting sympathetic tone to antagonize MAP perturbations.[29] A drop in MAP will trigger baroreflex-mediated sympathetic activation in order to increase CO and MAP via enhanced cardiac inotropy and chronotropy as well as peripheral vasoconstriction and enhanced venous return; this can enhance the increase in CO produced by a vasodilator.[2] Conversely, an increase in MAP will produce baroreflex-mediated sympathetic withdrawal, decreasing CO and MAP by reducing cardiac inotropy and chronotropy and peripheral vascular tone; this can attenuate the increase in MAP produced by a vasoconstrictor.[2]

Monitoring of Vasoactive Therapy

In order to individualize therapy by identifying the optimal vasoactive drug for a given patient and defining the clinical response to therapy, a number of hemodynamic monitoring devices and biomarkers are available to supplement clinician judgment.[30] Arterial blood pressure monitoring may be more accurate for measurement of MAP than noninvasive cuff blood pressure monitoring and has been recommended for patients with cardiogenic shock.[16,31] Studies in patients without shock have not demonstrated a consistent benefit of the pulmonary artery catheter (PAC), but no randomized studies exist in patients with shock—observational studies.[32,33] Direct measurement of cardiac filling pressures, CO, and SVR with a PAC can provide useful insights into the best pharmacological approach to reversing impaired tissue perfusion. Guidelines recommend PAC monitoring for patients with an uncertain mechanism of shock, as well as in patients with moderate-to-severe cardiogenic shock who have not responded to initial therapy.[31] Functional hemodynamic monitoring using arterial pulse contour analysis is an alternative to PAC monitoring, but less is known about the accuracy of this modality in patients with cardiogenic shock and/or those receiving MCS.[30,34]

The most commonly used biomarkers for monitoring of perfusion in patients with shock are lactate, SVO_2, and $AVDCO_2$, which can be measured serially to assess response to resuscitation with fluids and/or vasoactive drugs; elevated plasma renin levels are another recently proposed marker of hypoperfusion.[15,35-37] A low SVO_2 and/or elevated $AVDCO_2$ implies inadequate systemic or tissue-level oxygen delivery, and measures to improve blood flow should be considered.[15,35] Lactate clearance (a reduction in the lactate level over time) implies adequacy of tissue perfusion, and failure to achieve this goal of therapy should prompt assessment of other markers of perfusion, such as SVO_2 and $AVDCO_2$.[36] Among patients with septic shock, resuscitation can be guided by lactate clearance or monitoring of capillary refill; no randomized studies of biomarker-guided resuscitation in cardiogenic shock exist, but we believe that titration of inotropes to increase SVO_2 is potentially more relevant in this population.[36,38] Therefore, as emphasized in recent consensus guidelines, continuous clinical monitoring of perfusion is recommended, with serial biomarker monitoring utilized to supplement clinical assessment.[31]

Clinical Effects and Outcomes With Specific Vasopressors and Inotropes

Clinical Effects of Catecholamine Vasopressors

Catecholamine vasopressors activate vascular α_1AR to increase MAP (Table 1).[2] The endogenous catecholamines NE, EPI, and dopamine (DOPA) produce positive inotropic and chronotropic effects to a variable degree via βAR activity. Both NE and the synthetic α_1AR agonist phenylephrine (PHEN) produce primarily vasoconstrictor effects, while strong βAR effects dominate the hemodynamic profile of DOPA and EPI, increasing HR, SV, and CO.[2] Norepinephrine has relatively weak βAR activity, but can have direct inotropic and chronotropic effects via βAR stimulation at higher doses.[2,39] The effects of NE on HR and CO depend on the underlying cardiac physiology and may be driven to a greater extent by vascular effects on

Table 2. Randomized Outcome Trials of Vasopressors in Patients With Shock.[a]

Study, Year	Population	Comparison	Effect on Mortality	Adverse Events
CATS, 2007[49]	Septic shock	EPI + placebo vs NE + DOB	No difference	No difference
CAT, 2008[50]	Unselected shock	EPI vs NE	No difference	Greater with EPI
VASST, 2008[52]	Septic shock on vasopressors	VASO vs NE	No difference	Less AKI with VASO
SOAP-II, 2010[53]	Unselected shock	DOPA vs NE	No difference	Greater with DOPA
VANISH, 2016[54]	Septic shock not on vasopressors	VASO vs NE	No difference	Less RRT with VASO
VANCS, 2017[55]	Postcardiotomy vasoplegia	VASO vs NE	No difference	Fewer with VASO
ATHOS-3, 2017[56]	Vasodilatory shock on high-dose vasopressors	AT-II vs placebo	No difference	Fewer with AT-II
SEPSIS-ACT, 2019[57]	Septic shock on vasopressors	Selepressin vs placebo	No difference	No difference

Abbreviations: AKI, acute kidney injury; AT-II, angiotensin-II; ATHOS-3, angiotensin II for the treatment of high-output shock-3; DOB, dobutamine; DOPA, dopamine; EPI, epinephrine; NE, norepinephrine; RRT, renal replacement therapy; SEPSIS-ACT, selepressin evaluation program for sepsis-induced shock–adaptive clinical trial; SOAP-II, sepsis occurrence in acutely Ill patients-II; VASO, vasopressin; VASST, vasopressin and septic shock trial; VANISH, vasopressin vs norepinephrine as initial therapy in septic shock; VANCS, vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery.
[a] Only studies with >100 adult patients and mortality as an end point are included.

effective circulating blood volume than by direct cardiac inotropic effects—NE can increase CO by increasing venous return if the heart is preload-responsive, or else can decrease CO by increasing afterload.[40] Nonetheless, direct cardiac effects from βAR stimulation may contribute to the hemodynamic effects and toxicity of NE at higher doses.[2] Phenylephrine increases SVR without inotropic effects, and this can reduce HR and CO, leading to a lower efficacy for raising MAP.[2]

Low-dose DOPA (up to 5 μg/kg/min) increases renal blood flow and glomerular filtration via intrarenal hemodynamic effects, but increased urine output with low-dose DOPA is mediated predominantly by increased CO and MAP.[2,41] Critically ill patients often fail to respond to the renal effects of DOPA, and "renal-dose" DOPA has consistently failed to improve renal outcomes despite potentially increasing urine output.[41,42] Low-dose DOPA rarely increases diuresis or improves renal function in patients with HF, except in some patients with systolic dysfunction who respond to its inotropic effects.[43-46] The effects of DOPA on CO peak in the intermediate-dose range (5-10 μg/kg/min), and vasoconstriction predominates at high DOPA doses (>10 μg/kg/min), leading to increased MAP without further augmenting CO.[2,39] Limited data suggest similar dose-dependent effects of EPI compared with DOPA (at doses 100-fold lower), potentially with less tachycardia.[2] Choosing a catecholamine based on global hemodynamic effects alone ignores potential intrarenal and mesenteric effects of these drugs, which may be important in some patients but have not been conclusively linked to clinical outcomes.[47,48]

Randomized Trials of Catecholamine Vasopressors

Compared with NE in patients with septic shock, EPI is associated with similar mortality despite a greater incidence of tachycardia, arrhythmias, lactic acidosis, and hyperglycemia (Table 2).[49-51] Despite increasing CO, EPI is associated with worse clinical outcomes compared with NE in patients with cardiogenic shock, perhaps due to increased HR and oxygen consumption.[58,59] Overall, these data support the use of NE over EPI as a first-line vasopressor. We use EPI clinically at low doses (up to 0.1 μg/kg/min) as an inotrope that may not produce vasodilatory hypotension (particularly in mixed shock states or after cardiopulmonary bypass), and at higher doses (>0.1 μg/kg/min) as a second-line vasopressor for severe shock not responding adequately to NE.

Studies comparing DOPA with NE in broad shock populations have favored NE, with a markedly lower incidence of arrhythmias compared with DOPA (Table 2).[53,60] Meta-analyses have reported higher mortality in patients with septic or cardiogenic shock who received DOPA.[60,61] Many patients with severe shock fail to meet MAP goals with DOPA alone, likely because its indirect mechanism of action relies on release of NE from adrenergic nerve terminals, which can be exhausted.[47,53,62] For these reasons, we do not think DOPA has a role as a vasopressor for any common patient population, and we do not routinely use DOPA doses >10 μg/kg/min. The positive inotropic and chronotropic effects of low-to-intermediate DOPA doses up to 5 to 10 μg/kg/min may be useful for selected patients.

Randomized studies comparing NE and PHEN in shock have been underpowered to examine mortality and have reported variable overall hemodynamic effects.[63-65] In general, HR and CO are expectedly higher with NE, but pulmonary vascular resistance is higher with PHEN, increasing higher right ventricular afterload.[63-66] Due to the limited outcome data and potential harmful effects on the right ventricle, we believe that PHEN is not a first-line vasopressor for patients with shock. An important niche use for PHEN is in patients with proarrhythmia resulting from NE, as PHEN has no proarrhythmic βAR effects.

Noncatecholamine Vasopressors

Vasopressin (VASO) and angiotensin-II (AT-II) both act on their endogenous receptors to produce vasoconstriction without

significant inotropic effects, producing hemodynamic effects similar to PHEN including a reduction in HR and CO. Patients with severe shock may have absolute or relative deficiencies in endogenous production of VASO due to depletion of posterior pituitary VASO stores, and this may cause impaired vascular α_1AR responsiveness and vasoplegia, leading to worse outcomes and refractory shock.[8,27,28] Infusion of low "physiologic" VASO doses (0.03-0.04 U/min) can improve MAP and vasopressor responsiveness, allowing significant weaning of catecholamines in approximately half of patients with sepsis.[52] Addition of VASO in patients with septic shock requiring vasopressors was associated with less acute kidney injury (AKI) and nonsignificantly lower mortality compared with NE (particularly when initial NE dose was <15 μg/min and among those receiving corticosteroids).[52,67,68] The use of VASO or NE as the initial vasopressor in early septic shock did not produce a significant difference in mortality or major renal outcomes (Table 2).[54] Overall, the use of VASO in patients with septic shock does not clearly reduce mortality, and the potential effect on risk of AKI should be interpreted cautiously; when VASO is used, withdrawal of VASO before NE may increase the risk of recurrent hypotension and worse outcomes in patients requiring high doses of NE.[69-71] Compared with catecholamines, VASO is associated with a lower risk of arrhythmias, particularly atrial fibrillation.[72] Patients with postcardiotomy vasoplegia syndrome who receive VASO may have lower rates of postoperative complications (including AKI and atrial fibrillation) and similar mortality.[55,73] We use low-dose VASO as an adjunct agent for vasodilatory shock when patients require high NE doses (ie, >0.2-0.3 μg/kg/min), there are concerns for treatment-emergent tachycardia or arrhythmias, or for postcardiotomy vasoplegia. Although VASO can reduce CO, the use of VASO in refractory vasodilatory cardiogenic shock can improve MAP.[74,75] Despite theoretical benefits over VASO, the selective V_{1a}R agonist selepressin failed to improve outcomes when added to NE in patients with septic shock.[57]

Critically ill patients may become deficient in AT-II due to loss of pulmonary endothelial angiotensin-converting enzyme function, resulting in vasoplegia and AKI due to reduced efferent glomerular arteriolar tone.[28] Such patients may have a very robust response to low doses of AT-II infusion, resulting in rapid weaning of other vasopressors and a favorable prognosis.[76] Unlike other vasopressors, AT-II appears to constrict postcapillary arterioles, potentially improving tissue perfusion and preserving glomerular filtration.[28] Angiotensin-II infusion can safely and effectively increase MAP and reduce vasopressor requirements in approximately 70% of patients with severe vasodilatory shock requiring >0.2 μg/kg/min NE equivalent, with a nonsignificantly lower mortality than placebo.[56] Patients with AKI requiring renal replacement therapy (RRT) who received AT-II had significantly lower mortality and greater rates of liberation from RRT.[77] These data support potential use of AT-II infusion for patients with severe vasodilatory shock (especially those with acute respiratory distress syndrome or AKI requiring RRT) who do not respond well to initial therapy, as long as CO is adequate. Both VASO and AT-II have higher associated drug costs than catecholamine vasopressors, although cost-effectiveness analyses must take into account other relevant factors.[78]

Inodilators

Inotropic drugs producing vasodilatory effects are termed "inodilators" (Table 1). These include dobutamine (DOB), milrinone (MIL), and levosimendan (LEVO), which is not available in the United States.[2] Dobutamine is a direct βAR agonist, with strong β_1AR and weaker, dose-dependent β_2AR and α_1AR agonism. As with other strong βAR agonists, DOB significantly increases HR, which may drive the CO effect and can trigger tachyphylaxis due to downregulation of βARs.[2,39] Milrinone is a phosphodiesterase (PDE)-3 inhibitor, increasing cytosolic cAMP levels and potentially producing synergy with direct βAR agonists; PDE-3 inhibitors increase HR less than direct βAR agonists and may remain effective during β-blockade.[79,80] Levosimendan is a PDE-3 inhibitor that sensitizes myofilaments to calcium and has hemodynamic effects similar to MIL, but may increase CO more than either DOB or MIL.[81] Inodilators all produce vasodilation via increases in vascular myocyte cAMP, although the α_1AR agonist effects of DOB antagonize this effect.[2] The effects of inodilators on MAP depend on the baseline hemodynamic state and on their pharmacology. In patients with relatively low SVR, all inodilators may produce vasodilatory hypotension; hypotension from inodilators is less common in patients with low CO and high SVR, and DOB may increase MAP while PDE-3 inhibitors typically will not. Peripheral vasoconstriction produced by DOPA and EPI limits their maximum CO augmentation and increases cardiac filling pressures, but may also limit decreases in MAP.

Dobutamine is rapidly cleared in the bloodstream, achieving steady-state effects in minutes. Both MIL and LEVO have a longer half-life and renal clearance, leading to a delayed onset of steady-state effects and a risk of accumulation and prolonged hypotension in patients with renal dysfunction.[2] Compared with DOPA, DOB increases CO and reduces cardiac filling pressures more, with less augmentation of MAP; the combination of both drugs at moderate doses may produce a greater hemodynamic effect than either drug at a high dose.[2,82,83] Dobutamine produces a higher HR and stronger inotropic effect than MIL, while MIL is associated with greater vasodilation leading to lower MAP and lower filling pressures.[84-86] The combination of low doses of MIL plus DOPA or EPI can produce synergistic inotropic effects with a relatively neutral effect on MAP.[79]

The use of DOB doses >10 μg/kg/min may worsen tachycardia without increasing CO; similarly, doses of MIL > 0.5 μg/kg/min or use of a loading dose often produces problematic hypotension.[87] No large-scale randomized trials have compared clinical outcomes between inotropes, while observational studies suggest similar outcomes among patients with HF receiving either DOB or MIL.[88,89] Both DOB and MIL appear to increase adverse events (including mortality) when

compared with placebo; the harmful effects of inotropic drugs are likely greater in patients with ischemic cardiomyopathy.[90-92] Levosimendan does not appear to improve mortality when compared with placebo; a possible survival benefit when compared with DOB has been suggested, without a definite reduction in arrhythmias.[81,93] Data are likewise conflicting regarding the ability of LEVO to improving clinical outcomes in postcardiotomy low-output syndrome, despite favorable hemodynamic effects.[94-96]

Suggestions for Use of Inotropes and Vasopressors in Clinical Practice

When to Use Inotropes and Vasopressors

Simply stated, inotropes and vasopressors should only be used when critically low CO or MAP compromises end-organ function, representing a life-threatening shock state unresponsive to less toxic therapies. These drugs should be titrated to the lowest effective dose without trying to achieve supraphysiologic hemodynamic parameters. Restoration of end-organ perfusion is the goal of shock treatment, starting with restoring an adequate MAP to permit sufficient end-organ perfusion and blood-flow autoregulation, followed by ensuring adequate CO to permit global and regional tissue oxygen delivery. For most patients, an MAP of at least 65 mm Hg is required to ensure adequate end-organ perfusion and prevent adverse outcomes, but this level of MAP may not be adequate to prevent AKI in some patients with chronic hypertension or to optimize cerebral perfusion after cardiac arrest.[18,97-99] However, patients with chronically low blood pressure, particularly those with liver failure or chronic HF, may tolerate a lower MAP goal such as 60 mm Hg in the setting of vasodilatory shock. A recent study demonstrated lower vasopressor exposure and similar clinical outcomes when patients aged 65 years or older with vasodilatory shock were treated to a target MAP of 60 to 65 mm Hg versus usual care.[100]

Persistent organ hypoperfusion and objective evidence of low CO despite restoration of euvolemia and adequate MAP typically warrant inotropic therapy, titrated to the lowest dose that normalizes organ perfusion (Figure 2). For patients without critically low CO, inotropes have not been shown to reduce mortality when compared with placebo and can increase adverse events.[81,90-92] For patients with hypotension and critical organ hypoperfusion (ie, shock), restoring MAP is the initial treatment goal, typically with a vasopressor. When an inotrope is indicated in the setting of shock, DOB (up to 10 μg/kg/min) is preferred due to its greater augmentation of CO and more favorable effects on cardiac filling pressures than DOPA or EPI, recognizing that the vasodilatory properties of DOB can lead to hypotension in patients with lower SVR. For patients with low CO and preserved blood pressure without critical organ hypoperfusion, carefully titrated vasodilators are preferred; when low MAP accompanies low CO, typically an inotrope is indicated.[101] When an inotrope is indicated for patients with low-output HF without severe hypotension or critical organ hypoperfusion (ie, without shock), we typically prefer MIL due to its more favorable effect on cardiac filling pressures and the ability to potentially institute low-dose β-blockade after stabilization.[80,84,86]

Selection of Individual Inotrope and Vasopressor Drugs

Norepinephrine is an appropriate first-line vasopressor for most patients with shock due to a lower risk of adverse events and potentially lower mortality when compared with other catecholamine vasopressors.[2] Current evidence does not support the first-line use of noncatecholamine vasopressors for the majority of patients; one exception may be the use of VASO in postcardiotomy vasoplegia.[55,73] For patients with septic shock, NE remains the first-line vasopressor, with EPI or low-dose VASO added in patients not responding adequately to NE.[51] For patients with cardiogenic shock due to left ventricular systolic dysfunction, NE titrated to restore MAP followed by DOB titrated to restore CO and organ perfusion is a reasonable first-line strategy with greater efficacy than the use of high-dose EPI alone.[16,58,59] Using a low dose of DOPA (up to 10 μg/kg/min) or EPI (up to 0.1 μg/kg/min) instead is typically less effective for raising CO, may worsen pulmonary congestion and often produces dose-limiting tachycardia.[82,83,102] When CO is critically low and SVR is very high, NE alone may be relatively ineffective at raising MAP until CO is increased with an inotrope. For patients with undifferentiated or mixed shock, NE remains a reasonable first-line vasopressor due to its more favorable toxicity profile. Inodilators can worsen hypotension in mixed shock states, and low-dose EPI (up to 0.1 μg/kg/min) can be used as an inotrope instead.

For patients with cardiogenic shock from right ventricular failure, both the systemic and pulmonary effects of inotropes and vasopressors may contribute to their clinical efficacy. All α_1AR agonists can constrict the pulmonary vessels, increasing right ventricular afterload—VASO may be less prone to this effect and may be preferred.[103,104] Milrinone can provide beneficial right ventricular afterload reduction at the expensive of peripheral vasodilation often requiring the addition of VASO or low-dose DOPA or EPI.[85,103,104] A paradoxical treatment approach is required for patients with shock due to left ventricular outflow tract obstruction—aggressive fluid resuscitation, avoidance of any inotropic drugs, and use of pure vasoconstrictors such as PHEN or VASO that may trigger a beneficial reduction in HR.

Refractory (Vasodilatory) Shock

Definition and Pathophysiology of Refractory Shock

Severe shock is characterized by the need for high vasopressor doses and adjunctive therapies—patients requiring >0.2 μg/kg/min NE have a high mortality rate and can be considered to have severe shock.[8,52,56] Refractory shock is characterized by persistent hypotension despite standard interventions, requiring rescue therapies. Although definitions of refractory shock differ, patients requiring >0.5 μg/kg/min NE equivalent to

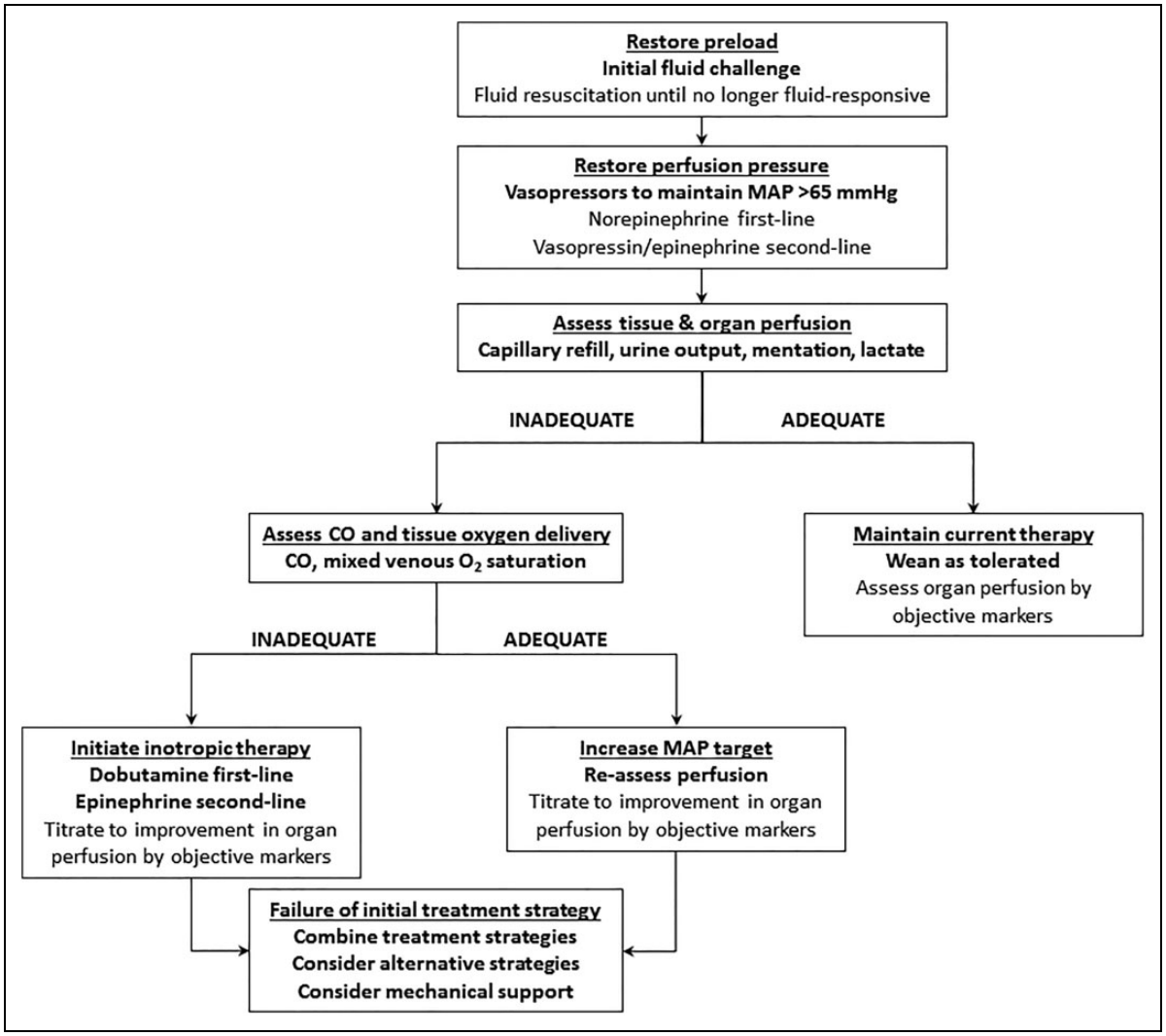

Figure 2. Clinical approach to selection of vasopressor and inotrope therapy in shock.

maintain adequate MAP are at very high risk of death and can be considered to have refractory shock.[8,9,56] Refractory shock is most commonly caused by severe vasodilation due to inflammatory vasoplegia, often resulting from sepsis; refractory cardiogenic shock is a different entity, requiring consideration of MCS. Vasoplegia in refractory vasodilatory shock is multifactorial and driven by uncontrolled pathologic activation of vasodilatory pathways involving NO, adenosine, and K_{ATP}, in addition to downregulation or decoupling of α_1AR leading to impaired vascular responsiveness to catecholamines.[8] Reversible contributors include occult hypovolemia, secondary disease processes, metabolic derangements such as severe acidosis or ionized hypocalcemia, and absolute or relative deficiencies of corticosteroids, VASO, or AT-II.

Treatment of Severe and Refractory Shock

The ideal time to intervene is prior to development of refractory shock, when a downward spiral of worsening hypotension and tissue hypoperfusion ensues. For patients requiring >0.2 to 0.3 μg/kg/min NE despite addressing reversible contributors, the addition of a second vasopressor is useful (Figure 3). Low-dose VASO (0.03-0.04 U/min) is used most commonly, but low-dose EPI (up to 0.1 μg/kg/min) is reasonable in patients with relatively lower HR, CO, or SVO_2.[51] Among patients with sepsis, the use of VASO as the second-line vasopressor may be associated with better outcomes compared with other agents.[78] Higher doses of VASO (up to 0.06-0.08 U/min) may further increase MAP, but the adverse effect profile is uncertain.[105,106] When this second-line vasopressor is added, we recommend adding stress-dose hydrocortisone (200-300 mg/d), which is the best-established adjunct therapy for severe septic shock.[51,107] Stress-dose hydrocortisone is safe and effective for hastening shock reversal and reducing overall vasopressor requirements and does not increased mortality despite predictable adverse effects.[107] In patients with refractory shock, it has been proposed that high-dose ascorbic acid can improve vasopressor requirements and thiamine can improve lactate clearance, but

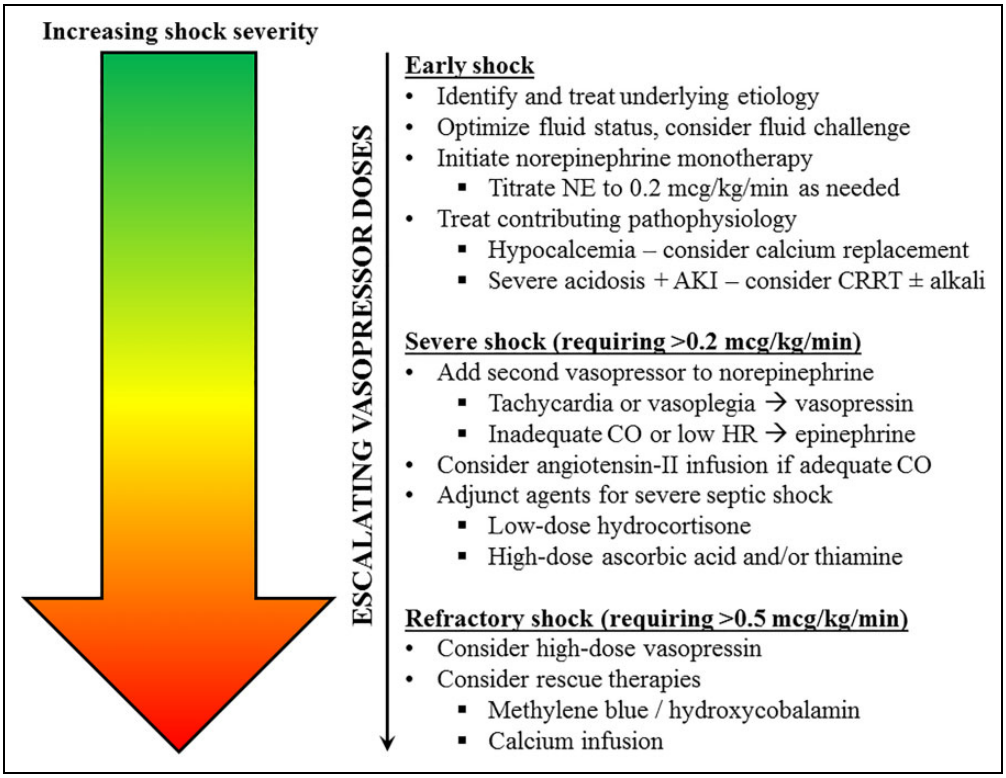

Figure 3. Selection of vasopressor drugs and adjunctive therapies as a function of shock severity. Adapted from Jentzer et al. *Chest.* 2018.[8]

recent studies have thus far failed to demonstrate improvements in vasopressor requirements or clinical outcomes with these adjunctive agents.[108-113] If a prompt response to the second vasopressor is not observed, a 3-drug combination may be attempted. We prefer a regimen that includes NE, VASO, and EPI; in our experience, the addition of PHEN or DOPA usually will not be effective for patients with severe shock.[2,8,62]

For patients requiring significant doses of NE despite addition of a second vasopressor (typically VASO) and adjunctive agents (such as hydrocortisone), AT-II infusion (starting at a dose of 10-20 ng/kg/min) should be considered as the third-line vasopressor.[8,56] Better outcomes and a higher response rate can be expected when AT-II is added before patients require 0.5 µg/kg/min NE or equivalent, as well as in patients with AKI requiring RRT.[56,77] For patients with severe septic shock requiring high doses of NE, addition of VASO and AT-II as the second- and third-line vasopressors may improve blood pressure, and there is a suggestion that outcomes are better when these agents are initiated before patients require high doses of NE (>0.5 µg/kg/min).[56,78] The theory is that lower doses of multiple agents maximizes efficacy and minimizes toxicity, but there are few if any high-quality studies examining the safety, efficacy, and clinical outcomes associated with different combinations of 3 or more vasopressors. Increasing the dose of NE up to very high levels (>1-2 µg/kg/min) can increase MAP in selected patients with refractory shock despite the expected finding that mortality in such patients is high.[8,9,99] Rescue therapies can be considered for patients who remain hypotensive despite high vasopressor doses and the above measures, but it is unclear whether these agents are beneficial when compared to simply increasing the existing vasopressor doses. Given the importance of excessive NO production as a contributor to vasoplegia, NO antagonists such as methylene blue and hydroxycobalamin can effectively increase MAP in some patients.[114-116] Unfortunately, the use of NO antagonists increased mortality in prior randomized trials in septic shock and failed to improve outcomes in cardiogenic shock.[117,118] Raising ionized calcium to supraphysiologic levels using a calcium chloride infusion may increase MAP, but the safety of this approach remains uncertain.[8,119]

Adverse Effects of Inotropes and Vasopressors

Vasopressors and inotropes have a curvilinear dose–response relationship, with the majority of the therapeutic effect occurring at relatively low doses and toxicity accumulating at higher doses without substantial increases in efficacy.[2] This may be particularly prominent with catecholamine vasopressors.[39] Higher rates of cardiovascular adverse events were observed when a higher MAP was targeted using higher vasopressor doses in patients with sepsis.[97] β-Adrenergic receptor agonists produce harmful dose-dependent cardiovascular effects, such as sinus tachycardia, tachyarrhythmias (including atrial fibrillation and ventricular arrhythmias), myocardial ischemia, and direct cardiac myocyte toxicity.[39]

Excessive βAR stimulation likely explains the adverse outcomes seen with high-dose EPI and DOPA, especially in patients with cardiogenic shock, and underscores our

recommendation to avoid using these drugs as vasopressors.[11,53,58] The risk of proarrhythmia is high with DOPA, DOB, and EPI (perhaps worse with DOPA); moderate with MIL, LEVO, and NE; and much lower with VASO, PHEN, and AT-II—importantly, the underlying cardiac substrate will modify the risk of arrhythmia, and patients with ischemic heart disease and cardiogenic shock are at higher risk.[2,49,52,53,56,58] The PDE-3 inhibitors typically do not produce substantial tachycardia, yet are clearly proarrhythmic. Any inotropic agent can produce myocardial ischemia by increasing HR and myocardial oxygen demand; coronary vasoconstriction may modulate these effects, and DOB may have more favorable effects on myocardial blood flow than other βAR agonists.[39,102]

All vasopressors can produce excessive vasoconstriction in any target vascular bed, leading to complications such as coronary, mesenteric, or digital ischemia; most large studies have not shown substantial differences in rates of these ischemic adverse events between different drugs.[39,49,50,52,53,56] Epinephrine can produce metabolic adverse effects such as hyperglycemia and lactic acidosis by activation of β_2AR, although it remains unclear whether these effects are overtly harmful.[50] Catecholamines can produce harmful noncardiovascular effects, including promoting bacterial growth by increasing bacterial iron availability, increasing levels of anti-inflammatory cytokines, and producing immunosuppressive effects by decreasing activity and survival of immune cell populations.[120]

Rationale for Catecholamine-Sparing Combination Vasopressor Therapy

A high dose of an individual vasopressor may yield lower efficacy and a more adverse effect, which might be mitigated by adding a second drug with a complementary mechanism of action. Preventing adverse effects from excessive adrenergic stimulation is an important potential mechanism by which noncatecholamine vasopressors could produce a clinical benefit. Although studies with VASO have not consistently demonstrated an improvement in mortality, there was a clear decrease in the rates of cardiac arrhythmias.[69,72] Catecholamines can produce strong intrarenal vasoconstriction, and a reduction in this effect by using VASO could explain the improved renal outcomes observed in some studies.[70,73] The overall occurrence of adverse events was lower with AT-II than placebo in the angiotensin II for the treatment of high-output shock-3 (ATHOS-3) trial, suggesting that reducing catecholamine requirements by AT-II prevented catecholamine-mediated toxicity.[56,121] Development of persistent severe tachycardia or treatment-emergent arrhythmias warrants consideration of catecholamine-sparing vasopressors, but whether to add these drugs early to prevent such effects remains speculative.

Conclusions

The ultimate goals of hemodynamic therapy in shock are to restore effective tissue perfusion and to normalize cellular metabolism. Hemodynamics in CICU patients can be complex, involving right- and left-sided cardiac dysfunction and interactions of vascular and myocardial perturbation. The pathophysiology of organ dysfunction in shock is complex as well, and restoring hemodynamic stability after organ failure is established may not be adequate to ensure a good outcome.

Despite this complexity, the use of vasoactive agents for hemodynamic support of patients with shock can be guided by an underlying approach that takes both arterial pressure and tissue perfusion into account when choosing therapeutic interventions. The efficacy of hemodynamic therapy should be assessed by monitoring a combination of clinical and hemodynamic parameters and tailoring vasoactive therapy based on clinical response. Specific end points for therapy can vary in different clinical scenarios and in different patients and can evolve over time as the clinical course progresses. Nonetheless, the idea that clinicians should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis remains a fundamental principle.

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