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REVIEW

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Pharmacology of vasopressors and inotropes during extracorporeal membrane oxygenation

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Abstract

Background This review aims to provide a concise summary of hemodynamic considerations and the pharmacology and current evidence of vasoactive support, including inotropes and vasopressors, during extracorporeal membrane oxygenation (ECMO) support.

Main text Patients requiring ECMO for cardiogenic shock or cardiac arrest have a high mortality rate. Despite advancements in medical and mechanical therapies, optimal use of vasoactive in patients receiving venoarterial ECMO is not well defined. Venoarterial ECMO introduces unique hemodynamic disturbances and considerations for the provision of vasoactive medications. Many different pharmacotherapies with varying inotropic, vasoconstrictive, and vasodilating effects are available and include catecholamine and non-catecholamine agents. Mechanisms and level of evidence vary based on agent, yet distinct characteristics may make certain agents more attractive than others depending on the clinical situation faced during ECMO.

Conclusions A nuanced understanding of receptor pharmacology and ECMO specific considerations is essential to tailor the vasoactive strategy in this unique population.

Keywords Extracorporeal life support, Extracorporeal membrane oxygenation, Inotrope, Pharmacology, Shock, Vasoactive, V-AECMO, Vasopressor

Background

Cardiogenic shock is a life-threatening condition that has become increasingly common, while its associated mortality has remained largely unchanged. One epidemiologic study suggested that the incidence of cardiogenic shock rose from 33.1 to 53.7 per 100,000 person-years between 2007 and 2017 [1]. Hospitalizations have also risen from 122 per 100,000 in 2004 to 408 per 100,000 in 2018 [2]. Despite these trends, hospital mortality rates for cardiogenic shock have remained stable at approximately 40 to 50%.

Multiple therapeutic strategies are employed in the management of cardiogenic shock [3]. When medical therapy fails, mechanical circulatory support, including extracorporeal membrane oxygenation (ECMO), can provide vital organ support for patients with cardiogenic shock [3]. Although recent trials of ECMO use in

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patients with cardiogenic shock have yielded equivocal results concerning mortality, these studies have important limitations [4, 5]. In contrast, ECMO use in cardiac arrest (extracorporeal cardiopulmonary resuscitation or eCPR) has shown more favorable outcomes, particularly among patients with in-hospital cardiac arrest. A systematic review and meta-analysis of in-hospital cardiac arrest showed that eCPR was associated with lower all-cause mortality than conventional cardiopulmonary resuscitation (OR 0.67, 95% CI 0.51–0.87) [6]. However, this benefit was not observed in patients with out-of-hospital cardiac arrest where eCPR did not significantly improve survival compared to standard CPR [7]. Given the high prevalence of vasodilatory shock in the ECMO population, there is growing interest in understanding how vasopressor and inotropic therapy may influence outcomes in patients supported by ECMO for cardiogenic shock and cardiac arrest [8]. Therefore, the purpose of this review is to summarize the pharmacology of vasopressor and inotropic therapy, particularly as it pertains to patients supported by ECMO. For detailed information on indications and management of ECMO, the reader is guided to the medical literature [9–11].

Hemodynamic dysregulation

The pathophysiologic disruption caused by cardiogenic shock leads to multiple hemodynamic perturbations. Acute or chronic ischemia of the epicardial coronary supply contributes to regional cardiac myocyte necrosis, resulting in ventricular dysfunction, systemic hypoperfusion, and tissue hypoxia. Key hemodynamic indicators of cardiogenic shock severity include reduced cardiac output, increased lactate production, initially high compensatory systemic vascular resistance followed by decline, and elevated cardiac filling pressures [12–14].

The inflammatory response in cardiogenic shock is highly variable, with multiple biomarkers and vasoactive molecules, including nitric oxide, contributing to myocardial dysfunction [15, 16]. Nitric oxide alters preload and afterload while promoting adrenoreceptor downregulation and reduced responsiveness to catecholamine inotropes [17]. An important hemodynamic consequence is cardiogenic shock-induced vasoplegia, resulting in a potentially lethal combination of low cardiac output and low systemic vascular resistance [18, 19]. Multiple mechanisms have been proposed, including microvascular dysfunction, oxidative stress, and abnormal mitochondrial function related to increased cellular permeability [15, 16, 20–22]. Importantly, the circulatory blood volume is in continuous contact with a very high surface area of non-biologic, non-endothelialized, artificial surfaces of ECMO circuit components that trigger a hyper-inflammatory response. Specifically, these interactions activate the complement and contact systems contributing to anaphylatoxin production, endothelial activation, neutrophil extravasation and activation, platelet degranulation, and stimulation of the coagulation cascade [23, 24]. Consequently, these inflammatory responses contribute to vasoplegia and multiple organ dysfunction, and ultimately impact survival outcomes [24, 25]. The combined phenotype of cardiogenic shock and vasoplegia is most observed in post-cardiotomy and post-arrest patients, largely due to an additional exaggerated inflammatory response. Physical examination, invasive hemodynamic monitoring, and echocardiography should be used to further delineate characteristics of the shock state to guide the rational application of vasoactive therapy [18].

Right ventricular dysfunction occurs in approximately 30–40% of all cardiogenic shock cases and is defined by parameters including a right atrial pressure > 12 mm Hg and a pulmonary artery pressure index below 1 or 1.5 (depending on the etiology) within the first 24 h of diagnosis [26, 27]. Timely identification can lead to earlier therapeutic intervention and potential benefit [26–28].

Unique considerations during ECMO

There are several alterations to native circulatory physiology that ECMO introduces which are central to the appropriate selection and use of vasoactive medications. Importantly, veno-arterial (V-A) ECMO provides a mechanism for tissue and organ perfusion in the setting of profound cardiac failure, rather than simply serving as a substitute for impaired cardiac pump function.

In-parallel circulation and afterload mismatch

For most configurations, V-A ECMO provides partial cardiopulmonary bypass and thus creates in-parallel circulation where retrograde ECMO flow competes and mixes with antegrade left ventricular ejection [29]. The location at which these two circulations converge is influenced primarily by the degree of native cardiac dysfunction, amount of ECMO blood flow, and level of systemic vascular resistance. Importantly, the location of this so-called "mixing point" is dynamic, may be influenced by vasoactive use, and has serious implications on regional perfusion, particularly when native oxygenation is impaired [30, 31].

Concomitant circulatory devices and unloading

High afterload from peripheral V-A ECMO flow may result in left ventricular distension, pulmonary edema, and subendocardial ischemia [32]. While concomitant unloading devices may be deployed, careful titration of pharmacologic inotropes, with or without concomitant vasodilating effects (i.e., inodilators) may be sufficient to increase myocardial contractility and promote

adequate left ventricular ejection and unloading [33]. When pharmacologic support is insufficient or poorly tolerated, additional mechanical devices such as intra-aortic counter pulsation, micro axial flow pumps, direct left ventricular drainage, atrial septostomy, or left atrial or pulmonary arterial drainage may be necessary [34]. The choice of strategy for mechanical left ventricular decompression should be guided by the hemodynamic profile, degree of unloading necessary, anticipated support needed after ECMO separation, available vascular access, and local expertise [34]. In severe cases, where left ventricular contractility cannot overcome aortic root pressure and the aortic valve may not open, positive inotropes may be necessary to maintain intermittent aortic valve opening to wash out the aortic root, even in the absence of complete left ventricular ejection [35]. In this context, concomitant vasoactives may still be necessary, particularly upon weaning attempts [36]. Specifically, during ECMO wean trials as circuit flow is progressively reduced, the heart is increasingly loaded with native stroke volume. Pre-emptive application of inotropic and/or vasopressor agents, or increases in their dosages should be guided by the underlying hemodynamic profile including degree of remaining left and right ventricular dysfunction and presence of concomitant vasoplegia [37, 38]. The Extracorporeal Life Support Organization provides recommendations regarding vasoactive dosing thresholds below which are sufficient for V-A ECMO weaning provided that specific hemodynamic criteria are satisfied with reduced ECMO flow [10].

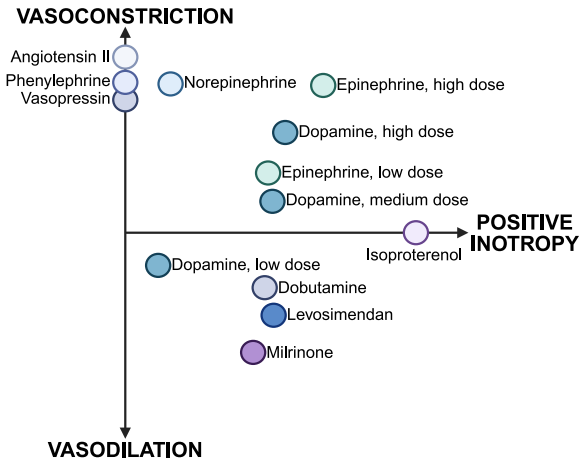


Fig. 1 Vasoactive agents plotted on a grid that estimates their spectrum of the degree of their vasoconstrictive, vasodilatory, and inotropic effects [41–43]. Agents that fall on a line are expected to have only those effects (e.g., phenylephrine: vasoconstriction only) and not mixed effects (e.g., norepinephrine: vasoconstriction and inotropy)

Catecholamines and derivatives

Endogenous catecholamines play an essential role in the maintenance of circulatory homeostasis [39]. Through activation of G-protein-coupled adrenergic receptors, catecholamines and their derivatives modulate key sympathetic physiological functions including heart rate, myocardial contractility, and blood pressure (Fig. 1) [40]. The vascular smooth muscle expresses the α_1 receptor which induces vasoconstriction and β_2 receptor which induces vasodilation. The myocardial β_1 receptor is responsible for many cardiac functions including inotropy, chronotropy, dromotropy, and lusitropy (Table 1) [44]. In cardiogenic shock, endogenous norepinephrine plasma concentrations increase and are independently associated with increased mortality, although the relationship between this and vasopressor selection remains unclear [45].

Epinephrine

Epinephrine offers non-selective alpha and beta receptor agonism and is commonly used in patients with cardiogenic shock for its inoconstrictor effects. The high frequency of concomitant cardiogenic shock and vasodilatory shock confers practical utility to this catecholamine [18]. In a recent survey of inotropic use following cardiovascular surgery across 29 institutions, clinicians utilized epinephrine in 80% of patients with postoperative cardiac dysfunction [46]. Multiple observational studies have evaluated the impact of epinephrine on clinical outcomes in patients supported by ECMO for cardiogenic shock or cardiac arrest. In one study of 231 patients supported by V-A ECMO, with about half for eCPR, early epinephrine was associated with an increased risk of 30-day mortality [47]. Similarly, another study of 589 patients supported by V-A ECMO primarily for post-cardiotomy and medical cardiogenic shock, epinephrine was independently associated with greater 30-day mortality [48]. Higher dosages of epinephrine (> 3 mg) during cardiac arrest, have also been found to reduce the likelihood of favorable neurologic outcome in patients receiving eCPR [49].

Because epinephrine increases both cardiac output and vascular tone, titration may be challenging in patients requiring V-A ECMO who may have mixed cardiogenic and vasodilatory shock [18]. Furthermore, epinephrine can increase myocardial oxygen consumption, arrhythmogenicity, and potentiate lactate production via activity on β_2 receptors in skeletal muscle [50]. However, β_2-mediated bronchodilation of the airway smooth muscle may be advantageous in patients where the suspected etiology of cardiac arrest is anaphylaxis or severe asthma exacerbation [51].

Table 1 Pharmacologic summary of vasoactive agents [41–43]

Drug	Class/mechanism	Target receptor(s)	Hemodynamic effects				Typical dosing	Key characteristics and clinical effects
			CO/CI	SVR	MAP	HR		
Norepinephrine	Catecholamine, direct-acting agonist	$\alpha > \beta_1 > > \beta_2$	~/↑	↑↑	↑↑	~/↑	0.01 to 0.3 mcg/kg/min	• Potent vasoconstrictor • Leads to modest increase in CO
Epinephrine	Catecholamine, direct-acting agonist	$\beta_1 \geq \alpha \geq \beta_2$	↑↑	↑	↑↑	↑↑	0.01 to 0.1 mcg/kg/min	• Potent vasoconstriction due to α_1 effects • Increased chronotropy and inotropy due to β_1 effects • Bronchodilation due to β_2 effects • Effects are dose-dependent
Dopamine	Catecholamine, direct-acting agonist	$\beta_1 \approx \alpha > \beta_2$ D_1	↑	↑	↑	↑↑	5 to 20 mcg/kg/min	• **Low dose** (up to 2 mcg/kg/min): renal/ mesenteric vasodilation • **Medium dose** (5 to 10 mcg/kg/min): increased inotropy and chronotropy (β_1 effect) • **High dose** (10 to 20 mcg/kg/min): vasoconstriction (α_1 effect)
Phenylephrine	Catecholamine derivative, direct-acting agonist	α_1	~	↑↑	↑↑	~	0.5 to 5 mcg/kg/min	• Pure vasoconstrictor, which can cause reflex bradycardia
Dobutamine	Synthetic catecholamine, direct-acting agonist	$\beta_1 > \beta_2$	↑	~	↑	↑	2.5 to 20 mcg/kg/min	• Primarily increases inotropy and chronotropy • Leads to vasodilation • Used more as an inotrope than a vasopressor
Isoproterenol	Synthetic catecholamine, direct-acting agonist	β_1, β_2	↑	~/↓	~	↑	2 to 20 mcg/min	• Approved indications encompass heart block not requiring pacing or cardiac arrest from heart block, with pacing therapy unavailable • Leads to relaxation of bronchial, gastrointestinal, and uterine smooth muscle
Vasopressin	Non-catecholamine peptide, direct-acting agonist	V_1, V_2	↓	↑↑	↑↑	~/↑	0.03 to 0.06 units/min	• Potent vasoconstriction via V_1 receptors on vascular smooth muscle (no V_1 receptors in pulmonary vascular smooth muscle) • Also has antidiuretic effects via V_2 receptors in the kidney
Angiotensin II	Non-catecholamine peptide, direct-acting agonist	AT1, AT2	↓	↑↑	↑↑	~/↑	10 to 80 ng/kg/min	• Potent vasoconstriction by directly acting on AT1 receptors in the vasculature, thus increasing SVR
Milrinone	Non-catecholamine enzymatic phosphodiesterase inhibitor	PDE-III	↑↑	↓↓	↓	↑	0.125 to 0.5 mcg/kg/min	• PDE-III selective at low doses, non-selective at high doses • PDE-III inhibition in the myocardium leads to higher concentration of cAMP, with the effect of increased inotropy and lusitropy • PDE-III inhibition in the vasculature prevents cGMP metabolism and results in vasodilation of both arteries and veins • Accumulation may occur in the setting of renal failure

Table 1 (continued)

Drug	Class/mechanism	Target receptor(s)	Hemodynamic effects				Typical dosing	Key characteristics and clinical effects
			CO/CI	SVR	MAP	HR		
Levosimendan	Non-catecholamine calcium sensitizer	Binds to troponin C and KATP	↑↑	↓↓	↓	↑	0.05 to 0.2 mcg/kg/min	• Binds to cardiac troponin C thus stabilizing the molecule in a conformation that triggers contraction • Activates ATP-sensitive potassium channels in smooth muscle • Dose-dependent decrease in PCWP, mean PAP, mean RAP • Metabolized to a long-acting metabolite

Abbreviations: AT angiotensin receptor, *ATP* adenosine triphosphate, *cAMP* cyclic adenosine monophosphate, *CI* cardiac index, *cGMP* cyclic guanosine monophosphate, *CO* cardiac output, *KATP* ATP-sensitive potassium channels, *MAP* mean arterial pressure, *HR* heart rate, *PAP* pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *PDE-III* phosphodiesterase-3, *RAP* right atrial pressure, *SVR* systemic vascular resistance

Norepinephrine

Norepinephrine functions primarily as a vasoconstrictor while still providing modest inotropic support. For patients requiring peripheral V-A ECMO, norepinephrine corrects competing vasodilation from systemic inflammation and reduced cardiac output from the initial cardiac insult by increasing mean arterial pressure, stroke volume, and coronary perfusion pressure while minimizing tachycardia and arrhythmias. Because of its balanced effects, norepinephrine is recommended as first-line therapy in cardiogenic and vasodilatory shock, which is supported by randomized trials demonstrating fewer adverse effects compared with dopamine or epinephrine [52–55]. The dosage of norepinephrine should always be expressed in its pure molecular ("base") form [56, 57].

Phenylephrine

As a catecholamine derivative, phenylephrine exhibits exclusive activity on α_1 receptors and is generally regarded as a "pure vasoconstrictor." Phenylephrine is less preferred in patients with systolic dysfunction, as isolated vasoconstriction may lead to inability to maintain sufficient stroke volume and cardiac output when used without inotropic agents [41]. However, it may be advantageous in rare circumstances where the native cardiac output is completely offloaded by mechanical support and minimal pulsatility or myocardial contraction is desired, such as known severe myocardial depression with formed thrombus [58]. Additionally, phenylephrine may be beneficial in patients with hyperdynamic left ventricular function or left ventricular outflow tract obstruction where beta-mediated contractility is avoided to increase the diastolic filling time [58].

Dopamine

Dopamine has dose-dependent activity on the dopaminergic, β_1, and α_1 receptors. When stimulated, the peripheral D_1 receptor leads to increased mesenteric blood flow through vasodilation and natriuresis. The β_1 effects of dopamine are realized at moderate dosages, while α_1 effects necessitate higher doses. Although early studies of patients with circulatory shock showed similar hemodynamic outcomes between norepinephrine and dopamine, subgroup analysis demonstrated higher mortality in patients with cardiogenic shock treated with dopamine [52]. Furthermore, rates of arrhythmias are higher with dopamine compared to other catecholamines [52, 59], decreasing its utility in patients supported by V-A ECMO who already have increased risk of arrhythmia [60, 61].

Dobutamine

Dobutamine is a synthetic catecholamine that primarily stimulates the β_1 and β_2 receptors and is classified as an inodilator. While the augmentation of cardiac output through inotropic effects is beneficial in patients with cardiogenic shock, the vasodilatory effects are important to recognize if concomitant vasodilatory shock is present. Dobutamine may increase myocardial oxygen demand from direct simulation of the β_1-receptors in cardiac myocytes along with compensatory tachycardia from vascular smooth muscle vasodilation. Randomized trials have found dobutamine to produce largely similar outcomes as milrinone in patients with cardiogenic shock [62, 63]. Importantly, the effect of dobutamine may be diminished in patients on long-term beta-blocker therapy, such as that commonly encountered in acute on chronic heart failure [64].

Isoproterenol

Isoproterenol is a potent β_1 and β_2 agonist that provides chronotropy, although it may provide more efficient inotropy than dobutamine [65, 66]. Isoproterenol improves right ventricular to pulmonary artery coupling and may be useful in patients receiving ECMO for post-cardiotomy right ventricular dysfunction following heart transplantation [67]. Its strong chronotropic effects make it an attractive option for patients with hemodynamically unstable bradycardia or heart block until durable pacing can be established. However, isoproterenol increases the use of myocardial oxygen and expands lesion size [68, 69].

Non-catecholamines

Vasopressin

Vasopressin is an endogenous neuropeptide released by the posterior pituitary in response to hypoperfusion [39]. In states of shock, circulating concentrations of vasopressin are initially elevated from release of stores but rapidly deplete, resulting in 'relative vasopressin deficiency' [70]. Importantly, vasopressin release varies in different shock states with initially higher concentrations in cardiogenic shock compared to septic shock [71]. Vasopressin produces a dose–response vasoconstriction through the V1 receptor in systemic vascular arterial and venous smooth muscle [72]. Due to the lack of V1 receptors in the pulmonary vascular bed, vasopressin produces no contractile response in isolated human pulmonary artery [73]. In patients receiving nitric oxide post cardiac surgery with norepinephrine-refractory vasoplegia, vasopressin reduced the pulmonary-to-systemic vascular resistance ratio [74], making it a useful vasopressor in patients supported by V-A ECMO with right ventricular dysfunction or those who may not tolerate increases in pulmonary vascular resistance. Compared to catecholamines alone, adjunctive vasopressin reduces the risk of atrial fibrillation [75].

Several studies have shown that vasopressin produces more beneficial effects when it is applied earlier from shock onset [76, 77]. In one observational study, the odds of in-hospital mortality increased by 21% for every 10 mcg/min of norepinephrine delay to vasopressin initiation [78]. In a similar study, those odds were as high as 39% for every 10 mcg/min delay to adding vasopressin [79]. In another study, when vasopressin was initiated within 6 h of shock onset, the odds of in-hospital mortality were 31% lower than if it was started later [80]. Specifically in patients supported by V-A ECMO, a recent study found those who received vasopressin within 6 h of ECMO initiation were much less likely to develop acute kidney injury than those who did not receive vasopressin (OR 0.42, 95% CI 0.23–0.77) [81]. Taken altogether, vasopressin may be a useful vasopressor during ECMO when vasodilation persists despite adequate cardiac output delivery, particularly to reduce the risk of arrhythmia, in those with pulmonary hypertension or right ventricular dysfunction, or at risk for acute kidney injury, but when used, it should be applied early.

Angiotensin II

Angiotensin II is an octapeptide and end-product of the renin-angiotensin system with direct vasoconstrictive effects through angiotensin type 1 receptor agonism of vascular smooth muscle and additional effects through water and sodium regulation. The angiotensin-converting enzyme is primarily found in the pulmonary capillary endothelium and is responsible for conversion of angiotensin I to angiotensin II. Damage to the pulmonary endothelium with lung injury, global inflammation, or exclusion of pulmonary blood flow such as during partial cardiopulmonary bypass, or with V-A ECMO, inhibits the functional and synthetic capacity of angiotensin-converting enzyme [82]. This results in an accumulation of renin and production of vasodilatory angiotensin metabolites [83]. Importantly, in such patients with "high-renin" shock, angiotensin II has been found to suppress this negative feedback loop of vasodilatory substance generation [84] and produce an improved hemodynamic response and survival benefit compared to catecholamine vasopressors [85]. Similar to vasopressin, angiotensin II has been associated with survival benefit when initiated early in shock when catecholamine doses are lower [86].

In two studies of patients supported by mechanical circulatory support devices, including V-A ECMO, angiotensin II was associated with hemodynamic stabilization and reduction in catecholamine requirements [87, 88]. Importantly, cardiac output and pulmonary artery pressures were not significantly changed after angiotensin II administration in patients supported on V-A ECMO [88]. In a randomized trial of patients with vasoplegia after cardiac surgery, angiotensin II produced similar changes in pulmonary vascular resistance as norepinephrine [89].

Milrinone

Milrinone inhibits phosphodiesterase-3 to increase cyclic adenosine monophosphate levels and thereby intracellular calcium to provide inotropy, lusitropy, and vasodilation. While enhancing cardiac output through inotropic support can be advantageous in cardiogenic shock, milrinone's vasodilatory effects may be harmful if vasoplegia is present or be helpful if right ventricular failure is present. In a propensity-matched study of 382 patients with cardiogenic shock supported by V-A ECMO, inodilator use (including milrinone) was associated with lower in-hospital mortality (HR 0.70, 95% CI 0.55–0.94) [90]. Compared to dobutamine, milrinone produces greater reductions in pulmonary artery peak pressures, end-systolic pressures, and right ventricular end-systolic volume [91]. Milrinone's longer half-life and renal elimination distinguish it from dobutamine, which may make titration challenging, particularly in patients with evolving acute kidney injury. An ex vivo study found that ECMO circuits appear to have minimal effect on milrinone concentration while continuous renal replacement therapy effectively removes milrinone [92].

Levosimendan

Levosimendan is an inodilator that enhances cardiac contractility by binding to myocardial troponin C in the presence of calcium and induces smooth muscle relaxation and thereby vasodilation via activation of adenosine triphosphate-dependent potassium channels. Levosimendan has active metabolites with effects that can persist for 7–14 days. In adults supported by ECMO, a population pharmacokinetic study found that levosimendan concentrations were similar to non-critically ill controls, although there were slightly lower metabolite concentrations, which may have been impacted by critical illness itself rather than ECMO circuitry [93].

Levosimendan has principally been investigated in the context of weaning from V-A ECMO. While results have been mixed in the general ECMO population, outcomes appear more favorable in patients receiving eCPR [94–97]. One observational study of 159 patients receiving ECMO for cardiogenic shock or cardiac arrest found that use of levosimendan within 24 h of ECMO initiation was associated with greater weaning success (83% vs. 49%, $p < 0.001$) and lower hospital mortality (44% vs. 68%, $p = 0.007$) compared to no levosimendan [97]. Similarly, another study of 108 patients receiving eCPR found levosimendan to be associated with higher weaning success (87% vs. 23%, $p < 0.001$) and lower in-hospital mortality (39% vs 89%, $p < 0.001$) compared to no levosimendan

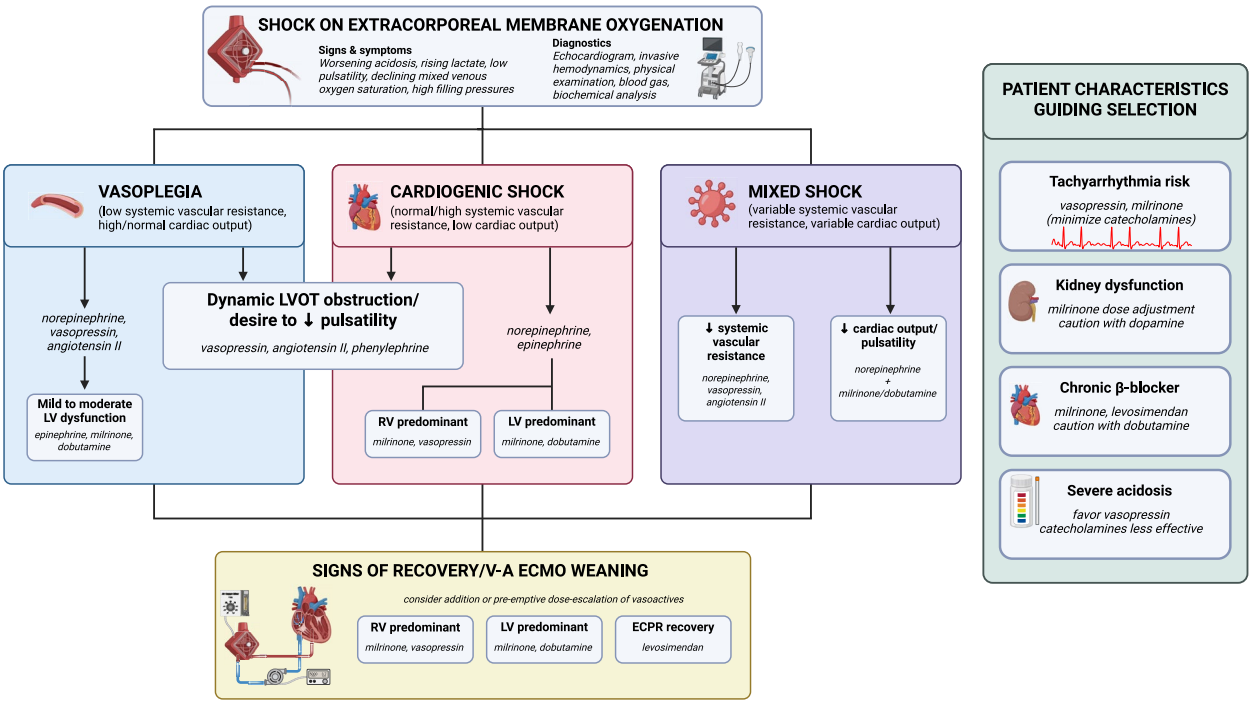


Fig. 2 Clinical decision-making framework for selection of vasoactive agents in patients supported by veno-arterial extracorporeal membrane oxygenation depending on the underlying shock states, hemodynamic profiles, patient characteristics, and conditions. ECPR, extracorporeal cardiopulmonary resuscitation; extracorporeal membrane oxygenation; LV, left ventricle; LVOT, left ventricular outflow obstruction; RV, right ventricle; V-A, veno-arterial

[96]. In a meta-analysis of 16 observational studies, levosimendan use in V-A ECMO was associated with greater odds of successful weaning (OR 2.44, 95% CI 1.72–3.48) and reduced hospital mortality (OR 0.47, 95% CI 0.26–0.88); however, there was moderate to high risk of bias and considerable heterogeneity [98]. The recent multinational LEVOECMO trial randomized 205 patients with cardiogenic shock supported by V-A ECMO to early levosimendan or placebo and found no differences in successful weaning, length of stay, or mortality [95].

Conclusions

A strong understanding of receptor pharmacology is crucial to optimizing vasoactive agent management in patients supported by V-A ECMO. Commonly used vasoactive medications have mechanistic differences that require clinicians to critically evaluate the underlying native and mechanical circulatory support physiology and facilitate optimal selection of vasoactive strategies. Specific choice, dosage, and combination of agents must be tailored to the underlying hemodynamic profiles and phase of ECMO support (Fig. 2). Continuous hemodynamic assessment is crucial for identifying mixed shock states and changes in hemodynamic profiles to guide vasoactive therapy titration to align with gradual recovery of native heart function.

Abbreviations

ECMO	Extracorporeal membrane oxygenation
eCPR	Extracorporeal cardiopulmonary resuscitation
V-A	Veno-arterial

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Authors' contributions

Hannah M. Brinkman: Conceptualization, Investigation, Data Curation and Writing – Original Draft, Writing – Review & Editing. **Jamel P. Ortoleva**: Methodology and Writing – Review & Editing. **Abigail G. Elliott**: Methodology and Writing – Review & Editing. **Dominic V. Pisano**: Methodology and Writing – Review & Editing. **Juan G. Ripoll**: Methodology and Writing – Review & Editing. **Nathaniel J. Martin**: Methodology and Writing – Review & Editing. **Troy G. Seelhammer**: Methodology and Writing – Review & Editing. **Mary A. Kraybill**: Methodology and Writing – Review & Editing. **Omar Elmadhoun**: Methodology and Writing – Review & Editing. **Alice Bottussi**: Methodology and Writing – Review & Editing. **Marc Leone**: Methodology and Writing – Review & Editing. **Erica D. Wittwer**: Methodology and Writing – Review & Editing. **Elena Giovanna Bignami**: Methodology and Writing – Review & Editing. **Jacopo D'Andria Ursoleo**: Methodology and Writing – Review & Editing. **Patrick M. Wieruszewski**: Conceptualization, Supervision, Investigation, Methodology and Writing – Review & Editing.

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Consent for publication
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