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REVIEW

A global perspective on vasoactive agents in shock

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Abstract

Purpose: We set out to summarize the current knowledge on vasoactive drugs and their use in the management of shock to inform physicians' practices.

Methods: This is a narrative review by a multidisciplinary, multinational—from six continents—panel of experts including physicians, a pharmacist, trialists, and scientists.

Results and conclusions: Vasoactive drugs are an essential part of shock management. Catecholamines are the most commonly used vasoactive agents in the intensive care unit, and among them norepinephrine is the first-line therapy in most clinical conditions. Inotropes are indicated when myocardial function is depressed and dobutamine remains the first-line therapy. Vasoactive drugs have a narrow therapeutic spectrum and expose the patients to potentially lethal complications. Thus, these agents require precise therapeutic targets, close monitoring with titration to the minimal efficacious dose and should be weaned as promptly as possible. Moreover, the use of vasoactive drugs in shock requires an individualized approach. Vasopressin and possibly angiotensin II may be useful owing to their norepinephrine-sparing effects.

Keywords: Shock, Cardiovascular system, Adrenergic agonists, Clinical trials, Practice guidelines

Introduction

Acute illnesses are often characterized by a loss in cardiovascular homeostasis. Underlying mechanisms may include multiple factors altering blood volume (actual or effective), cardiac (diastolic and/or systolic) function or the vessels (large vessels and/or microvasculature). Vasopressors and inotropes are vasoactive drugs that have been developed to act on the vessels and the heart. In practice, a number of drugs are available with heterogeneous mechanisms of action and varying benefit to risk balance. This narrative review provides a summary of current knowledge about vasopressors and inotropes to guide intensive care physicians' practices when managing patients with shock.

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Pharmacological basis

Catecholamines

Vasoactive agents are classified into sympathomimetics, vasopressin analogues, and angiotensin II. Catecholamines are further subdivided in categories of indirect, mixed-acting, and direct acting. Only the direct acting agents have a role in shock. Direct agents are further delineated by their selective nature (e.g., dobutamine, phenylephrine) or non-selective activity (e.g., epinephrine, norepinephrine) on α_1, α_2, β_1, β_2, and β_3 receptors [1]. Catecholamines are most often linked to clinical improvement in shock states [1, 2]. Catecholamines act by stimulation of either α or β receptors, exerting excitatory action on smooth muscle and resulting in vasoconstrictive or

vasodilatory effects in skin, kidney, and lung. Intravenous (IV) administration of epinephrine or norepinephrine results in increasing blood pressure with increasing dose. The rise in blood pressure is due to vasoconstriction and β receptor stimulation. β-stimulation directly increases inotropy and heart rate. Although receptor responses have classically been presented as linear, all responses follow a sigmoidal type curve resulting in a pharmacological response to increasing doses followed by a plateau affect. Dopamine receptors include at least five subtypes that are broadly distributed in the central nervous system, in pulmonary and systemic blood vessels, cardiac tissues and the kidneys [1]. The impact on receptors provides the pharmacologic basis for catecholamine therapy in shock. Clinicians should also be aware of their effects on glycogenolysis in the liver and smooth muscle, free fatty acid release from adipose tissue, modulation of insulin release and uptake, immune modulation, and psychomotor activity in the central nervous system.

Vasopressin and analogues

Vasopressin is a potent nonapeptide vasopressor hormone released by the posterior pituitary gland in response to hypotension and hypernatremia [3]. Vasopressin stimulates a family of receptors—V1a (vasoconstriction), V1b (ACTH release), V2 (anti-diuretic effects), oxytocin (vasodilator) and purinergic receptors (of limited relevance to septic shock). Vasopressin paradoxically induces synthesis of nitric oxide (NO) [4]. NO may limit vasopressin's vasoconstriction, while preserving renal perfusion [5]. However, it may also contribute to vasopressin/NO-induced cardiac depression. Notably, V1a-receptor activation of vascular smooth muscle induced vasoconstriction is catecholamine-independent and may explain why vasopressin complements norepinephrine in septic shock. The main rationale for vasopressin infusion in septic shock is well-established. Vasopressin deficiency in early septic shock [6] is due to depletion of vasopressin stores and inadequate synthesis and release from the hypothalamic-pituitary axis. Low dose vasopressin infusion of 0.01–0.04 units/min, increased blood pressure and decreased norepinephrine requirements [6–10]. Vasopressin deficiency and its anti-diuretic effects only become apparent later, during septic shock recovery with about 60% of patients having inadequate vasopressin responses to an osmotic challenge 5 days post recovery from septic shock [11]. Highly selective V1a agonists could have better effects in septic shock than vasopressin because of the narrow focus on the V1a receptor [12]. In addition to minimizing V2 anti-diuresis, less or no von Willebrand factor release is reported (V2 mediated) and there is some evidence in animal models of less vascular leak with V1a agonists compared to vasopressin [13–16]. The highly selective V1a agonist selepressin decreased lung oedema and fluid balance more than vasopressin and control groups with concomitant mitigation of decreased plasma total protein concentration and oncotic pressure [16].

Calcium sensitizers

Calcium sensitizers produce their inotropic effect by sensitizing the myocardium to existing calcium, rather than increasing intracellular concentrations. This has the advantage of producing increased myocardial contraction (inotropy) without the same increases in oxygen demand as other inotropes. Furthermore, as calcium levels fall in diastole, calcium sensitizers do not impair relaxation in the same way as other inotropes.

Levosimendan is the only calcium sensitizer in clinical use [17]. Opening of ATP-sensitive potassium channels in vascular smooth muscle results in vasodilatation and through actions in the mitochondria of cardiomyocytes, it is reported as cardioprotective in ischaemic episodes. At higher doses it also exhibits phosphodiesterase III inhibitor effects. Although the parent drug has a short half-life of about 1 h, an active metabolite, OR1896, has a long half-life and therefore a 24-h infusion of levosimendan can have haemodynamic effects for about 1 week.

Selective beta-1 antagonists

Although sympathetic stimulation is an appropriate physiological response to sepsis there is evidence that if excessive this can become pathological [18]. Both high levels of circulating catecholamines and tachycardia have been associated with increased mortality in septic shock [19]. Although myocardial dysfunction is common in sepsis, short-acting β1 antagonists may have beneficial cardiovascular effects through slowing heart rate, improving diastolic function and coronary perfusion [20]. Esmolol is a cardioselective β_1 receptor antagonist with rapid onset and very short duration of action [21]. Landiolol is an ultra-short acting β blocker about eight times more selective for the β1 receptor than esmolol [22].

Others

Historically, angiotensin was recognized as a potent vasoconstrictor [23]. Angiotensin increases blood pressure mainly by stimulating NADH/NADPH membrane bound oxidase with subsequent oxygen production by vascular smooth muscles [24]. Recently, a synthetic human angiotensin II was shown to act synergistically with norepinephrine to increase blood pressure in patients with vasodilator shock [25]. Methylene blue and non-selective inhibitors of NO synthase induced vasoconstriction by modulating endothelial vascular relaxation, and phosphodiesterase type III inhibitors exert inotropic effects

and vasodilation by modulating cyclic AMP metabolism [26].

Cardiovascular effects

Effects of catecholamines on the cardiovascular system are summarized in Fig. 1.

Effects on the heart

Catecholamines

Vasoactive agents are utilized in shock with the intent of counteracting vasoplegia, myocardial depression or a combination of both. Potential benefits are balanced against the possible negative impact on cardiac output (CO), myocardial oxygen consumption, myocardial perfusion and cardiac rhythm. Norepinephrine effects on cardiac function and CO are inconsistent and time-dependent [27–29], which may be related to baseline cardiovascular state, ventriculo-arterial coupling [30] and potential unmasking of myocardial depression with increased afterload [31]. Usually the direct positive chronotropic effects of norepinephrine are counterbalanced by the vagal reflex activity of the increased blood pressure [1]. Norepinephrine also increases stroke volume and coronary blood flow partly by stimulating coronary vessel β_2-receptors [32]. These potential positive effects of norepinephrine on cardiac function are often transient. Epinephrine is a much more powerful stimulant of cardiac function than norepinephrine, i.e., has more β-adrenergic effects. Epinephrine accelerates heart rate, improves cardiac conduction, stimulates the rate of relaxation, and reinforces systolic efficiency, with subsequent increase in CO at the cost of dramatic increase in cardiac work and oxygen consumption [1]. Epinephrine does not shorten diastole as a result of increased end diastolic time by shortening systole, decreased the resistance of the myocardium during diastole, accelerating relaxation after contraction, or increasing filling pressure [1]. Epinephrine may be associated with a higher risk of tachycardia and arrhythmias than norepinephrine [29, 33, 34]. Dopamine acts through several receptors; at infusion rates of 2–15 μg/kg/min, this drug stimulates β_1-receptors with increased myocardial contractility at the cost of tachycardia and increased risk of arrhythmias [2, 26, 35, 36]. The clinical effects in shock, of stimulation

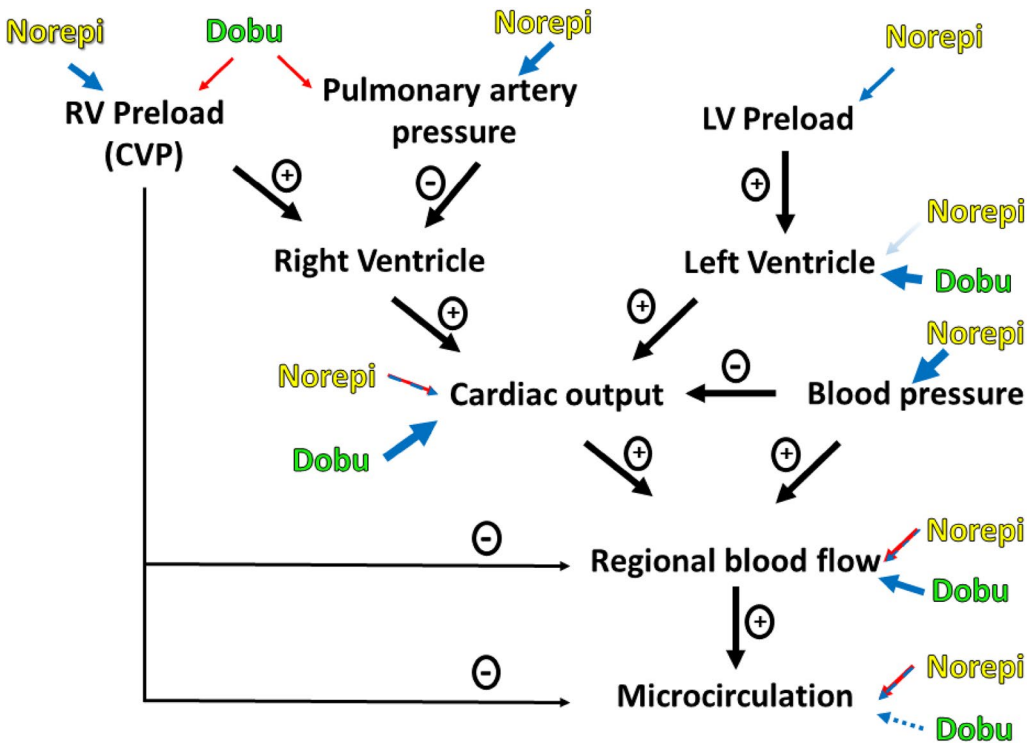

Fig. 1 Impact of norepinephrine and dobutamine on cardiac output and its determinants, regional and microvascular perfusions. The effects of norepinephrine and dobutamine are denoted with colored arrows: blue arrows denote an increase in the corresponding hemodynamic variable, red arrows denote a decrease in the corresponding hemodynamic variable, bicolor red/blue arrows denote variable effects (can be either positive or negative, depending on time, patient condition or blood pressure level). Plain arrows denote an effect observed in the majority of the patients, dotted arrow represent an effect observed in some but not all patients (but without detrimental effect). The thickness of the arrow represents the magnitude of the effect. An evanescent arrow represents an effect that decreases over time

of cardiac dopamine receptors remain unclear. Phenylephrine is a pure α-agonist, which increases afterload and reduces heart rate and CO [37].

Vasopressin and analogues

Vasopressin and its analogues may impair cardiac contractility via vasopressin V1a receptor–mediated decreased β-adrenergic receptor sensitivity [38]. Likewise, angiotensin may impair CO via increased afterload.

Inotropes

Inotropes are used in patients with myocardial depression, to improve CO through enhanced cardiac myofibril contractility [39]. Although dobutamine may initially decrease vascular tone, MAP is usually improved with the increased CO except in condition of low systemic vascular resistance. Phosphodiesterase III inhibitors also increase myocardial contractility (possibly synergistically with dobutamine) but are often associated with hypotension and arrhythmias. While these agents are potentially interesting for right ventricular failure due to their effects on right ventricular afterload, great caution should be observed in preserving coronary perfusion. Levosimendan increases contractility and CO with minimal tachycardia and without increasing myocardial oxygen consumption but often with significant decrease in MAP (especially with loading dose). In cardiogenic shock, as compared to dobutamine, levosimendan may result in higher CO and lower cardiac preload [40].

Selective β_1-antagonists

Administration of short-acting selective β_1-antagonists increased systolic function and left ventricle end-diastolic volume, reduced myocardial oxygen consumption, and restored cardiac variability during both experimental sepsis and heart failure [20]. These drugs showed substantial improvement in stroke volume and CO in patients with severe septic shock and tachycardia [41].

Effects on systemic and pulmonary circulations

Norepinephrine and epinephrine are equipotent with regard to their effects on systemic blood pressure and systemic vascular resistance [33, 34]. Low dose epinephrine may lower systemic blood pressure, via activation of vascular β_2 adrenergic receptors, an effect not seen with norepinephrine [1]. Norepinephrine and epinephrine similarly increase pulmonary artery pressure and pulmonary vascular resistance with little effects on pulmonary capillary wedge pressure [42]. Norepinephrine also decreases preload dependency [43] possibly by increasing venous return via a shift of unstressed to stressed volume, with subsequent transient increase in CO [44]. High dose dopamine (10–20 μg/kg/min) stimulates α-adrenergic receptors and increase systemic vascular resistance. However, clinically it increases MAP through increased CO with little to no peripheral vasoconstriction [2, 35, 36]. Dobutamine decreases systemic and pulmonary vascular resistance with little change in systemic blood pressure owing to increased CO. Vasopressin is usually used for its norepinephrine sparing effects. This drug increases afterload without pulmonary vasoconstriction [8]. Vasopressin may have beneficial effects for right heart function [9, 10]. However, conflicting reports regarding its use as a primary agent in post-cardiac surgery vasoplegic syndrome include dysrhythmia and myocardial infarction [45–47]. In septic shock, selepressin decreased norepinephrine requirements and limited positive fluid balance [14]. This drug has been investigated in a Phase IIB/III trial which is now completed after the recruitment of 868 patients [48]. In adults with vasoplegic shock, a new synthetic human angiotensin II substantially increased systemic vascular resistance without alteration in CO, and subsequently increased blood pressure [25]. In septic shock, infusion of levosimendan was associated with significant reduction in systemic vascular resistance necessitating increased doses of norepinephrine [49]. Interestingly, levosimendan may decrease pulmonary vascular resistance, and may improve right ventricular function when pulmonary artery pressure is high [17].

Effects on regional circulation

In general, β-adrenergic agents, phosphodiesterase III inhibitors and levosimendan increase splanchnic perfusion while α-adrenergic agents and vasopressin have more variable effects. Several studies have shown that dobutamine usually increases splanchnic perfusion but with high individual variability [50, 51]. The effects were observed at low doses (5 μg/kg/min), and dose escalation did not affect splanchnic perfusion further.

Vasoactive drugs can improve splanchnic perfusion by restoring organ perfusion pressure. Pressures higher than autoregulation pressure can be either neutral or detrimental. Two factors need to be taken into account: both the nature of the agent and that dose may affect the response. At low doses, adrenergic agents have relatively similar and neutral effects; while at high doses can impair splanchnic perfusion and metabolism [52]. Similarly, vasopressin has modest effects on the splanchnic circulation at low doses but markedly impaired it at high doses [53].

Inotropic agents improve renal perfusion only in the setting of low CO. Vasoactive drugs improve renal perfusion when correcting hypotension during euvolemia. Vasopressin may have a greater impact on glomerular filtration pressure through a preferential effect on efferent arteriole, explaining the greater urine output and creatinine clearance obtained at the same blood pressure, compared to norepinephrine [10].

Table 1 Summary of Non-Cardiovascular Effects of Vasoactive Drugs

Metabolic Effects
● ↓ Insulin release by Pancreas (Stimulation of α-adrenergic receptors)
● Inhibition of lipolysis in adipose tissue (Stimulation of α-adrenergic receptors)
● ↑ Hepatic glucose production and glycogen breakdown (Stimulation of β-adrenergic receptors)
● ↑ Skeletal muscle glycogenolysis and lactate production (Stimulation of β-adrenergic receptors)
Endocrine Effects
● ↓ Serum concentrations of anterior pituitary hormones: prolactin, TRH, hGW, and LH (Dopamine)
● ↓ TSH secretion (Dopamine)
● Stabilization of the hypothalamic-pituitary axis (Vasopressin)
Immunological Effects
● Transient T-cell hyperresponsiveness (Dopamine)
● ↓ Endotoxin mediated release of pro-inflammatory cytokines (Norepinephrine and Epinephrine)
● Upregulation of anti-inflammatory cytokines (Norepinephrine and Epinephrine)
● Potential stimulation of bacterial growth (Norepinephrine and Epinephrine)
● ↓ Levels of circulating proinflammatory cytokines (Levosimendan, Vasopressin))
● ↓ IL-6 levels and nitrite/nitrate levels (Selepressin)

TRH thyrotrophic releasing hormone, *hGW* human growth hormone, *LH* luteinizing hormone, *TSH* thyroid stimulating hormone, *IL-6* interleukin 6

Effects on the microcirculation

When mean arterial pressure decreases below an autoregulatory threshold of 60–65 mm Hg, organ perfusion becomes pressure-dependent. In this setting, increasing MAP with vasopressors might improve microcirculatory flow in severely hypotensive septic shock patients [54]. On the other hand, above the autoregulation threshold, vasopressor-induced excessive vasoconstriction could also be deleterious [55]. In septic shock, increasing MAP above 65 mm Hg with incremental doses of norepinephrine showed considerable variations in individual responses depending on basal microcirculatory status, timing, or other factors [56–58]. Phenylephrine has detrimental effects on microvasculature perfusion in shock patients [59, 60]. Vasopressin (or analogues) has variable effects on microcirculation [61–64]. Recent studies suggest comparable effects to norepinephrine [65–67]. In clinical practice with refractory hypotension, increasing MAP with norepinephrine improves microcirculatory perfusion. Nevertheless, the optimal MAP and dose of vasoactive drug for an optimal microcirculatory perfusion are fairly variable, should be tailored to individuals and whenever possible monitored.

The microcirculatory response to dobutamine had a high individual variability, resulting in different results between trials [51, 68–70]. Dobutamine improved the microcirculation mainly in patients in whom it was severely altered via unclear mechanisms that are independent of its effects on the macro-circulation [68, 69]. The effects of levosimendan and phosphodiesterase III inhibitors are still uncertain with beneficial effects in experimental models and scarce data in humans [71–73].

Metabolic and endocrine effects

Effects on metabolism

Non-cardiovascular effects of vasoactive drugs are summarised in Table 1. Stimulation of α-adrenergic-receptors results in reduced insulin release by B cells of the pancreas, reduced pituitary function, and inhibited lipolysis in adipose tissues [1]. Stimulation of β-adrenergic receptors in the liver increases glucose production and glycogen breakdown via formation of cyclic AMP. In skeletal muscles, owing to the absence of glucose-6-phosphatase, β-adrenergic stimulation activates glycogenolysis and lactate production [74]. In practice, compared to norepinephrine, epinephrine infusion was associated with a transient, non-clinically relevant, increase in serum lactate levels and decrease in arterial pH [29, 33, 34]. There is no evidence of any metabolic effects of vasopressin or its analogues, human synthetic angiotensin II, and levosimendan when administered to critically ill patients.

Effects on hormones

Dopamine decreases serum concentrations of all anterior pituitary hormones (prolactin, thyrotrophic releasing hormone, growth hormone, and luteinizing hormone) via D_2 receptors in the anterior pituitary and the hypothalamic median eminence [75]. Dopamine can also induce or aggravate the low-T_3 syndrome by suppressing thyroid stimulating hormone secretion and decreasing thyroxin and tri-iodo-thyroxin levels. Moreover, dopamine may suppress serum dehydroepiandrosterone sulphate, an effect mediated by low levels of prolactin or thyroid hormones. Moreover, dopamine blunts pulsatile growth hormone secretion and decreases concentrations

of insulin-like growth factor-1, which is implicated in peripheral tissue and bone anabolism. Vasopressin modulates ACTH release by the hypothalamus-pituitary axis via V1b receptors and cortisol release by the adrenal cortex via V1a receptors [76].

Immune effects

Immune dysfunction during critical illness varies from excessive inflammatory response to immune paralysis. Sepsis may be characterized by defective antigen presentation, T and B cell mediated immunity, and defective Natural killer cell mediated immunity, relative increase in T-regs, activation of PD-1, decreased immunoglobulin levels, quantitative and qualitative alterations in neutrophils, hypercytokinaemia, complement consumption, and defective bacterial killing/persistence of neutrophil extracellular traps [77]. Catecholamines may aggravate sepsis associated immune paralysis [20]. Dopamine decreases serum levels of prolactin that triggers a transient T cell hyporesponsiveness and may reduce lymphocyte count, although decreased serum dehydroepiandrosterone may also play a role. In addition, dopamine may also inhibit the transformation of lymphocytes by mitogens. Epinephrine and norepinephrine may downregulate endotoxin induced immune cells release of proinflammatory cytokines and upregulate anti-inflammatory cytokines (e.g., IL-10). They may also stimulate bacterial growth by removal of iron from lactoferrin and transferrin by the catechol moiety and its subsequent acquisition by bacteria. By contrast, selective β_1 blockade may decrease the concentrations of circulating and tissue inflammatory cytokines, may inhibit bacterial growth, and may improve fibrinolysis [20]. In patients with decompensated heart failure, levosimendan reduced significantly circulating levels of proinflammatory cytokines (IL-6, TNFα, and TNFα/IL-10 ratio) and soluble apoptosis mediators (soluble Fas and Fas ligand), partly as a result of improved haemodynamics [78]. Vasopressin decreased plasma cytokines more than norepinephrine [79], especially in patients with less severe shock and vasopressin has other complex immune effects [80]. Selepressin-induced reduction of IL-6 and nitrite/nitrate levels may limit vascular permeability associated with vasodilatory shock [15].

Effects on survival

The extent to which vasoactive drugs can improve haemodynamic parameters in shock is influenced by the choice, dose and timing of individual and/or combinations of agents. Unfortunately, a definitive survival benefit for the commonest agents administered is lacking. A Cochrane review of high quality randomised trials found no survival advantage related to the choice of the vasoactive drugs [81]. Accordingly, recommendations are made based on organ dysfunction effects and safety issues, not survival benefits [2].

Septic shock

Norepinephrine is the recommended first-line vasoactive drug [2]. Epinephrine, phenylephrine and vasopressin are usually considered second-line agents, with dopamine reserved for bradycardic patients [2]. Norepinephrine and epinephrine achieve similar shock reversal and no randomised trial demonstrates survival advantage when using one agent over the other [81]. Likewise, 28-day survival when combining norepinephrine and dobutamine is similar to epinephrine alone [33]. Notably, kidney failure-free days and mortality were not different in the VANISH trial comparing early vasopressin versus norepinephrine [82]. The addition of low-dose vasopressin to norepinephrine did not improve survival in a large, double-blind trial of vasopressor-dependent shock, although a potential benefit for patients with less severe shock (norepinephrine < 15 μg/min) was not excluded [83]. In this trial, there was a synergic effect of vasopressin and hydrocortisone on survival [84]. However, these beneficial effects were not confirmed in the VANISH trial [82]. Similarly, there are no large-scale trials with mortality as the primary outcome comparing norepinephrine and either phenylephrine or other V1a agonists such as terlipressin or selepressin. Finally, a large blinded trial comparing norepinephrine versus dopamine in generalised shock (SOAP II) reported an increase in arrhythmic events with dopamine as first-line therapy, but no difference in survival either overall (primary endpoint) or in the pre-defined sub-group with septic shock [85]. Moreover, mortality rates increased during a 6 month period of norepinephrine shortage in 26 US hospitals (during that period norepinephrine was mostly replaced by phenylephrine and dopamine) [86].

Inotropes such as dobutamine and levosimendan have also been suggested as second-line agents for the management of refractory shock [2]. A network meta-analysis of 33 randomised trials of vasoactive agents in septic shock reported that levosimendan, dobutamine, epinephrine, vasopressin and norepinephrine with dobutamine were all significantly associated with survival, with levosimendan and dobutamine affording the greatest benefit [87]. In contrast, a multicentre, double-blind trial in vasopressor-dependent shock reported increased arrhythmias and ventilator weaning difficulties with levosimendan (versus placebo) and no difference in survival [49]. In this trial the randomization was not stratified according to the presence or absence of left ventricular dysfunction [49]. A small ($n = 77$) single-centre trial reported decreased mortality with esmolol in selected septic shock patients [41]. Interestingly, drugs

with positive chronotropic effects may be associated with higher risk of death than those without or with negative chronotropic effects (Fig. 2).

Other forms of shock

In other forms of distributive shock provoked by anaphylaxis or pancreatitis, there is a paucity of high quality evidence and randomised trials examining the effect of vasoactive agents on survival. Synthetic human angiotensin II has recently been reported to improve MAP in a multicentre, double-blind trial of vasodilatory shock due to a variety of causes and refractory to traditional vasoactive drugs [25]. However, caution is advised in low cardiac output shock. A non-significant trend to improved survival (secondary outcome) was also noted. Vasopressin (up to 0.06 U/min) and early methylene blue administration may also improve survival in vasoplegic shock post-cardiac surgery [45, 88].

Despite the widespread utilization of vasoactive drugs in cardiogenic shock, there is a paucity of evidence to guide selection. The SOAP II trial reported a statistically significant higher risk of mortality with dopamine compared to norepinephrine in the pre-defined sub-group of patients with cardiogenic shock [85]. Despite being the largest randomised trial to date supporting norepinephrine in cardiogenic shock, some have raised questions regarding the widespread validity of its results [36]. Norepinephrine is associated with fewer arrhythmias and based on current data is likely the vasoactive drug of choice for most patients with cardiogenic shock [36].

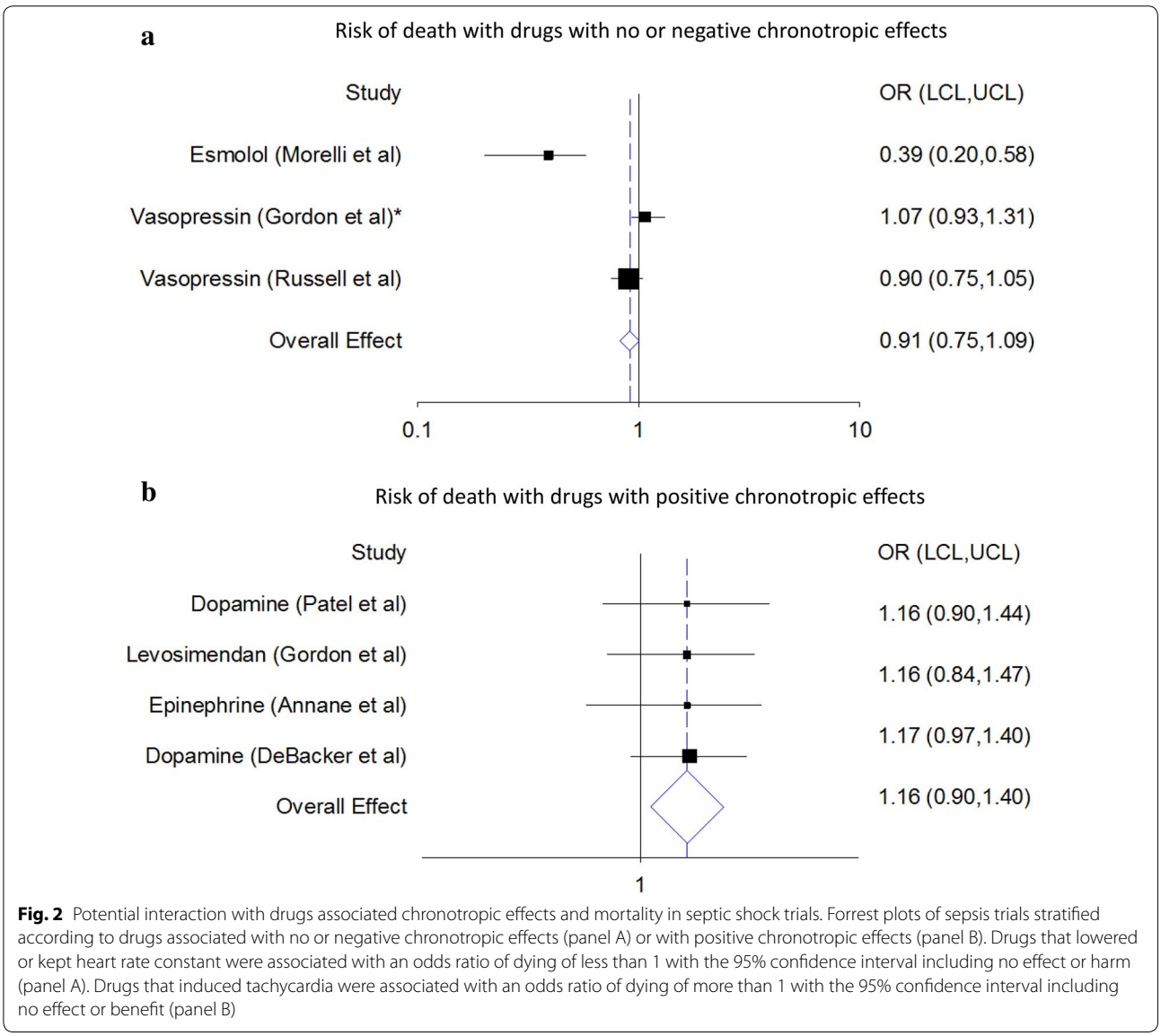

Fig. 2 Potential interaction with drugs associated chronotropic effects and mortality in septic shock trials. Forrest plots of sepsis trials stratified according to drugs associated with no or negative chronotropic effects (panel A) or with positive chronotropic effects (panel B). Drugs that lowered or kept heart rate constant were associated with an odds ratio of dying of less than 1 with the 95% confidence interval including no effect or harm (panel A). Drugs that induced tachycardia were associated with an odds ratio of dying of more than 1 with the 95% confidence interval including no effect or benefit (panel B)

Additional considerations such as the cause or presentation type of cardiogenic shock may also influence vasoactive drug selection. Routine use of inotropes in patients with heart failure has been associated with increased mortality [89]. However, in patients with cardiogenic shock, inotropes are utilised for haemodynamic support and have an important role in optimising perfusion to vital organs [90]. Dobutamine and milrinone both improve inotropy that increases cardiac output. Both agents are associated with arrhythmias and systemic hypotension. Studies comparing these two agents suggest similar clinical outcomes although milrinone has a longer half-life and is associated with more profound hypotension [91].

Haemorrhagic shock is the most common type of shock seen with trauma [92]. The therapeutic goals are restoration of blood volume and definitive control of bleeding [93]. Vasoactive drugs can be transiently utilised in the presence of life-threatening hypotension [94]. The impact of vasoactive drugs on trauma outcome is poorly understood. Animal studies and a small clinical trial suggest that vasopressin in conjunction with rapid haemorrhage control may improve blood pressure without causing increased blood loss, leading to improved outcomes [95–97]. However, observational studies have shown that vasoactive drug use in general is an independently associated with increased mortality in trauma patients [98–100].

Practical use

In routine, physicians should consider as much as possible to individualize the use of vasoactive drugs taking into account patient's comorbidities and physiological characteristics, the aetiology of shock, the local environement and their own experiences with the various vasoactive drugs available on the market.

Choice of vasoactive drugs

After adequate fluid resuscitation and assessment, determining vasoactive drug choice depends upon the aetiology and pathophysiology of the hypotensive episode (Fig. 3). In hypovolaemic, cardiogenic and obstructive shock, hypotension results from decreased CO. In these types of shock, regional perfusion may correlate with global perfusion [100]. However, distributive shock (sepsis, pancreatitis etc.) is more complicated with vasoplegia, shunting, decreased oxygen extraction and low, normal or high CO.

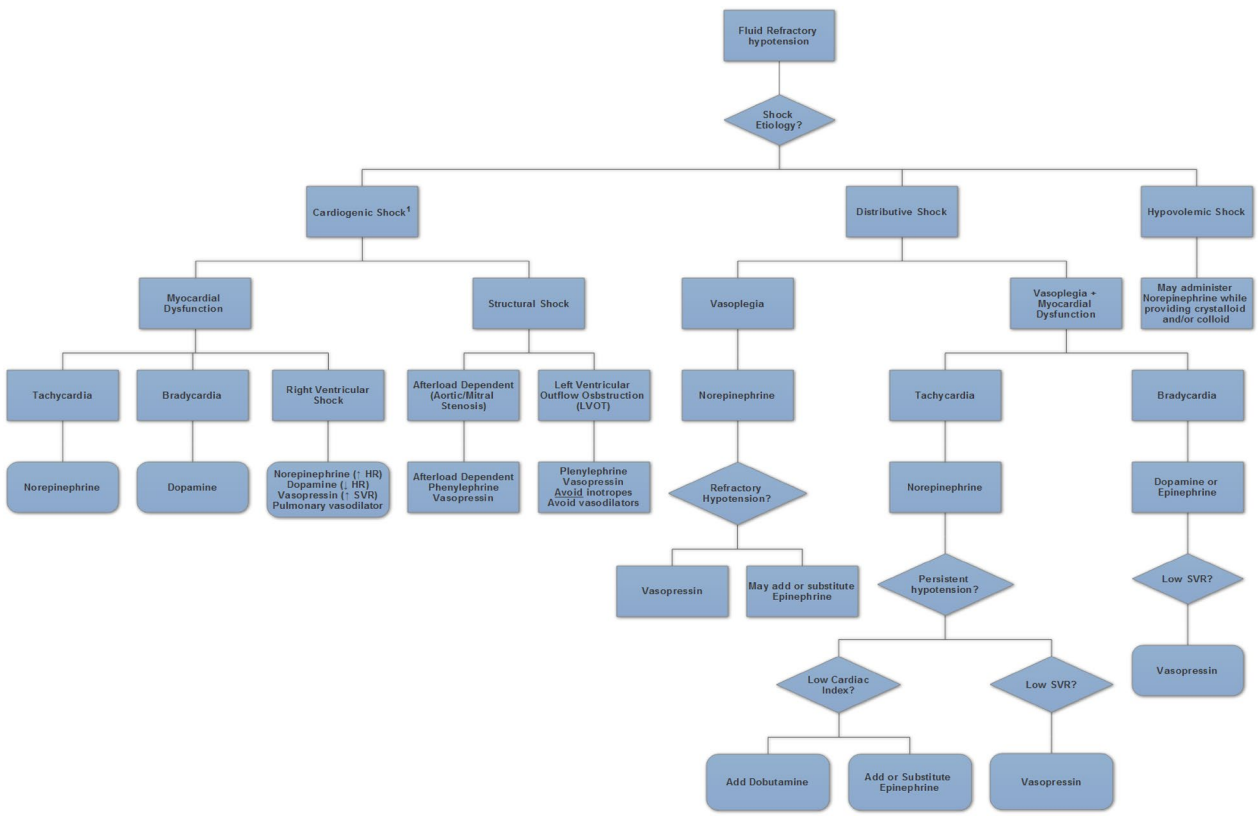

Fig. 3 Decision tree for the use of vasoactive drugs according to the aetiology of circulatory failure

In fluid-refractory hypotension, vasoactive agents are indicated and may be initiated during fluid resuscitation, and subsequently weaned as tolerated [26]. Ultrasound, when possible, can help ascertain shock aetiology and/or assist continued management.

In cardiogenic shock, decreased CO aetiology is generally due to poor myocardial function. Individualized MAP goals are required as the hypoperfusion risk is balanced against the potential negative impact on CO, myocardial oxygen consumption, ischaemia and dysrhythmias. In acute heart failure (excluding pre-revascularisation myocardial infarction), guidelines recommend inotropes (dobutamine, dopamine, phosphodiesterase III inhibitors) as the first line agent [35, 101]. In persistently hypotensive cardiogenic shock with tachycardia, norepinephrine is advised [35, 101] and in patients with bradycardia, dopamine may be considered [36]. In specific afterload dependent states (aortic stenosis, mitral stenosis), phenylephrine or vasopressin is advised [36].

In distributive shock, norepinephrine is recommended as the initial vasoactive drug after appropriate fluid resuscitation [2, 102]. If hypotension persists, vasopressin (up to 0.03 UI/min) should be considered for reducing norepinephrine [83] and possibly renal replacement therapy requirements [82].

Myocardial depression is common in septic shock [103]. Persistent hypotension with evidence of myocardial depression and decreased perfusion may benefit from inotropic therapy by adding dobutamine to norepinephrine or using epinephrine as a single agent. Dopamine is only recommended in hypotensive patients with bradycardia or low risk for tachycardia [2, 35, 104]. Phenylephrine should be reserved for salvage therapy.

Uncertainty surrounding the optimal use of levosimendan exists and should be clarified prior to including it in standardized treatment guidelines. Likewise, β_1 antagonists cannot be recommended while we await for their evaluation in a multicentre trial (https://doi.org/10.1186/ISRCTN12600919).

Therapeutic targets

Haemodynamic support should optimise perfusion to vital organs ensuring adequate cellular delivery of oxygen. Vasoactive drugs titrated to specific targets reflect optimal end-organ perfusion (e.g., urinary output, serum lactate clearance). Mean arterial pressure reflects tissue perfusion. Specific organs have different tolerance to hypotension based on their ability to autoregulate blood flow. However, there is a threshold MAP where tissue perfusion may be linearly dependent on blood pressure. Current guidelines recommend that vasopressors be titrated to maintain a MAP of 65 mm Hg in the early resuscitation of septic shock [2]. However, the optimal MAP target for patient with shock is still a point of debate. Small studies targeting higher MAPs (85 versus 65 mm Hg) were associated with higher cardiac index but no significant change in other measurements of global and regional perfusion [105, 106]. A multicentre trial compared vasopressor titration to MAP of 65–70 versus 80–85 mm Hg on mortality in patients with septic shock [107]. Although no mortality difference was reported (28 or 90 days), the higher target (80–85 mm Hg) was associated with more arrhythmias. In patients with documented chronic hypertension, the higher target MAP (80–85 mm Hg) was associated with decreased renal replacement therapy. Patients 75 years or older, may benefit from lower rather than higher target (MAP 60–65 vs 75–80 mm Hg). These finding suggests that although 65 mm Hg may be a good starting target for most patients, clinicians may need to individualize the target based on specific patient history and findings.

Inotropes should be titrated with concomitant measurements of CO and tissue perfusion. Targeting supraphysiologic cardiac output does not improve outcomes and should be avoided [108]. Clinicians should complement haemodynamic targets with other serial markers of systemic and organ perfusion, such as lactate, mixed or central venous oxygen saturations, urine output, skin perfusion, renal and liver function tests, mental status and other haemodynamic variables. Elevated lactate has been shown to correlate with increased mortality in various types of shock. Although lactate does not increase solely because of poor tissue perfusion it can be utilised as a marker of the adequacy of haemodynamic support. Lactate guided resuscitation has been consistently shown to be effective [109, 110].

Monitoring and weaning

Administration of vasoactive agents should always be targeted to effect and not based on a fixed dose (but a maximal dose may be considered for some agents, e.g., vasopressin or angiotensin). Vasoactive drugs should target a precise blood pressure level using intra-arterial monitoring. As inotropes and vasopressors impact cardiac function and tissue perfusion, CO monitoring is desired primarily using echocardiographic evaluations and measurements of blood lactate and mixed-venous or central venous O_2 saturation at regular intervals. However, some patient populations may benefit from pulmonary artery catheter or pulse wave analysis with or without calibration [111, 112].

The importance of vasoactive agent de-escalation is comparable to the indication for initiation [26]. Physicians and nurses may maintain a higher blood pressure than desired or continue a supra-therapeutic dose of inotropes, as they overestimate the risk of re-aggravation.

We suggest that weaning of vasoactive drugs should be performed as soon as haemodynamic stabilisation is achieved. Computerised assisted weaning may reduce unnecessary exposure to vasoactive drugs [113].

The sequence of withdrawal of vasopressin is usually after weaning of norepinephrine, as performed in VASST and VANISH, as withdrawing vasopressin first was associated with more haemodynamic instability [114, 115].

Serious adverse events

Arrhythmias are the most frequent complications of vasoactive drugs, ranging from 2 –25%. 2–15% with norepinephrine [33, 82–84], about 15% with epinephrine [33, 34], up to 25% with dopamine [85], about 1–2% with vasopressin [82, 83], about 6% with synthetic human angiotensin II [25], up to 25% with dobutamine [108], and about 6% with levosimendan [49] (Table 2). The risk of arrhythmias may be lower with norepinephrine and vasopressin than with dopamine, epinephrine, dobutamine, or levosimendan. In a multinational prospective cohort study, treatment with catecholamines was the main trigger of life-threatening arrhythmias in ICU patients, which were independently associated with hospital mortality and neurological sequelae [116]. The prevalence of arrhythmias may be higher when catecholamines are titrated toward MAP values of 80–85 [107].

Acute coronary events occurred in 1–4% of research participants, a prevalence that was consistent across trials (and between groups) investigating catecholamines, vasopressin, angiotensin II or levosimendan (33, 34, 49, 82–84). The prevalence of stroke, limb ischemia, and intestinal ischemia was 0.3–1.5, 2, and 0.6–4% [33, 82, 83]. Central nervous bleeding was reported in roughly 1% of catecholamine-treated septic shock [33]. These serious cerebrovascular complications are more likely to occur

Table 2 Main serious adverse reactions associated with vasoactive drugs

Molecules	Arrhythmias		Vascular				Metabolic
	Supra-ventricular	Ventricular	Myocardial ischemia	Stroke	limbs	Other tissues/ organs	
Dopamine	Atrial fibrillation; multifocal atrial tachycardia; cardiac conduction abnormalities	Ventricular tachycardia/fibrillation	+	+	+	+	Not described
Dobutamine	Atrial fibrillation; multifocal atrial tachycardia,	Ventricular tachycardia/fibrillation	+	Not described	Not described	Not described	Hypokalemia
Epinephrine[a]	Atrial fibrillation; multifocal atrial tachycardia,	Ventricular tachycardia/fibrillation	+++	+	+	+	Lactic acidosis; hyperglycaemia; hypoglycaemia; insulin resistance; hypokalemia;
Norepinephrine	Atrial fibrillation; multifocal atrial atchycardia, bradycardia	Ventricular tachycardia/fibrillation	++	+	+	+	Not described
Vasopressin	Atrial fibrilation; bradycardia	Ventricular tachycardia/fibrillation	++	+	+	+	hyponatremia
AngiotensinII[b]	±	Ventricular tachycardia	Not described	Not described	+	Not described	Not described
Levosimendan	Atrial fibrillation; multifocal atrial tachycardia; junctional tachycardia	Ventricular tachycardia/fibrilation	Not described	Not described	Not described	Not described	Metabolic alkalosis; hypokalemia
Esmolol/ Landiolol	Bradycardia; conduction abnormalities; sinus arrest; asystole		+	Not described	+	Not described	Hyperkalemia; metabolic acidosis

[a] Epinephrine my also be associated with brain haemorrhage

[b] Synthetic human angiotensin II

with rapid variations in the infusion rate of vasoactive drugs, and in patients with coagulation disorders.

Catecholamine infusion was associated with for one-third of all cases of drug-induced Takotsubo cardiomyopathy in a recent systematic review of the literature [117]. β_2 adrenergic receptors agonists may aggravate lactic acidosis and ICU-acquired hyperglycaemia.

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Compliance with ethical standards

Conflicts of interest
DA reports having received a grant from the French Ministry of Health to conduct a trial comparing epinephrine to norepinephrine plus dobutamine for septic shock (CATS). DDB reports that he acts as a consultant to and material for studies by Edwards Lifesciences. ACG reports that outside of this work he has received speaker fees from Orion Corporation Orion Pharma and Amomed Pharma. He has consulted for Ferring Pharmaceuticals, Tenax Therapeutics, Baxter Healthcare, Bristol-Myers Squibb and GSK, and received grant support from Orion Corporation Orion Pharma, Tenax Therapeutics and HCA International with funds paid to his institution. GH reports no financial conflict of interest. JR reports patents owned by the University of British Columbia (UBC) that are related to PCSK9 inhibitor(s) and sepsis and related to the use of vasopressin in septic shock. JR is an inventor on these patents. JR is a founder, Director and shareholder in Cyon Therapeutics Inc. (developing a sepsis therapy (PCSK9 inhibitor)). JR has share options in Leading Biosciences Inc. JR is a shareholder in Molecular You Corp. JR reports receiving consulting fees in the last 3 years from: (1) Asahi Kesai Pharmaceuticals of America (AKPA)(developing recombinant thrombomodulin in sepsis). (2) La Jolla Pharmaceuticals (developing angiotensin II; JR chaired the DSMB of a trial of angiotensin II from 2015 to 2017)—no longer actively consulting. (3) Ferring Pharmaceuticals (manufactures vasopressin and was developing selepressin)—no longer actively consulting. (4) Cubist Pharmaceuticals (now owned by Merck; formerly Trius Pharmaceuticals; developing antibiotics)—no longer 3 actively consulting. (5) Leading Biosciences (was developing a sepsis therapeutic that is no longer in development)—no longer actively consulting. (6) Grifols (sells albumin)—no longer actively consulting. (7) CytoVale Inc. (developing a sepsis diagnostic)—no longer actively consulting. JR reports having received an investigator-initiated grant from Grifols (entitled "Is HBP a mechanism of albumin's efficacy in human septic shock?") that is provided to and administered by UBC.

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