REVIEW

A global perspective on vasoactive agents in shock

Djillali Annane^{1*}, Lamia Ouanes-Besbes², Daniel de Backer³, Bin DU⁴, Anthony C. Gordon⁵, Glenn Hernández⁶, Keith M. Olsen⁷, Tiffany M. Osborn⁸, Sandra Peake^{9,10}, James A. Russell¹¹ and Sergio Zanotti Cavazzoni¹²

© 2018 Springer-Verlag GmbH Germany, part of Springer Nature and ESICM

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.

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

*Correspondence: Djillali.annane@aphp.fr

¹ General ICU, Raymond Poincaré Hospital (APHP), School of Medicine Simone Veil U1173 Laboratory of Infection and Inflammation (University of Versailles SQY, University Paris Saclay/INSERM), CRICS-TRIGERSEP Network (F-CRIN), 104 boulevard Raymond Poincaré, 92380 Garches, France

Full author information is available at the end of the article

All authors have equally contributed to this manuscript.

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 effect. 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 β_1 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 β_1 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 $\mu\text{g/kg/min}$, 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 $\mu\text{g/kg/min}$) 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, selevpressin 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 $\mu\text{g/kg/min}$), 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 euolemia. 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
<ul style="list-style-type: none"> ● ↓ 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
<ul style="list-style-type: none"> ● ↓ Serum concentrations of anterior pituitary hormones: prolactin, TRH, hGW, and LH (Dopamine) ● ↓ TSH secretion (Dopamine) ● Stabilization of the hypothalamic-pituitary axis (Vasopressin)
Immunological Effects
<ul style="list-style-type: none"> ● 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 thyroxine and tri-iodo-thyroxine 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, TNF α , and TNF α /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 $\mu\text{g}/\text{min}$) 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 environment 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.

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 findings suggest 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 supra-physiologic 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 tachycardia, bradycardia	Ventricular tachycardia/fibrillation	++	+	+	+	Not described
Vasopressin	Atrial fibrillation; 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/fibrillation	Not described	Not described	Not described	Not described	Metabolic alkalosis; hypokalemia
Esmolol/Landiolo	Bradycardia; conduction abnormalities; sinus arrest; asystole		+	Not described	+	Not described	Hyperkalemia; metabolic acidosis

^a Epinephrine may 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.

Author details

¹ General ICU, Raymond Poincaré Hospital (APHP), School of Medicine Simone Veil U1173 Laboratory of Infection and Inflammation (University of Versailles SQY, University Paris Saclay/INSERM), CRICS-TRIGERSEP Network (F-CRIN), 104 boulevard Raymond Poincaré, 92380 Garches, France. ² Intensive Care Unit, CHU F. Bourguiba, Monastir, Tunisia. ³ Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium. ⁴ Medical ICU, Peking Union Medical College Hospital, 1 Shuai Fu Yuan, 100730 Beijing, China. ⁵ Section of Anaesthetics, Pain Medicine and Intensive Care, Imperial College London, London, UK. ⁶ Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile. ⁷ UAMS College of Pharmacy, Little Rock, AR, USA. ⁸ Section of Acute Care Surgical Services, Surgical/Trauma Critical Care, Barnes Jewish Hospital, St. Louis, MI, USA. ⁹ Department of Intensive Care, The Queen Elizabeth Hospital School of Medicine, University of Adelaide, Adelaide, SA, Australia. ¹⁰ School of Epidemiology and Preventive Medicine, Monash University, Victoria, Australia. ¹¹ Centre for Heart Lung Innovation, St. Paul's Hospital, University of British Columbia, 1081 Burrard Street, Vancouver, BC, Canada. ¹² Sound Critical Care, Sound Physicians, Houston, TX, USA.

Acknowledgements

ACG is funded by an NIH Research Professorship award (RP-2015-06-018).

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 Kasei 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.

Received: 20 March 2018 Accepted: 22 May 2018

Published online: 4 June 2018

References

- Goodman and Gilman's (2011) Pharmacological Basis of Therapeutics Twelfth (ed). New York
- Rhodes A, Evans LE, Alhazzani W et al (2017) Surviving sepsis campaign: international guidelines for the management of sepsis and septic shock: 2016. *Intensive Care Med* 43:304–377
- Aguilera G, Rabadan-Diehl C (2000) Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: implications for stress adaptation. *Regul Pept* 96(1–2):23–29
- Yamamoto K, Ikeda U, Okada K et al (1997) Arginine vasopressin increases nitric oxide synthesis in cytokine-stimulated rat cardiac myocytes. *Hypertension* 30(5):1112–1120
- Rudichenko VM, Beierwaltes WH (1995) Arginine vasopressin-induced renal vasodilation mediated by nitric oxide. *J Vasc Res* 32(2):100–105
- Landry DW, Levin HR, Gallant EM et al (1997) Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 95(5):1122–1125
- Landry DW, Levin HR, Gallant EM et al (1997) Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 25(8):1279–1282
- Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA (2001) The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. *Intensive Care Med* 27(8):1416–1421
- Malay MB, Ashton RC Jr, Landry DW, Townsend RN (1999) Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma* 47(4):699–703
- Patel BM, Chittock DR, Russell JA, Walley KR (2002) Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 96(3):576–582
- Siami S, Polito A, Porcher R et al (2013) Thirst perception and osmoregulation of vasopressin secretion are altered during recovery from septic shock. *PLoS One* 8(11):e80190
- Boucheix OB, Milano SP, Henriksson M, Reinheimer TM (2013) Selepressin, a new V1A receptor agonist: hemodynamic comparison to vasopressin in dogs. *Shock* 39(6):533–538
- Asfar P, Russell JA, Tuckermann J, Radermacher P (2016) Selepressin in septic shock: a step toward decatecholaminization? *Crit Care Med* 44(1):234–236
- Russell JA, Vincent JL, Kjolbye AL et al (2017) Selepressin, a novel selective vasopressin V1A agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients. *Crit Care* 21(1):213
- He X, Su F, Taccone FS, Laporte R et al (2016) A selective V(1A) receptor agonist, selepressin, is superior to arginine vasopressin and to norepinephrine in ovine septic shock. *Crit Care Med* 44(1):23–31
- Maybauer MO, Maybauer DM, Enkhbaatar P et al (2014) The selective vasopressin type 1a receptor agonist selepressin (FE 202158) blocks vascular leak in ovine severe sepsis*. *Crit Care Med* 42(7):e525–e533
- Farmakis D, Alvarez J, Gal TB et al (2016) Levosimendan beyond inotropy and acute heart failure: evidence of pleiotropic effects on the heart and other organs: an expert panel position paper. *Int J Cardiol* 222:303–312
- Annane D, Bellissant E, Cavaillon JM (2005) Septic shock. *Lancet* 365(9453):63–78
- Boldt J, Menges T, Kuhn D, Diridis C, Hempelmann G (1995) Alterations in circulating vasoactive substances in the critically ill—a comparison between survivors and non-survivors. *Intensive Care Med* 21(3):218–225
- de Montmollin E, Aboab J, Mansart A, Annane D (2009) Bench-to-bedside review: beta-adrenergic modulation in sepsis. *Crit Care* 13(5):230
- Reynolds RD, Gorczynski RJ, Quon CY (1986) Pharmacology and pharmacokinetics of esmolol. *J Clin Pharmacol* 26(suppl A):A3–A14
- Atarashi H, Kuruma A, Yashima M et al (2000) Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. *Clin Pharmacol Ther* 68(2):143–150
- Page IH, Helmer OM (1940) A crystalline pressor substance (Angiotonin) resulting from the reaction between renin and renin-activator. *J Exp Med* 71(1):29–42
- Rajagopalan S, Kurz S, Münzel T et al (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. *J Clin Invest* 97(8):1916–1923

25. Khanna A, English SW, Wang XS et al (2017) Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 377:419–430
26. Vincent JL, De Backer D (2013) Circulatory shock. *N Engl J Med* 369(18):1726–1734
27. Perez P, Kimmoun A, Blime V, Levy B (2014) Increasing mean arterial pressure in cardiogenic shock secondary to myocardial infarction: effects on hemodynamics and tissue oxygenation. *Shock* 41(4):269–274
28. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR (2013) Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. *Crit Care Med* 41(1):143–150
29. Levy B, Perez P, Perny J, Thivillier C, Gerard A (2011) Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit Care Med* 39(3):450–455
30. Guinot PG, Longrois D, Kamel S, Lorne E, Dupont H (2018) Ventriculo-arterial coupling analysis predicts the hemodynamic response to norepinephrine in hypotensive postoperative patients: a prospective observational study. *Crit Care Med* 46(1):e17–e25
31. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F (2008) Actual incidence of global left ventricular hypokinesia in adult septic shock. *Crit Care Med* 36(6):1701–1706
32. Sun D, Huang A, Mital S et al (2002) Norepinephrine elicits beta2-receptor-mediated dilation of isolated human coronary arterioles. *Circulation* 106(5):550–555
33. Annane D, Vignon P, Renault A et al (2007) Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet* 370(9588):676–684
34. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J, CAT Study investigators (2008) A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med* 34(12):2226–2234
35. Marik PE, Mohedin M (1994) The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA* 272(17):1354–1357
36. van Diepen S, Katz JN, Albert NM et al (2017) Contemporary management of cardiogenic shock: a scientific statement from the American heart association. *Circulation* 136(16):e232–e268
37. Mon W, Stewart A, Fernando R et al (2017) Cardiac output changes with phenylephrine and ephedrine infusions during spinal anesthesia for cesarean section: a randomized, double-blind trial. *J Clin Anesth* 37:43–48
38. Wasilewski MA, Grisanti LA, Song J et al (2016) Vasopressin type 1A receptor deletion enhances cardiac contractility, β -adrenergic receptor sensitivity and acute cardiac injury-induced dysfunction. *Clin Sci* 130(22):2017–2027. <https://doi.org/10.1042/CS20160363>
39. Bouferrache K, Amiel JB, Chimot L et al (2012) Initial resuscitation guided by the surviving sepsis campaign recommendations and early echocardiographic assessment of hemodynamics in intensive care unit septic patients: a pilot study. *Crit Care Med* 40(10):2821–2827
40. Schumann J, Henrich EC, Strobl H et al. (2018) Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome. *Cochrane Database of Systematic Reviews*. Issue 1, Art. No.: CD009669
41. Morelli A, Ertmer C, Westphal M et al (2013) Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA* 310(16):1683–1691
42. Aviado DM Jr, Schmidt CF (1957) Effects of sympathomimetic drugs on pulmonary circulation: with special reference to a new pulmonary vasodilator. *J Pharmacol Exp Ther* 120(4):512–527
43. Monnet X, Jabot J, Maizel J, Richard C, Teboul JL (2011) Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. *Crit Care Med* 39(4):689–694
44. Persichini R, Silva S, Teboul JL et al (2012) Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. *Crit Care Med* 40(12):3146–3153
45. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR et al (2017) Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: the vancs randomized controlled trial. *Anesthesiology* 126(1):85–93
46. James A, Amour J (2018) Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: a discussion of the level of evidence. *Anesthesiology* 128(1):228
47. Cheng Y, Pan T, Ge M, et al. (2018) Evaluation of vasopressin for vasoplegic shock in patients with preoperative left ventricular dysfunction after cardiac surgery: a propensity-score analysis. *Shock*. Feb 7. 10.1097/shk.0000000000001114
48. Lewis RJ, Angus DC, Laterre PF et al (2018) Rationale and design of an adaptive phase 2b/3 clinical trial of selepressin for adults in septic shock, Selepressin evaluation program for sepsis-induced shock-adaptive clinical trial. *Ann Am Thorac Soc* 15(2):250–257
49. Gordon AC, Perkins GD, Singer M et al (2016) Levosimendan for the prevention of acute organ dysfunction in sepsis. *N Engl J Med* 375(17):1638–1648
50. De Backer D, Creteur J, Noordally O, Smail N, Gulbis B, Vincent JL (1998) Does hepato-splanchnic V_{O_2}/D_{O_2} dependency exist in critically ill septic patients? *Am J Respir Crit Care Med* 157:1219–1225
51. Hernandez G, Bruhn A, Luengo C et al (2013) Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study. *Intensive Care Med* 39:1435–1443
52. De Backer D, Creteur J, Silva E, Vincent JL (2003) Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Crit Care Med* 31:1659–1667
53. van Haren FM, Rozendaal FW, van der Hoeven JG (2003) The effect of vasopressin on gastric perfusion in catecholamine-dependent patients in septic shock. *Chest* 124:2256–2260
54. Georger JF, Hamzaoui O, Chaari A, Maizel J, Richard C, Teboul JL (2010) Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients. *Intensive Care Med* 36:1882–1889
55. Boerma EC, Ince C (2010) The role of vasoactive agents in the resuscitation of microvascular perfusion and tissue oxygenation in critically ill patients. *Intensive Care Med* 36:2004–2018
56. Jhanji S, Stirling S, Patel N, Hinds CJ, Pearce RM (2009) The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock. *Crit Care Med* 37:1961–1966
57. Dubin A, Pozo MO, Casabella CA et al (2009) Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. *Crit Care* 13:R92
58. Thooft A, Favory R, Salgado DR et al (2011) Effects of changes in arterial pressure on organ perfusion during septic shock. *Crit Care* 15:R222
59. Morelli A, Ertmer C, Rehberg S et al (2008) Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: a randomized, controlled trial. *Crit Care* 12:R143
60. Morelli A, Lange M, Ertmer C et al (2008) Short-term effects of phenylephrine on systemic and regional hemodynamics in patients with septic shock: a crossover pilot study. *Shock* 29:446–451
61. Dubois MJ, De Backer D, Creteur J, Anane S, Vincent JL (2003) Effect of vasopressin on sublingual microcirculation in a patient with distributive shock. *Intensive Care Med* 29:1020–1023
62. Nygren A, Thoren A, Ricksten SE (2009) Vasopressin decreases intestinal mucosal perfusion: a clinical study on cardiac surgery patients in vasodilatory shock. *Acta Anaesthesiol Scand* 53:581–588
63. Boerma EC, van der Voort PHJ, Ince C (2005) Sublingual microcirculatory flow is impaired by the vasopressin-analogue terlipressin in a patient with catecholamine-resistant septic shock. *Acta Anaesthesiol Scand* 49:1387–1390
64. Asfar P, Bracht H, Radermacher P (2008) Impact of vasopressin analogues on the gut mucosal microcirculation. *Best Pract Res Clin Anaesthesiol* 22:351–358
65. Morelli A, Donati A, Ertmer C et al (2011) Short-term effects of terlipressin bolus infusion on sublingual microcirculatory blood flow during septic shock. *Intensive Care Med* 37:963–969
66. Morelli A, Donati A, Ertmer C et al (2011) Effects of vasopressinergic receptor agonists on sublingual microcirculation in norepinephrine-dependent septic shock. *Crit Care* 15:R217
67. Qiu X, Huang Y, Xu J, Qiu H, Yang Y (2014) Effects of terlipressin on microcirculation of small bowel mesentery in rats with endotoxic shock. *J Surg Res* 188:503–509

68. De Backer D, Creteur J, Dubois MJ et al (2006) The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. *Crit Care Med* 34:403–408
69. Enrico C, Kanoore Edul VS et al (2012) Systemic and microcirculatory effects of dobutamine in patients with septic shock. *J Crit Care* 27:630–638
70. Ospina-Tascón GA, García Marin AF, Echeverri GJ et al (1985) Effects of dobutamine on intestinal microvascular blood flow heterogeneity and O₂ extraction during septic shock. *J Appl Physiol* 122:1406–1417
71. Dubin A, Murias G, Sottile JP et al (2007) Effects of levosimendan and dobutamine in experimental acute endotoxemia: a preliminary controlled study. *Intensive Care Med* 33:485–494
72. Morelli A, Donati A, Ertmer C et al (2010) Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. *Crit Care* 14:R232
73. Fuchs C, Ertmer C, Rehberg S (2016) Effects of vasodilators on haemodynamic coherence. *Best Pract Res Clin Anaesthesiol* 30:479–489
74. Webber J, MacDonald A (1993) Metabolic actions of catecholamines in man. *Baillière's Clin Endocrinol Metab* 7:393–413
75. Van den Berghe G, de Zegher F (1996) Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med* 24(9):1580–1590
76. Sharshar T, Annane D (2008) Endocrine effects of vasopressin in critically ill patients. *Best Pract Res Clin Anesthesiol* 22:265–273
77. Bermejo-Martin JF, Andaluz-Ojeda D, Almansa R et al (2016) Defining immunological dysfunction in sepsis: a requisite tool for precision medicine. *J Infect* 72(5):525–536
78. Parissis JT, Adamopoulos S, Antoniades C et al (2004) Effects of levosimendan on circulating pro-inflammatory cytokines and soluble apoptosis mediators in patients with decompensated advanced heart failure. *Am J Cardiol* 93(10):1309–1312
79. Russell JA, Fjell C, Hsu JL et al (2013) Vasopressin compared with norepinephrine augments the decline of plasma cytokine levels in septic shock. *Am J Resp Crit Care Med* 188(3):356–364
80. Russell JA, Walley KR (2010) Vasopressin and its immune effects in septic shock. *J Innate Immun* 2(5):446–460
81. Gamper G, Havel C, Arrich J et al (2016) Vasopressors for hypotensive shock. *Cochrane Database Syst Rev* 2:CD003709
82. Gordon AC, Mason AJ, Thirunavukkarasu N et al (2016) Effect of early vasopressin vs norepinephrine on kidney failure patients with septic shock. The Vanish randomised clinical trial. *JAMA* 316(5):509–518
83. Russell JA, Walley KR, Singer J et al (2008) Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 358:877–887
84. Russell JA, Walley KR, Gordon AC et al (2009) Interaction of vasopressin infusion, corticosteroid treatment and mortality of septic shock. *Crit Care Med* 37(3):811–818
85. De Backer D, Biston P, Devriendt J et al (2010) Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 362:779–789
86. Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H (2017) Association Between US norepinephrine shortage and mortality among patients with septic shock. *JAMA* 317(14):1433–1442
87. Belletti A, Benedetto U, Biondi-Zoccai G et al (2017) The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. *J Crit Care* 37:91–98
88. Mehaffey JH, Johnston LE, Hawkins RB et al (2017) Methylene blue for vasoplegic syndrome after cardiac operation: early administration improves survival. *Ann Thorac Surg* 104:36–41
89. Elkayam U, Tasissa G, Binanay C et al (2007) Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J* 153(1):98–104
90. Shah P, Cowger JA (2014) Cardiogenic shock. *Crit Care Clin* 30(3):391–412
91. Aranda JM Jr, Schofield RB, Pauly DF et al (2003) Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. *Am Heart J* 145(2):324–329
92. Harris T, Davenport R, Mak M, Brohi K (2018) The evolving science of trauma resuscitation. *Emerg Med Clin North Am* 36(1):85–106
93. Cannon JW (2018) Hemorrhagic Shock. *N Engl J Med* 378(4):370–379
94. Rossaint R, Bouillon B, Cerny V et al (2016) The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care* 20:100
95. Bayram B, Hocaoglu N, Atilla R, Kalkan S et al (2012) Effects of terlipressin in a rat model of severe uncontrolled hemorrhage via liver injury. *Am J Emerg Med* 30(7):1176–1182
96. Cohn SM, McCarthy J, Stewart RM et al (2011) Impact of low-dose vasopressin on trauma outcome: prospective randomized study. *World J Surg* 35(2):430–439
97. Westermann I, Dunser MW, Haas T et al (2007) Endogenous vasopressin and copeptin response in multiple trauma patients. *Shock* 28(6):644–649
98. Hylands M, Toma A, Beaudoin N et al (2017) Early vasopressor use following traumatic injury: a systematic review. *BMJ Open* 7(11):e017559
99. Plurad DS, Talving P, Lam L et al (2011) Early vasopressor use in critical injury is associated with mortality independent from volume status. *J Trauma* 71(3):565–570 **[discussion 570–572]**
100. Sperry JL, Minei JP, Frankel HL (2008) Early use of vasopressors after injury: caution before constriction. *J Trauma* 64(1):9–14
101. Ponikowski P, Voors AA, Anker SD et al (2016) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC) Developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J* 37(27):2129–2200
102. Excellence NIfHaC (2016) Sepsis : recognition, assessment and early management. In: sepsis: recognition, Assessment and early management. London.
103. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F (2008) Actual incidence of global left ventricular hypokinesia in adult septic shock. *Crit Care Med* 36(6):1701–1706
104. Hollenberg SM (2009) Inotrope and vasopressor therapy of septic shock. *Crit Care Clin* 25(4):781–802 **[ix]**
105. LeDoux D, Astiz ME, Carpati CM, Rackow EC (2000) Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med* 28:2729–2732
106. Bourgoin A, Leone M, Delmas A, Garnier F, Albanese J, Martin C (2005) Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. *Crit Care Med* 33:780–786
107. Asfar P, Meziani F, Hamel JF et al (2014) High versus low blood-pressure targets in patients with septic shock. *N Engl J Med* 370:1583–1593
108. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 330(24):1717–1722
109. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA, Emergency Medicine Shock Research Network (EMShockNet) Investigators (2010) Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 303(8):739–746
110. Jansen TC, van Bommel J, Schoonderbeek FJ et al (2010) LACTATE study group: early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 182:752–761
111. Teboul JL, Saugel B, Cecconi M et al (2016) Less invasive hemodynamic monitoring in critically ill patients. *Intensive Care Med* 42:1350–1359
112. Cecconi M, De Backer D, Antonelli M et al (2014) Consensus on circulatory shock and hemodynamic monitoring. task force of the European society of intensive care medicine. *Intensive Care Med* 40:1795–1815
113. Merouani M, Guignard B, Vincent F et al (2008) Norepinephrine weaning in septic shock patients by closed loop control based on fuzzy logic. *Crit Care* 12:R155

114. Hammond DA, McCain K, Painter JT et al (2017) Discontinuation of vasopressin before norepinephrine in the recovery phase of septic shock. *J Intensive Care Med* 2017:885066617714209
115. Bissell BD, Magee C, Moran P, Bastin MLT, Flannery AH (2017) Hemodynamic instability secondary to vasopressin withdrawal in septic shock. *J Intensive Care Med* 2017:885066617716396
116. Annane D, Sébille V, Duboc D et al (1998) Incidence and prognosis of sustained arrhythmias in critically ill patients. *Am J Respir Crit Care Med* 178(1):20–25
117. Kido K, Guglin M (2017) Drug-induced takotsubo cardiomyopathy. *J Cardiovasc Pharmacol Ther* 22(6):552–563