Clinical Management of Endotoxemia: Vasoactive and Cardiostimulant Drugs

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9.1 Introduction

Endotoxin has well-known vasoplegic and cardiodepressant effects. All of the information on vasopressors and inotropes provided in this chapter apply to all patients with distributive or cardiogenic shock, including endotoxemic patients.

Vasopressors induce vasoconstriction, thereby limiting vasoplegia and elevating mean arterial pressure (MAP), while inotropes increase cardiac contractility. These drugs are routinely used in clinical practice to control tissue perfusion in patients with shock.

Endotoxemic patients may develop septic shock, which is a complex condition characterized by circulatory, cellular, and metabolic abnormalities usually associated with adverse patient outcomes. Septic shock is defined by persistent hypotension requiring vasoactives to maintain a mean arterial pressure of 65 mmHg or higher and a serum lactate level above 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

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Under these circumstances, besides antibiotics administration and source control (i.e., etiological treatments of infection and sepsis), fluid resuscitation, vasopressors, and inotropes are the cornerstone of hemodynamic support in patients with septic shock.

9.2 Vasoactive Agents

According to the Surviving Sepsis Guidelines [1], norepinephrine is recommended as the first-line vasopressor for treating hypotension in patients with endotoxic shock. It acts on both alpha-1 and beta-1 adrenergic receptors, thus producing vasoconstriction and an increase in cardiac output (see after). Being an alpha-1 vasopressor, norepinephrine increases MAP during endotoxic shock without any concomitant increase in heart rate. Furthermore, its beta-1 adrenergic effect could increase myocardial contractility and improve cardiac function during septic shock. Norepinephrine may improve coronary artery perfusion in patients who were previously hypotensive by increasing diastolic arterial pressure. Finally, the increase in arterial pressure may increase left ventricular afterload, thus inducing the Anrep response (i.e., a physiological response of the ventricle resulting in increased intrinsic contractility) [2]. In addition, patients with hypotensive septic shock admitted to the intensive care unit (ICU) commonly have reduced ventriculo-arterial coupling with a marked decrease in arterial elastance. In fact, left ventricular systolic performance, while influenced by arterial pressure, is also determined by ventriculo-arterial coupling, which reflects the relationship between the left ventricular contractility (end-systolic elastance) and the arterial vascular stiffness (arterial elastance) [3–5]. Thus, if ventriculo-arterial coupling is either too large or too small, poor left ventricular performance or left ventricular failure may occur, and this ratio is independently influenced by both arterial elastance and end-systolic elastance (Fig. 9.1). Norepinephrine has been shown to increase arterial elastance in septic

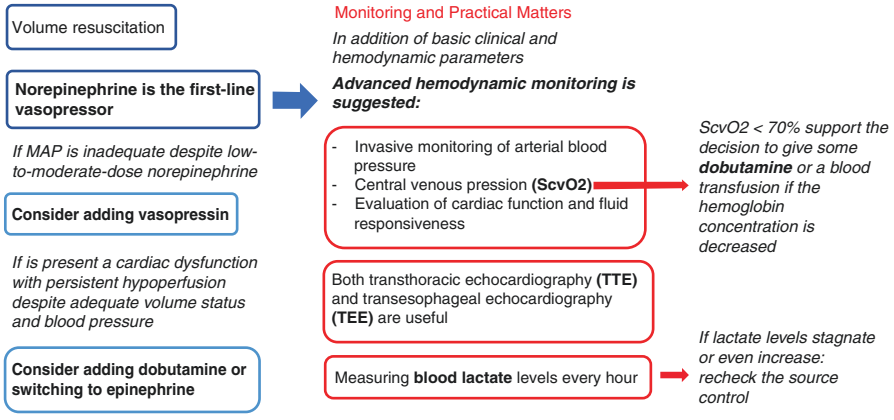

Fig. 9.1 Vasoactive agents management in endotoxic shock

patients with increased cardiac output when the ratio of arterial to end-systolic elastance is normalized. In fact, in the setting of reduced baseline arterial elastance, norepinephrine-increased arterial elastance improves left ventricular ejection by restoring normal coupling quantified as an increased stroke volume despite a small increase in arterial pressure [6–8].

In patients with endotoxic-associated vasoplegic distributive shock, norepinephrine increases stressed volume by decreasing unstressed circulatory volume; this effect would increase mean systemic pressure for the same total blood volume. In preload responsive patients, this mechanism will increase the pressure gradient for venous return, improve blood flow back to the heart, and increase cardiac output. Finally, through its alpha- and beta-adrenergic effects, norepinephrine may induce immunoparalysis. While alpha adrenergic receptors result into both pro- and anti-inflammatory actions, beta-adrenergic stimulation exerts anti-inflammatory effects [9–11].

Norepinephrine is more effective than dopamine and is nowadays suggested as the first-line vasoconstrictor for septic shock. A systematic review and meta-analysis [12] including 32 trials (total of 3544 patients) is cited in the SSC [1]. Compared to dopamine, norepinephrine was associated with a decrease in all-cause mortality and a lower risk of major adverse events and cardiac arrhythmias. No other mortality benefit was demonstrated for the comparisons between norepinephrine and epinephrine, phenylephrine and vasopressin/terlipressin. Hemodynamic data were similar between the different vasopressors, with some advantage for norepinephrine in central venous pressure, urinary output, and blood lactate levels. Evidence suggests that norepinephrine, as compared with dopamine, is associated with survival benefit, improved hemodynamic profile, and reduced adverse event rate. Although the beta-1 activity of dopamine may be useful in patients with myocardial dysfunction, the increased risk of arrhythmias limits its use.

Targeted continuous intravenous infusion is suggested for norepinephrine to maintain hemodynamic targets during septic shock. However, considering the numerous side effects associated with the pharmacological stimulation of adrenergic receptors (including increased oxidative stress, interaction with cellular energy metabolism, and/or modulation of the inflammatory response), a new concept called "decatecholaminization" has recently emerged, which involves use of non-catecholamine vasopressors to decrease catecholamine exposure [13]. Many studies reveal that high doses of administered catecholamines and high levels of circulating catecholamines are associated with poor outcomes and serious side effects, including myocardial injury and peripheral ischemia. Although necessary and life-saving in the early fight or flight reaction to any insult, prolonged adrenergic stress is harmful and contributes to organ dysfunction in septic shock. While high catecholamine levels could be a marker of disease severity, they may also be a perpetrator of other organ dysfunctions. To minimize catecholamine dosing, in addition to volemic adjustment and optimization of sedatives and other hypotensive/myocardial depressant agents, a combination of vasopressor drugs is recommended [14].

Studies as VANISH [15] and VASST [16] have demonstrated the catecholamine-sparing effect of vasopressin in sepsis and septic shock. Early use of vasopressin in

combination with norepinephrine may help reduce the adrenergic burden associated with traditional vasoactive agents. Vasopressin (antidiuretic hormone) binds V1 receptors on vascular smooth muscle, resulting in vasoconstrictive activity and increased arterial blood pressure. These studies show that vasopressin concentration is elevated in the early stages of septic shock but decreases to normal range in most patients between 24 and 48 h as shock continues. This finding has been called "relative vasopressin deficiency" as vasopressin should be elevated in the presence of hypotension. The significance of this finding is unknown. If MAP is inadequate despite low-to-moderate dose norepinephrine, addition of vasopressin is suggested. The VANCS study [17] suggests that vasopressin can be used as a first-line vasopressor agent in postcardiac surgery vasoplegic shock and improves clinical outcomes.

For adults with endotoxin-induced cardiac dysfunction and signs of persistent hypoperfusion despite adequate fluid resuscitation and arterial blood pressure, dobutamine may be administered with norepinephrine or epinephrine may be used as an alternative to norepinephrine. In patients with septic shock and persistent hypotension despite treatment with norepinephrine and vasopressin, addition of epinephrine is suggested. Furthermore, epinephrine has been suggested as a second or third-line vasopressor for patients with septic shock.

No randomized controlled trial compared dobutamine with placebo in patients with severe sepsis and septic shock. In an indirect comparison, a network meta-analysis showed that dobutamine with norepinephrine had no clear impact on mortality compared to no inotropic agents [18]. No evidence supported the superiority of dobutamine over epinephrine. Therefore, the SSC [1] considered the desirable and undesirable consequences to be comparable for both drugs and issued a weak recommendation to add dobutamine or switch to epinephrine in patients with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate fluid status and MAP [19, 20].

Selepressin is a highly selective V1 agonist that has been studied for administration in septic shock in two randomized trials [21, 22]. Selepressin has been shown to effectively maintain MAP > 60 mmHg without co-administration of norepinephrine. Unfortunately, the follow-on phase of the study was stopped for futility, with no significant differences between any of the key endpoints (ventilator- and vasopressor-free days, 90-day all-cause mortality, 30-day RRT-free days, 30-day ICU-free days); adverse event rates were also similar between groups [22]. A meta-analysis of the two studies showed no significant differences in mortality [1]. Since selepressin failed to demonstrate clinical superiority over norepinephrine, the SSC [1] considered the desirable and undesirable consequences to be in favor of norepinephrine and issued a weak recommendation against the use of selepressin as first-line therapy. Selepressin does not induce release of the procoagulant Willebrand factor; unlike the mixed vasopressin type 1a receptor/vasopressin type 2 receptor agonist arginine vasopressin, the selective vasopressin type 1a receptor agonist FE202158 does not release von Willebrand factor. Also, it is not currently commercially available.

In the SSC [1], weak recommendations are available for other drugs to be used in combination with vasoactive and inotropic drugs, such as angiotensin II, terlipressin, and levosimendan.

Angiotensin II is a physiologic substance with marked vasoconstrictor effects, triggered through stimulation of the renin-angiotensin system. The endotoxin associated with Gram-negative sepsis has the potential to inactivate the angiotensin-converting enzyme. In diseases affecting the pulmonary capillary endothelium, such as acute respiratory distress syndrome (ARDS) due to endotoxinemia and pneumonia sustained by gram negative bacteria, angiotensin-converting enzyme activity is altered at an early stage, resulting in a reduced ability to convert Angiotensin I to Angiotensin II. Angiotensin II is antagonized by the endogenous vasodilator, nitric oxide (NO), and each has a role in influencing the production and function of the other. A meta-analysis found no difference in mortality rates between angiotensin II and norepinephrine [1]. There was no clear increase in adverse events associated with use of angiotensin II. In the ATHOS-3 study [23], angiotensin II effectively increased blood pressure in patients with vasoplegic shock who did not respond to high doses of conventional vasopressors. Since the available evidence is of very low quality and clinical experience in sepsis and, therefore, demonstration of safety remains limited, the panel considered that angiotensin should not be used as a first-line agent. However, having demonstrated physiological efficacy, it could have a role as an adjunctive drug to provide a "balanced" approach to vasopressor therapy [24].

Terlipressin is a prodrug that is converted to vasopressin lysine by endothelial peptidases, producing a "slow-release" effect and giving an effective half-life of about 6 h. Terlipressin is more specific for the V1 receptors and has been studied in nine clinical trials of patients with sepsis, with or without cirrhosis. The SSC meta-analysis [1] showed no difference in mortality, but an increase in adverse events such as digital ischemia was observed in patients receiving terlipressin; diarrhea was also more common in the terlipressin group. There were three cases of mesenteric ischemia in the terlipressin group compared with one in the norepinephrine group. Therefore, the panel considered the undesirable consequences to be higher with terlipressin and made a weak recommendation against its use in patients with septic shock [25].

Levosimendan acts on the cardiovascular system through various mechanisms. The main indication for its use is acute heart failure. In septic shock, it is a second-line drug. Its use is currently encouraged in cases of acute heart failure where β-blockers are suspected of contributing to the state of hypoperfusion. A certain degree of septic heart disease is common in advanced stages of septic shock and contributes to the persistence of hypotension, in which cases the use of levosimendan may be indicated [26]. To date, trials comparing levosimendan with dobutamine are scarce, and do not show a clear mortality advantage. Patients with severe septic shock often require very high doses of norepinephrine to reach the target MAP, thus potentially leading to adverse side effects. In this kind of patients, levosimendan may provide a "catecholamine-sparing effect" [27]. The half-life of levosimendan is approximately 1 h; its active metabolite can reach 80 h, leading to persistence of cardiovascular effects for approximately 7–9 days after discontinuation of a 24-h infusion.

9.3 Use in Clinical Practice

The dose-response curves of vasopressors and inotropes depend on the hematic concentration of the drug. However, their hemodynamic effects depend on multiple factors, including the high interpersonal variability of receptors, pharmacodynamic interaction, and strong reliance on the patient's clinical, hemodynamic, and pharmacological status. Furthermore, these drugs act on different receptors involved in different hemodynamic responses and may have both direct and indirect effects through activation of the autonomous system. Close multiparametric hemodynamic monitoring should be carried out when administering vasopressor and cardiostimulant infusions in patients with endotoxic shock [28, 29].

Assessment of volemic status is crucial, and adequate resuscitation of intravascular volume should be obtained before vasopressor prescription. Early goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand [30, 31].

The resuscitation phase should be followed by an optimization phase in which the objective of treatment is to ensure adequate transport of O_2 to the peripheral organs to prevent organ damage related to hypoperfusion and/or edema. In the optimization phase, advanced hemodynamic monitoring is suggested which may include, in addition to basic clinical and hemodynamic parameters (diuresis and water balance), central venous pressure, evaluation of cardiac function and fluid responsiveness.

Despite concerns about the studies on early targeted therapy, monitoring of central venous oxygen saturation ($ScvO_2$) is suggested, because a low value (<70%) may assist in the decision to give some dobutamine or a blood transfusion if the hemoglobin concentration has decreased.

Measuring blood lactate levels every hour after shock development is useful to determine the decrease due to clearance. If lactate levels stagnate or even increase, it would be necessary to reassess source control.

Basic (Rapid) Assessment by Cardiac Echo (RACE) plays a particularly pivotal role in the hemodynamic evaluation of septic shock. An analytical study of sepsis in the MIMIC-III database showed that CCUS can effectively reduce the 28-day mortality rate of critically ill patients with sepsis. Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) should be available, the latter being considered part of today's technologically advanced physician's armamentarium. Besides guiding the de-escalation phase, which follows the optimization phase, hemodynamic monitoring should minimize flow and assess the need for negative water balance in case of fluid overload [32, 33].

Because of considerable variability in cardiovascular effects (arrhythmias, ischemia, hypertension or hypotension), use of these drugs should be guided by the results of continuous hemodynamic monitoring.

The dose should be titrated up to achieve effective blood pressure or end-organ perfusion, as evidenced by criteria such as urine output or mental status. If the maximal dose of a first agent is inadequate, then a second drug should be added to the

first (Fig. 9.2). In situations where this is ineffective, such as refractory septic shock, anecdotal reports describe the addition of a third agent, although no controlled study has demonstrated the utility of this approach [1].

These drugs can be administered intravenously either as a bolus dose or by continuous infusion. A central venous catheter must be used to avoid extravasation and subsequent tissue necrosis. Low-dose administration through a peripheral venous catheter over a limited period has been shown to be safe.

Responsiveness to these drugs may decrease over time due to tachyphylaxis. Doses should be constantly titrated to adapt to this phenomenon and changes in the patient's clinical condition.

Dosage increase should not be attempted simply because of persistent or worsening hypotension, without reconsidering the patient's clinical situation and the appropriateness of the current strategy.

Finally, few clinical studies have been conducted to compare the efficacy and safety of one drug versus another and determine whether their use improves patient outcomes [34]. Decision to use these drugs is therefore based on expert opinion, considering their molecular mechanism of action and according to evidence derived from the few currently available clinical studies [35, 36].

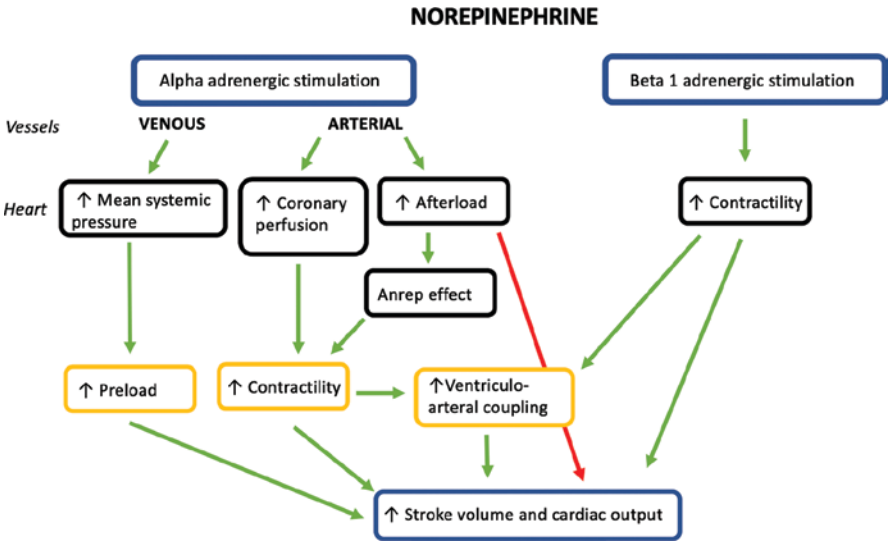

Fig. 9.2 Schematic representation of the potential mechanisms by which norepinephrine might increase cardiac output and stroke volume in patients with sepsis and septic shock. Blue boxes represent the primary receptor stimulation, black boxes their immediate effect in the heart, and yellow boxes the functional impact of those effects. The green arrows represent the positive consequences while the red ones represent the negative consequences compared to the effects present in the boxes

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