Inotropes and vasopressors use in cardiogenic shock: when, which and how much?

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Purpose of review
Data and interventional trials regarding vasopressor and inotrope use during cardiogenic shock are scarce. Their use is limited by their side-effects and the lack of solid evidence regarding their effectiveness in improving outcomes. In this article, we review the current use of vasopressor and inotrope agents during cardiogenic shock.

Recent findings
Two recent Cochrane analyses concluded that there was not sufficient evidence to prove that any one vasopressor or inotrope was superior to another in terms of mortality. A recent RCT and a meta-analysis on individual data suggested that norepinephrine may be preferred over epinephrine in patients with cardiogenic shock . For inotrope agents, when norepinephrine fails to restore perfusion, dobutamine represents the first-line agent. Levosimendan is a calcium sensitizer agent, which improves acute hemodynamics, albeit with uncertain effects on mortality.

Summary
When blood pressure needs to be restored, norepinephrine is a reasonable first-line agent. Dobutamine is the first-line inotrope agent wheraes levosimendan can be used as a second-line agent or preferentially in patients previously treated with beta-blockers. Current information regarding comparative effective outcomes is nonetheless sparse and their use should be limited as a temporary bridge to recovery, mechanical circulatory support or heart transplantation.

Keywords
cardiogenic shock inotropes, norepinephrine, vasopressors

INTRODUCTION

Cardiogenic shock is defined as a state of critical end-organ hypoperfusion because of primary cardiac dysfunction. Cardiogenic shock forms a spectrum ranging from mild hypoperfusion to profound shock [1▪▪]. Established criteria for the diagnosis of cardiogenic shock are: SBP less than 90 mmHg or need of vasopressor therapy to achieve a blood pressure at least 90 mmHg; pulmonary congestion or elevated left-ventricular filling pressures; signs of impaired organ perfusion in a normovolemia or hypervolemia state, with at least one of the following criteria: altered mental status; cold, clammy skin; oliguria; and increased serum lactate. The diagnosis of cardiogenic shock can usually be made on the basis of easy-to-assess clinical criteria without advanced hemodynamic monitoring with the exception of echocardiography. Certain clinical trial criteria have also included hemodynamic parameters, such as reduced cardiac index (*CI*, i.e. <1.8 or <2.2 l/min/m^2 with cardiac support) or elevated left ventricular filling pressures (i.e. pulmonary capillary wedge pressure >15 mmHg [1▪▪]. Vasopressors and inotropes are administered in almost 90% of patients with cardiogenic shock with a positive class IIb recommendation and level of evidence C in United States and European guidelines [2▪,3].

In this article, we will review the use of vasopressors and inotrope agents for the treatment of acute cardiogenic shock mainly based on recent literature.

CARDIOGENIC SHOCK PHYSIOPATHOLOGY AND CARDIOVASOACTIF AGENT USE

Our understanding of the complexity and pathophysiology of cardiogenic shock has evolved over the past 2 decades [4]. Classically, there is a

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Curr Opin Crit Care 2019, 25:384–390
DOI:10.1097/MCC.0000000000000632

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KEY POINTS

- There is limited information about comparative efficacy among pharmacological vasoactive agents used in cardiogenic shock.
- The utilization of vasopressors and inotropes is recommended as a temporary measure as a bridge to recovery, mechanical circulatory support or heart transplantation. Inotropes and vasopressors should be used at the lowest dose and shortest time span possible.
- The combination of norepinephrine–dobutamine is generally recommended as a first-line strategy.
- Levosimendan should be considered as a second-line therapy in well selected patients with cardiogenic shock.

profound depression of myocardial contractility resulting in a potentially deleterious spiral of reduced cardiac output, low blood pressure and further coronary ischemia, followed by additional reductions in contractility [5], a cycle, which can lead to death. This classic paradigm also includes compensatory, albeit pathological systemic vasoconstriction resulting from acute cardiac injury and ineffective stroke volume. Therefore, in this setting of low cardiac output syndrome, the use of inotropes is fully justified. The so-called new paradigm states that patients with cardiogenic shock exhibit a decrease in vascular resistance through numerous pro-inflammatory pathways including the nitric oxide pathway but also the over-production of peroxynitrite and cytokines, thus leading to an indication of vasopressor therapy in these patients. From pathophysiological data, the first conclusion is that agents that exhibit both inotropic and vasopressor effects are likely the most indicated in cardiogenic shock treatment. Nevertheless, all of the potentially useful agents have deleterious side effects that must be taken into account.

THE USE OF ADRENERGIC AGENTS

The use of catecholamines is considered to be the angular stone of hemodynamic cardiogenic shock treatment. This therapeutic class includes dopamine, epinephrine, norepinephrine and phenylephrine [6▪]. All of these molecules increase mean arterial pressure (MAP) by stimulating the α_1 adrenergic receptor. Nevertheless, aside from phenylephrine, which is a pure alpha-1 vasoconstrictor, all of the above catecholamines stimulate other adrenergic receptors leading to various hemodynamic, metabolic, and inflammatory effects. Comparison of the affinity of these different drugs for receptor subtypes as well as the effects associated with receptor stimulation is depicted in Table 1 [7]. Hence, the choice of best adrenergic agent should take into account not only its cardiac effect but also its vascular, metabolic, microcirculatory, and immune effects.

CURRENT RECOMMENDATIONS

First, it is important to highlight that vasoactive trials in cardiogenic shock have historically been difficult to perform. Therefore, current recommendations are mainly based on meta-analyses and expert opinions. The French, Scandinavian and German recommendations are very similar and unanimously recommend norepinephrine and dobutamine as first-line agents [3,8,9]. A Scientific Statement from the American Heart Association [1▪▪] surprisingly continues to advocate dopamine use in cardiogenic shock. Two

Table 1. Vasopressors and inotropes drugs used in cardiogenic shock

Drug	Mechanism/receptor	MAP	HR	CO	Therapeutic dose
Potential recommended drugs for improving hemodynamics in cardiogenic shock					
Norepinephrine	α1+++, β1 +	↑↑	⇔ or ↓	↑	0.05–1 μg/kg/min
Dobutamine	β1 ++	⇔ or ↓	↑↑	↑↑	2–20 μg/kg/min
Levosimendan	Calcium sensitizer	⇔ or ↓	↑↑	↑↑	0.5–2 μg/kg/min
Enoximone	PDE-3 inhibitor	⇔ or ↓	↑	↑↑	0.125–0.75 μg/kg/min
Generally nonindicated drugs for improving hemodynamics in cardiogenic shock					
Epinephrine	α1+++, β1 +++, β2 ++	↑↑	↑↑	↑↑	0.1–1 μg/kg/min
Dopamine	β1 +++, α1++	↑	↑↑↑	↑	5–20 μg/kg/min
Vasopressin	V1 (Vascular smooth muscle cell)	↑↑	⇔ or ↓	⇔ or ↓	0.01–0.04 UI/min

Adapted from ref. [7]. CO, cardiac output; HR, heart rate; MAP, mean arterial pressure. ⇔: no change; ↓: decrease; ↑: increase.

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recent Cochrane analyses concluded that there was not sufficient evidence to prove that any one vasopressor or inotrope was superior to another in terms of mortality and that the choice of a specific agent may, therefore, be individualized and left to the discretion of treating physicians [10▪,11]. Finally, despite low levels of evidence, an expert recommendation was published based on the physiological effects of vasopressors/inotropes and selection of inotrope/vasopressor combinations in cardiogenic shock outlined in an extensive number of literature reviews [12▪▪].

NOREPINEPHRINE AS A FIRST-LINE AGENT

Norepinephrine is a very potent and reliable vasopressor with interesting inotropic properties. The use of vasopressor agents during severe and hypotensive cardiogenic shock is justified by the fact that, for many patients, the adequacy of end-organ blood flow is roughly correlated with blood pressure, with low blood pressures being associated with an increased risk of mortality [13]. Norepinephrine is a very potent and reliable vasopressor. It increases MAP without any concomitant increase in heart rate. Generally, cardiac index is increased because of a direct effect on cardiac myocytes as a result of β1 adrenergic receptor stimulation. Norepinephrine has numerous advantages when compared with other vasopressors, including: a very potent vasopressor effect equivalent to epinephrine and phenylephrine and greater than dopamine [14]; contrary to epinephrine, norepinephrine does not act on β2 adrenergic receptors, hence lactate levels do not increase and may be used to guide resuscitation [15]; contrary to dopamine and epinephrine, norepinephrine increases cardiac index without increasing heart rate, and thus without excessively increasing myocardial oxygen consumption [16]; contrary to phenylephrine, which acts only on α1 adrenergic receptors, norepinephrine also acts on cardiac β1 adrenergic receptor, and may therefore preserve ventricular–arterial coupling [17]. Norepinephrine and epinephrine [18] are currently the most commonly used vasopressor agents in cardiogenic shock [13,18–21]. Studies comparing epinephrine and norepinephrine in patients with septic shock found no significant differences in outcome [22]. Nevertheless, these drugs may have certain specific effects in patients with cardiogenic shock that could influence outcome. To illustrate the latter, the Optima CC study compared epinephrine and norepinephrine in myocardial infarction complicated by cardiogenic shock [23▪▪]. This double-blind, multicenter and randomized study included 57 patients. With regard to study drugs, the dose needed to obtain a MAP of 70 mmHg was 0.7 ± 0.5 μg/kg/min in the epinephrine group and 0.6 ± 0.7 μg/kg/min in the norepinephrine group ($P = 0.66$). For the primary efficacy endpoint, cardiac index (*CI*) increased similarly between the 2 groups ($P = 0.43$) from H0 to H72 (Fig. 1). However, for the main safety endpoint, the observed higher incidence of refractory shock in the epinephrine group (10/27 (37%) versus norepinephrine 2/30 (7%) ($P = 0.008$) led to the early termination of the study. Heart rate increased significantly with epinephrine from H2 to H24 while remaining unchanged with norepinephrine ($P < 0.0001$). Mean pulmonary artery pressure ($P = 0.48$) and pulmonary occlusion pressure (PAOP) ($P = 0.38$) evolved similarly between both groups. Lastly, left ventricular ejection fraction (LVEF) progressively increased in a similar manner between both groups ($P = 0.87$). Several metabolic changes were unfavorable to epinephrine compared with norepinephrine including an increase in cardiac double product ($P = 0.0002$) and lactic acidosis from H2 to H24 ($P < 0.0001$) (Fig. 1). Therefore, the authors concluded that in patients with cardiogenic shock secondary to AMI, the use of epinephrine when compared with norepinephrine was associated with similar effects on arterial pressure and *CI* and a higher incidence of refractory shock. These results were substantiated by a meta-analysis of individual data constituting 2583 patients, including the above 57 patients, in which the primary outcome was short-term mortality [24▪]. The main result was that in this very large cohort, epinephrine use for hemodynamic management of cardiogenic shock patients was associated with a three-fold increase in risk of death. Thus, from a physiological standpoint, a drug (epinephrine) that increases myocardial oxygen consumption (as assessed by the increase in double product) and increases lactate level (and therefore, confounds the interpretation of lactate clearance as a marker of restored systemic perfusion) without any advantages on arterial pressure restoration, oxygen delivery and organ failure is therefore, not a good choice to treat patients with cardiogenic shock . Finally, in the most recent recommendations, norepinephrine is recommended as the first-line inopressor in cardiogenic shock whereas epinephrine use is conversely not recommended.

DOPAMINE AND VASOPRESSIN SHOULD NOT BE USED IN CARDIOGENIC SHOCK

Dopamine has been shown to be associated with increased 28-day mortality as compared with norepinephrine, although this effect may be explained

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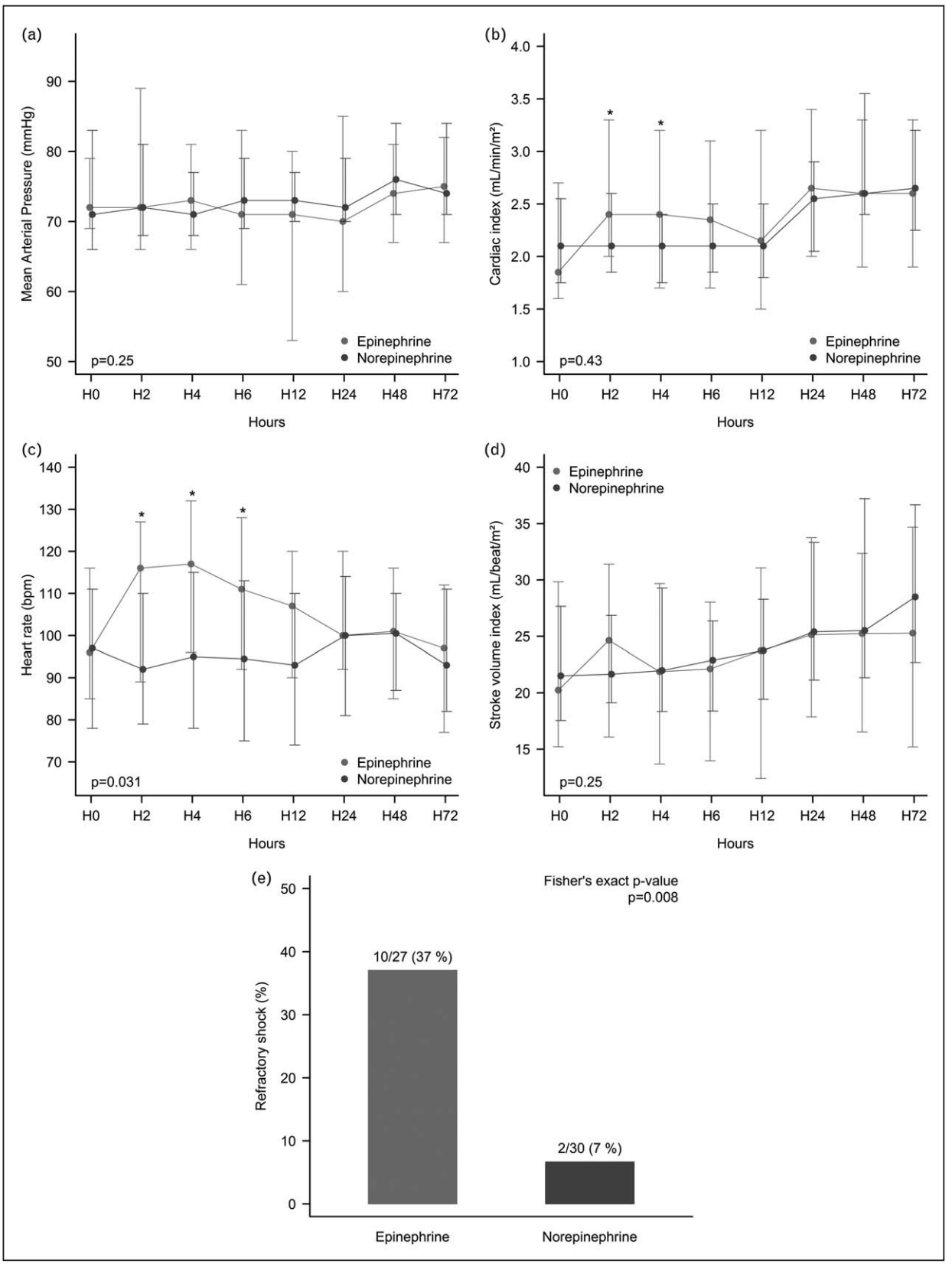

FIGURE 1. Epinephrine versus norepinephrine in cardiogenic shock after acute myocardial infarction. Compared effects on hemodynamics and refractory shock incidence. Reproduced with permission from [23▪▪].

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by chance [16]. In this multicenter, randomized trial, 1679 patients, of whom 858 were assigned to dopamine and 821 to norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure. There was no significant between-group difference in the rate of death at 28 days (52.5% in the dopamine group and 48.5% in the norepinephrine group). However, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine [207 events (24.1%) versus 102 events (12.4%), $P < 0.001$]. A subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock but not among the 1044 patients with septic shock or the 263 with hypovolemic shock ($P = 0.03$ for cardiogenic shock, $P = 0.19$ for septic shock, and $P = 0.84$ for hypovolemic shock, in Kaplan–Meier analyses). Finally, a recent meta-analysis revealed that norepinephrine was associated with a lower 28-day mortality, a lower risk of arrhythmic events as well as lower gastrointestinal reaction when compared with dopamine. This superiority of norepinephrine over dopamine was observed irrespectively of whether or not cardiogenic shock is caused by coronary heart disease. Vasopressin is also not recommended [25] as this drug has no inotropic properties, and therefore, does not improve cardiac power index and *CI* whereas norepinephrine increases the latter [26]. Vasopressin use may be advocated during right ventricular failure as it does not increase pulmonary arterial pressure [27].

To summarize, when blood pressure needs to be rapidly restored, norepinephrine is a reasonable first-line agent. Clinical evidence suggests that clinicians should integrate clinical, laboratory and hemodynamic multimodal monitoring to determine patient response to therapy and drug titrations. Norepinephrine should be started at a low dose (0.1 μg/kg/min) and increased to obtain a MAP at about 65–70 mmHg. After having stabilized arterial pressure, the clinician must subsequently evaluate if norepinephrine alone was able to reverse the signs of hypoperfusion (low cardiac output, low SVO_2, hyperlactatemia, mottling, oliguria) [1▪▪].

If not, given the reduced cardiac output in cardiogenic shock, the addition of an inotropic agent may help to improve stroke volume after hemodynamic stabilization with norepinephrine. If norepinephrine fails to increase MAP, the use of a mechanical circulatory support should be discussed.

DOBUTAMINE AS A FIRST-LINE INOTROPE

Currently, there are no studies comparing pure inotrope or inodilator drugs during cardiogenic shock . In clinical practice, three agents can be used: dobutamine, which is a pure inotrope, as well as levosimendan and phosphodiesterase inhibitors (IPDE), both of which are inodilators. Interestingly, these three drugs act through different pathways. Dobutamine is a predominantly beta-1-adrenergic agonist, with weak beta-2 and alpha-1 activity. IPDE prevents the degradation of cyclic adenosine mono-phosphate (cAMP). In the myocardium, elevated levels of cAMP activate protein kinase A, which in turn phosphorylates calcium channels, increasing the influx of calcium into the cardiomyocyte, and promotes contractility. In smooth muscle, elevated cAMP inhibits myosin light chain kinase, producing arterial and venous vasodilation. Levosimendan is a calcium-sensitizing agent that binds to cardiac troponin C in a calcium-dependent manner. It also has a vasodilatory effect in vascular smooth muscle by opening adenosine triphosphate-sensitive potassium channels [7].

On the basis of clinical experience, availability and costs, dobutamine is generally recommended as first-line therapy. In cardiogenic shock , dobutamine has been shown to significantly increase heart rate, cardiac index and SVO_2 while decreasing both PAOP and lactate. Conversely, enoximone or milrinone was found not to significantly increase heart rate while decreasing PAOP and increasing cardiac index, as well as to neither increase SVO_2 nor decrease lactate levels [28,29▪]. Finally, both dobutamine and milrinone 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 [29▪].

LEVOSIMENDAN AS A SECOND-LINE THERAPY

On the basis of expert's opinions, the combination of norepinephrine–dobutamine is generally recommended as a first-line strategy. Dobutamine acts by stimulating cardiac beta-1-adrenergic receptors, increasing contractility, heart rate and myocardial oxygen consumption with limited effects on arterial pressure. In addition, dobutamine may increase the incidence of atrial/ventricular arrhythmias and extension of ischemia. Unlike traditional inotropes, such as dobutamine, levosimendan neither increases myocardial oxygen consumption nor impairs diastolic function or possess pro-arrhythmic effects. It could, therefore, represent an ideal agent in cardiogenic shock as it improves myocardial contractility without increasing cAMP or calcium concentration. Additionally, levosimendan, which has

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a long-lasting action (up to 7–9 days) resulting from the formation of active metabolite, can be used as a single 24 h perfusion. Lastly, levosimendan also has an anti-inflammatory effect via the reduction of pro-inflammatory cytokine and oxidative stress marker levels. Moreover, levosimendan acts independently of beta receptor activation, and is therefore, not sensitive to the action of beta-blockers or desensitization [30▪].

Levosimendan is also an activator of adenosine triphosphate (ATP)-sensitive potassium channels in smooth muscle cells, thus resulting in vasodilatation [31▪]. In the setting of cardiogenic shock , especially in vasoplegic patients or in vasopressor-dependent patients, this effect may be associated with hypotension leading to increased vasopressor dose. Finally, the very long half-life of levosimendan is a double-edged sword. On the one hand, its properties render its use particularly interesting for weaning patients from intravenous inotropes; on the other hand, once levosimendan has begun, it may be difficult to rapidly reverse the vasodilation.

Levosimendan has been tested in large RCTs against dobutamine or placebo in patients with decompensated heart failure [32], septic shock [33] and low cardiac output syndrome after cardiac surgery [34] but never in cardiogenic shock . One major point immediately stands out when reviewing the literature is that there is currently no high-quality study assessing the use of levosimendan in cardiogenic shock . Moreover, all of the meta-analyses were performed using only a few studies with a high risk of bias [10▪]. When analyzing the aforementioned data, it is clear that, when compared with dobutamine, levosimendan has no effect on short-term and long-term mortality, ischemic events, acute kidney injury, dysrhythmias or hospital length of stay [10▪]. On the other hand, levosimendan appears to be well tolerated at the expense of an increased vasopressor dose. Major hemodynamic changes include an increase in *CI* and cardiac power index, a decrease in left ventricular pressure and an increase in SVO_2 [35]. Finally, based on a low-quality study, levosimendan appears to be more efficient in refractory cardiogenic shock secondary to myocardial infarction when compared with enoximone. In cardiogenic shock , levosimendan may result in higher CO and lower cardiac preload compared with dobutamine.

Altogether, despite very promising properties and based on current evidence, levosimendan should be considered as a second-line therapy in well selected patients with cardiogenic shock. The conducting of well designed RCT is nevertheless warranted to address the gap between the potential use of levosimendan in cardiogenic shock and definitive proof. The role and place of levosimendan in this setting will be evaluated in the LevoHeartShock study, which will include 634 patients in France.

CONCLUSION

When and which drug

In hypotensive patients, the use of norepinephrine is recommended before the use of inotrope, including in the prehospital setting, the emergency room and the catheterization lab. In myocardial infarction-associated cardiogenic shock , patients should benefit as early as possible from prehospital management with norepinephrine and coronary revascularization [12▪▪]. In the ICU, a complete hemodynamic point should be performed including cardiac output measurement, SVO_2 or $SVCO_2$, venoarterial CO_2 difference and lactate level [1▪▪]. In case of persistence of hypoperfusion signs, dobutamine should be added to norepinephrine. In previously beta-blocked patients or in patients demonstrating catecholamine-related side effects (from excessive tachycardia to adrenergic cardiomyopathy), levosimendan could represent a good option especially if cardiac output and heart rate did not increase after a dobutamine test.

How much

In general, inotropes and vasopressors should be used at the lowest dose and shortest time span possible. Thus, as soon as the therapeutic objectives have been reached, the treating clinician should reduce the dose in conjunction with close clinical, biological and hemodynamic monitoring. Importantly, when shock becomes refractory (sustained hypotension despite high vasopressor/inotrope doses, hyperlactatemia, organ failure particularly kidney and liver failure), the use of a mechanical circulatory support instead of increasing or adding drugs should be promptly discussed [36▪]. There is no accurate threshold of norepinephrine dose in the literature for defining the refractory nature of cardiogenic shock. Nevertheless, the use of cardiac assistance should be evoked early and, in all cases before the onset of kidney and/or liver failure. Finally, recent data have suggested a beneficial role of cardiac assistance, in particular in using temporary left ventricular assist device when implanted early in order to unload the left ventricle and to decrease catecholamine requirements [37▪].

Acknowledgements

None.

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Financial support and sponsorship

None.

Conflicts of interest

B.L. received honoraria from Orion, Novartis, Gettinge, Amomed and A.K. received honoraria from Baxter, MSD, Gilead.

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