REVIEW

Inotropic agents in cardiogenic shock

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Purpose of review
Cardiogenic shock is a multifactorial and diverse entity in which inotropes are the cornerstone therapy. Although published clinical trials have focused on pharmacologic treatment of cardiogenic shock, there is lack of an established and widely accepted decision-making algorithm on the use of inotropic agents in cardiogenic shock.

Recent findings
The current review incorporates cardiogenic shock pathophysiology, inotropes and vasopressors pharmacodynamics. It emphasizes on each agent's indications, potential adverse effects, highlights special considerations and fsummarizes the recent guidelines.

Summary
Finally, proposes an algorithm of inotropes and vasopressors use and their potential combinations based on the clinical stage of cardiogenic shock. This algorithm can be used as a guide during the initial management of cardiogenic shock while underlying cause investigation is underway.

Keywords
algorithm, cardiogenic shock, inotropes, vasopressors

INTRODUCTION

Cardiogenic shock is defined as a state of decreased cardiac function that leads to a cascade of diminished cardiac output, end-organ hypoperfusion and tissue hypoxia. Importantly, it should be viewed as a spectrum of severe hemodynamic abnormalities with resultant clinical manifestations that range from a preshock state to fulminant cardiovascular collapse [1]. Definition of cardiogenic shock has evolved through the years from an earlier pure hemodynamic definition to recently adopted more practical definitions based on simple clinical evaluations that can be obtained even outside critical care settings owing to the contribution of landmark contemporary trials and international guideline updates [2▪,3,4,5]. Low SBP is a diagnostic criterion for cardiogenic shock, defined as SBP less than 90 mmHg for at least 30 min or the need for mechanical or pharmacological support to achieve the goal SBP of 90 mmHg. End-organ hypoperfusion is usually manifested by altered mental status, cool extremities, serum lactate of at least 2 mmol/l, and reduced urine output (<30 ml/h). Hemodynamic parameters although not considered as a prerequisite for the diagnosis of cardiogenic shock, they are commonly used in the critical care setting to confirm diagnosis if shock cardiac index (*CI*) is 2.2 l/min/m^2 or less and pulmonary capillary wedge pressure is at least 15 mmHg.

Inotropes play a key role in the physician's armamentarium when managing a patient with cardiogenic shock [5,6▪]. They are pharmacologic agents with positive inotropic effect that are used as first-line pharmacotherapy for cardiogenic shock in the inpatient setting. Due to their unfavorable adverse effect profile (most importantly arrhythmogenesis and myocardial ischemia) inotropes are administered as short-term therapy, while prolonged administration should be avoided as possible. In the present manuscript, we will review the use of inotropes in

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KEY POINTS

- Cardiogenic shock is an heterogenous entity, which requires tailored and targeted management.
- A world-wide accepted decision-making algorithm on the management of cardiogenic shock is missing.
- The mainstay of therapy for cardiogenic shock is the use of inotropes.
- Dobutamine and norepinephrine is the preferable initial pharmacological combination.
- Specific inotrope and vasopressor combinations based on the clinical stage of cardiogenic shock can be used as guidance.

cardiogenic shock based on recent literature with a focus on providing tips for the selection of the most appropriate agent according to the specific profile of cardiogenic shock patient.

PATHOPHYSIOLOGY

Pathophysiology of cardiogenic shock extends far beyond the basic mechanism of severe cardiac dysfunction leading to severely compromised central and peripheral hemodynamics [7]. In more detail, the inciting event that triggers the development of cardiogenic shock is an acute decrease or worsening of the cardiac contractility. As myocardial contractile dysfunction progresses, cardiac output rapidly decreases further, leading to severely reduced SBP with resultant compromise in coronary perfusion. This promotes coronary hypoperfusion resulting into myocardial ischemia, which further contributes to myocardial contractile dysfunction in a self-perpetuating vicious cycle of cardiogenic shock. Parallel to the severe myocardial contractile dysfunction, peripheral vasoconstriction that acts initially as a compensatory mechanism of the peripheral vasculature to maintain adequate perfusion pressures, ultimately increases myocardial workload thereby further promoting the self-perpetuating cycle of decreased myocardial contractility, ischemia and vasoconstriction, which rapidly spirals until the cardiovascular system as a whole collapses. Because of the principal cardiogenic shock pathophysiology as an acute severe low cardiac output syndrome, inotropes are a key component of its therapeutic management. Further to traditional considerations regarding the pathophysiology of cardiogenic shock, recently emerging data have highlighted the contribution of pro-inflammatory mechanisms in cardiogenic shock development. Various pro-inflammatory pathways have been shown to be activated in cardiogenic shock including the nitric oxide (NO) pathway, which lead to over secretion of inflammatory mediators, molecules, and cytokines all of which act directly and/or indirectly on the vasculature leading to decreased vascular resistance in the extreme end of refractory cardiogenic shock and circulatory collapse [2▪]. Therefore, in view of a pathophysiologic component of cardiogenic shock that predisposes to evolving and even overt vascular paralysis in its extreme end, vasopressors are also indicated in cardiogenic shock. Conclusively, agents that potentially combine inotropic and vasopressor properties could be 'ideal' pharmacologic molecules for the treatment of cardiogenic shock patients.

GUIDELINES

Clinical research in the field of inotropic agents in cardiogenic shock has been devoid of robust data largely because of the difficulty in designing and performing trials with inactive treatment arms in this population. Therefore, recommendations for the use of inotropes in cardiogenic shock in guidelines and consensus documents have relied mostly on metanalyses of smaller nonrandomized clinical studies and expert opinion data [8▪,9]. Current consensus depicted in the recent ESC heart failure guidelines and other European national recommendations, favors norepinephrine and dobutamine as first line agents in cardiogenic shock [5,10,11]. However, recent data from two Cochrane database systematic reviews failed to demonstrate superiority of any agent compared with the others regarding mortality, with the investigators concluding that the choice of agent should be highly individualized based on the specific patient profile [12,13]. Possibly the high heterogeneity of patients with cardiogenic shock may have contributed to the inconclusive results of clinical studies in this field [14,15]. According to current recommendations, inotropes and vasopressors should be used as a short-term therapy in hypotensive patients (SBP <90 mmHg) with signs and/or symptoms of persistent peripheral hypoperfusion despite adequate volume resuscitation (Class IIB, LoE C) (Table 2) [5].

CLASSICAL INOTROPES

Inotropes and inodilators that are widely available for use in patients with cardiogenic shock are categorized in three pharmacologic groups according to their mechanism of action: adrenergic agonists, phosphodiesterase III inhibitors, and calcium sensitizers. Recommended dosing, and main characteristics of most frequently utilized inotropic agents are shown in Tables 1 and 2.

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Table 1. Pharmacological characteristics of classic and new inotropes

Inotrope/vasopressor	Mechanism of action	Hemodynamic effects					Indications	Adverse effects
		Inotropy	Vasoconstriction	Vasodilation	Blood pressure	Diuretic effect		
Beta agonist								
Dobutamine	B1>b2>a1	↑↑	↑ Increased doses	↑	↑	↔	Hypotension, acute cardiorenal syndrome, cardiogenic shock of ischemic cause, CABG, sepsis related cardiogenic shock	Tachyarrhythmias, hypotension, headache, (rarely) eosinophilic myocarditis, peripheral blood eosinophilia
Norepinephrine	B1>a>b2	↑	↑↑	↔	↑	↑	Hypotension, sepsis-related cardiogenic shock	Tachyarrhythmias, hypertension, headache
Epinephrine	B1 = b2>a	↑↑	↑↑ Increased doses	↑	↔/↑	↔	ACLS	Tachyarrhythmias, headache, anxiety, cold extremities, pulmonary edema, cerebral hemorrhage,
Dopamine	Dopa>a, b in high doses	↑↑	↑↑ Increased doses	↑↑ decreased doses	↑ Increased doses	↑↑ decreased doses	Hypotension, acute cardiorenal syndrome	Tachyarrhythmias, hypertension, myocardial ischemia
PDE III inhibitor								
Milrinone	PDE III inhibition	↑	↔	↑↑	↓	↔	Beta-blockade, pHTN, CABG	Tachyarrhythmias, hypotension, headache
Ca sensitizer								
Levosimendan	Calcium sensitizer, PDE III inhibition, opening of vascular K_{atp} channels Inhibition in high doses	↑	↔	↑↑	↓	↑	Beta-blockade, pHTN, acute cardiorenal syndrome, cardiogenic shock of ischemic cause, CABG, sepsis-related cardiogenic shock	Hypotension, atrial and ventricular tachyarrhythmias, headache

ACLS, advanced cardiac life support; CABG, coronary artery bypass grafting.

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Table 2. Indications and dosing of inotropes

Inotrope/ vasopressor	Dosing	Recommendation/ LoE
Beta agonist		
Dobutamine	2–20 μg/kg/min (-) bolus dose	IIb/C
Norepinephrine	0.2–10 μg/kg/min (-) bolus dose	IIb/C
Epinephrine	0.05–0.5 μg/kg/min (+) bolus dose: 1 mg intravenously every 3–5 min during resuscitation	IIb/C
Dopamine	Renal effect <3 μg/kg/min, inotropic effect 3–5 μg/kg/min, vasoconstriction 5 μg/kg/min (-) bolus dose	IIb/C
PDE III inhibitor		
Milrinone	0.375–0.75 μg/kg (+) bolus dose: 25–75 μg/kg over 10–20 min (optional)	IIb/C
Ca sensitizer		
Levosimendan	0.05–0.2 μg/kg (+) bolus dose 12 μg/kg over 10 min (optional, not routinely recommended)	IIb/C

ADRENERGIC AGENTS

Dobutamine

Dobutamine exerts its positive inotropic effect predominantly by acting on the beta1 adrenergic receptor of the myocardial cells. In addition to that, dobutamine also affects the vasculature to a significantly lesser effect via its effect on the beta2 and alpha1 adrenergic receptors of the smooth muscle cells leading to vasodilation and thus reduction of afterload. On the basis of the above effects of dobutamine, one can mechanistically understand its role in patients in cardiogenic shock, especially in cases of significantly decreased cardiac output [8▪]. Additionally, it has been demonstrated that in cardiogenic shock, dobutamine augments the *CI* and decreases lactate and pulmonary capillary wedge pressure (PCAWP) albeit in the expense of increasing the heart rate [16,17]. As a result, it is considered the initial agent of choice in most cases of cardiogenic shock. However, physicians should be aware of its adverse effect profile largely and should use for the shortest possible duration of therapy since its use for long-term has been associated with increased mortality [6▪], hospital readmission and in-hospital mortality rates [18], arrhythmias [2▪] and eosinophilic myocarditis [19,20]. Lastly, practical limitations with the use of dobutamine are its possible suboptimal effect in patients receiving chronic b-blockade and its gradually decreasing potency with time, a phenomenon known as tachyphylaxis [6▪,21].

PHOSPHODIESTERASE III INHIBITORS

Milrinone

Milrinone enhances myocardial contractility by inhibiting phosphodiesterase III, the enzyme that is responsible for the degradation of cyclic adenosine monophosphate (cAMP), thus increasing the amount of intracellular camp [22]. The increased amounts of cAMP lead to increased phosphorylation of calcium influx channels via protein kinase A. As a result, intracellular calcium concentration rises promoting actin–myosin cross bridging leading to enhanced cardiomyocyte contractility. Therefore, because of the independence of mechanism of action of milrinone from the beta-adrenergic pathway, it is considered an attractive inotropic agent especially in cardiogenic shock patients receiving chronic beta-blockade [23]. In addition, milrinone acts simultaneously on the vascular bed where it promotes cAMP synthesis which inhibits activation of myosin light chain in the vascular smooth muscle cells. Through this action, milrinone causes peripheral arterial vasodilation, and therefore, usually reduces SBP [2▪]. Central hemodynamic effects of milrinone include increase in *CI* and reduction in PCWP, while it has been shown to have a neutral effect on the heart rate and lactate levels in cardiogenic shock patients [17,18]. Similar to other inotropes, milrinone has also been shown to be associated with adverse long-term cardiovascular effects [24,25]. Specifically, in the OPTIME-CHF trial,

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milrinone was not proven to be superior to placebo in terms of reduction of medium-term mortality or heart failure hospitalizations whereas it was associated with increased rates of arrhythmogenesis and hypotension [26,27]. Practically, milrinone can be used as an alternative to dobutamine in cases of patients receiving chronic beta-blockade and in patients with not severely reduced SBP (SBP 85–90 mmHg) in conjunction with a vasoconstrictor to counteract its peripheral vasodilatory effect [6▪].

CALCIUM SENSITIZERS

Levosimendan

Levosimendan is an inotropic agent with potentially promising properties based on its mechanism of action, especially for cardiogenic shock patients. Levosimendan acts by increasing the sensitivity of cardiomyocyte troponin C to existing amounts of intracellular calcium, therefore, enhancing myocardial contractility. Because of its neutral effect on intracellular calcium concentration, levosimendan does not appear to increase myocardial oxygen demand and consumption, and does not cause major electrolyte shifts that have been associated with the arrhythmogenic profile of the other classical inotropes [2▪]. Therefore, these properties appear attractive in the high-risk cardiogenic shock population. Furthermore, becauseof the long half-life of its active metabolite (7–9 days), levosimendan is particularly useful when attempting to wean patients off inotropes. Another effect of levosimendan that appears attractive in the setting of cardiogenic shock is its previously shown anti-inflammatory properties. Specifically, it has been shown to reduce inflammatory mediators and markers of oxidative stress in acute heart failure patients [28–30]. Importantly, its mechanism of contractile enhancement does not involve the beta-adrenergic pathway, and therefore, similarly to milrinone, it is preferable than beta adrenergic inotropes in cardiogenic shock patients who are chronically receiving beta blockers. As levosimendan activates the ATP-sensitive K channels of the smooth muscle cells of peripheral arterial vasculature, it has a net vasodilatory effect [6▪,31,32]. Therefore, in cardiogenic shock patients, levosimendan is administered in combination with a vasopressor. Lastly, another favorable pharmacologic property of levosimendan is the absence of of tachyphylaxis [33▪].

Levosimendan has been tested is several randomized clinical trials in acute heart failure. Early studies (LIDO, RUSSLAN) demonstrated its superiority over dobutamine in terms of improvement of hemodynamic parameters, mortality and heart failure worsening [34,35]. However, in subsequent large trials (SURVIVE, REVIVE-II) the earlier promising results were not replicated. In SURVIVE trial, 6-month mortality rates did not differ significantly between AHF patients randomized to the levosimendan versus dobutamine arm [36]. Also, in REVIVE-II, although levosimendan was shown to improve heart failure symptoms, it was not associated with any mortality benefit, while it led to increased rates of arrhythmias and hypotension compared with placebo [37]. However, no large-scale trials have been performed with levosimendan in patients with cardiogenic shock and only data from systematic reviews and metanalyses of smaller studies are currently available to assist our understanding of its possible role for the treatment of cardiogenic shock patients. Although levosimendan has been shown to improve hemodynamic parameters in cardiogenic shock patients (including increased *CI*, SVO_2, and decreased LV pressure) [38], these improvements have not been translated into improvement of clinical endpoints compared with dobutamine as demonstrated by a recent Cochrane analysis [12]. As a result, levosimendan is widely considered as a second-line inotropic agent that can be used in selected patients with cardiogenic shock that includes patients with hypoperfusion that can be attributed to beta-blockade [5].

VASOPRESSORS

Norepinephrine

Norepinephrine is a widely used vasopressor in cardiogenic shock that also exhibits positive inotropic properties [39]. It acts on the alpha1 adrenergic receptors of the vasculature, thereby exerting a potent vasopressive effect with resultant increase of blood pressure. Additionally, it stimulates the beta1 adrenergic receptors on cardiomocytes leading to enhanced contractility but not in the expense of prominently increased heart rate that may lead to increased oxygen consumption. This characteristic of norepinephrine makes it a useful tool in the management of cardiogenic shock compared with other vasopressors, such as dopamine and epinephrine [40]. In cardiogenic shock patients, norepinephrine is usually administered in conjunction with a more potent inotropic agent or an inodilator to mitigate the relative hypotensive effect of the latter [6▪]. As discussed below, an increasing amount of data supports the

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superiority of norepinephrine compared with other vasopressors in AHF and cardiogenic shock, rendering it the clear first-line agent.

Norepineprhine versus dopamine

Dopamine acts by regulating a multitude of receptors of the cardiovascular system depending on its dose: dopaminergic type 1, dopaminergic type 2, alpha 1 adrenergic, and beta 1 adrenergic receptors. Despite its supposed favorable effect on the renal vasculature, there are no data to support its use over norepinephrine [41]. The SOAP-II trial included 1679 patients with shock who were randomized either to dopamine or to norepinephrine as first-line vasopressor agent. Although mortality was comparable between the two groups, adverse events including arrhythmias were significantly more frequent in the dopamine arm (24.1 versus 12.4%, $P < 0.001$). Additionally, in a subsequent post hoc analysis of SOAP-II, it was shown that, in the subgroup of cardiogenic shock patients, norepinephrine was superior to dopamine with respect to mortality reduction ($P = 0.03$) [40].

Norepinephrine versus epinephrine

Epinephrine is an intrinsic catecholamine that when administered at usual doses (>0.2 μg/kg/min) stimulates beta 1 adrenergic and alpha 1 adrenergic receptors resulting in increased contractility and peripheral and pulmonary vasoconstriction, respectively. However, clinical studies have shown that epinephrine is inferior to norepinephrine in cardiogenic shock patients. In detail, a pilot study by Levy *et al.* has compared the addition of either epinephrine or norepinephrine to dobutamine in patients with cardiogenic shock. Whereas hemodynamic effects were similar between the two combinations, the safety profile of the epinephrine group was significantly worse, with higher rates of arrhythmias, lactic acidosis, gastric hypoperfusion, and tachycardias compared with the norepinephrine group [42]. Another study by the same group has compared (OPTIMA CC) the use of epinephrine versus norepinephrine in 57 patients with cardiogenic shock secondary to acute myocardial infarction. In terms of efficacy endpoints, the two agents had comparable outcomes, both increasing the *CI* and LVEF by a similar amount. However, the significant differences were identified in the safety profile of the two regimens, with the rate of refractory shock being considerably higher in the epinephrine versus the norepinephrine group (27 versus 7%, respectively, $P = 0.008$), leading to the premature termination of the OPTIMA CC trial [43]. Lastly, an recent individual patient data metanalysis by Leopold *et al.* that included 2583 patients with cardiogenic shock demonstrated a three-fold increase in the risk of death in patients who received epinephrine versus other drug regimens [OR (95% CI), 3.3 (2.8–3.9)] [44].

Norepinephrine versus vasopressin

Vasopressin acts by binding on a G-protein coupled V1 receptor of the smooth muscle cells of the vasculature, leading to increased influx of calcium in the cells thus leading to vasoconstriction. Vasopressin does not possess any inotropic properties, which theoretically renders it inferior vasopressor to norepinephrine in cardiogenic shock, where enhancement of cardiac output is needed [8▪,45,46]. Moreover, vasopressin has been shown to have a more unfavorable safety profile compared with norepinephrine [45]. However, because of its neutral effect on pulmonary resistances and pressures, vasopressin appears to be more attractive in cardiogenic shock patients with predominantly right ventricular failure [47].

On the basis of the multiface entity of cardiogenic shock and the above pharmacological agent mechanisms of action, potential inotropes and vasopressors combinations are shown in Fig. 1.

CONCLUSION

Existing inotropes have been associated with a safety profile that includes a multitude of adverse effects, notably arrhythmias and increased long-term mortality. However, until safer new agents become available, currently used inotropes are still widely used as first-line therapy in cardiogenic shock. As a general principle, inotropes should be used in the lowest possible dose for the shortest possible duration of time, whereas their administration should be carefully tailored based on patient's hemodynamic and clinical status, aiming to be discontinued when MAP and peripheral perfusion is restored. On the basis of existing data, dobutamine and norepinephrine are first-line inotropic agents, whereas other agents being reserved for specific patient groups. Novel molecules with a more favorable safety profile are needed, as well as more high-quality studies targeted at the cardiogenic shock patient population in an effort to provide adequate

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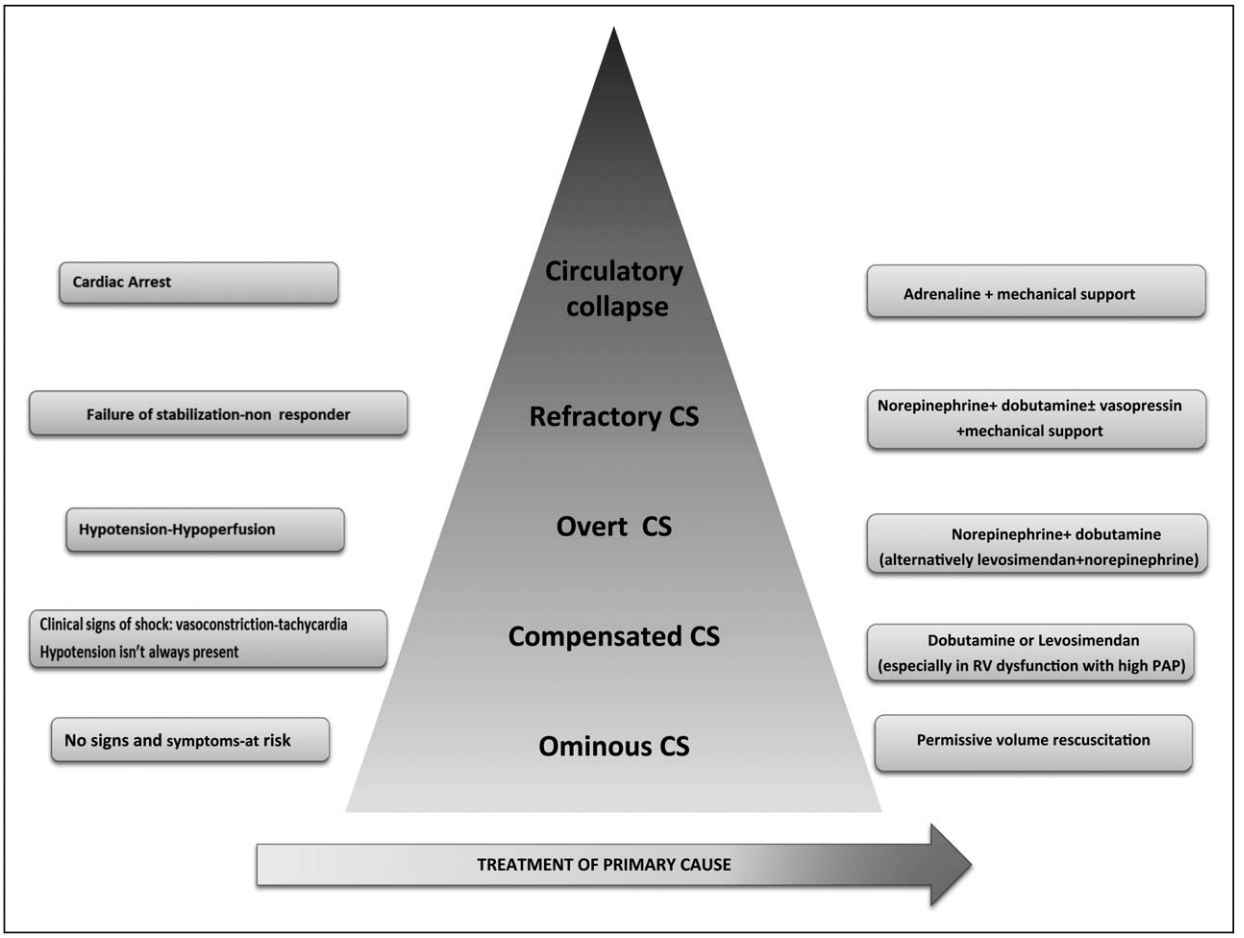

FIGURE 1. Optimal use of intravenous inotropes in the various phases of cardiogenic shock. Current approach for the optimal use of intravenous inotropes and their combinations in the various stages of cardiogenic shock.

care to some of the sickest patients in our healthcare system.

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