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Research paper

The current use of vasoactive agents in cardiogenic shock related to myocardial infarction and acute decompensated heart failure☆

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ABSTRACT

Cardiogenic shock (CS) is a heterogeneous condition associated with exceptionally high mortality rates, despite significant advances in the field of cardiology. The primary causes of CS are myocardial infarction-related CS (AMI-CS) and acute decompensated heart failure-related CS (ADHF-CS). Management of CS is inherently complex, with the initial focus—irrespective of the underlying etiology—centered on preserving end-organ perfusion. Parenteral vasopressors and inotropes are the cornerstone of therapy to achieve this objective. However, data on the comparative efficacy of different vasoactive agents in CS remain limited, and no single agent has demonstrated clear superiority. Recent progress in the staging and phenotyping of CS has provided a framework for more tailored therapeutic approaches. This review offers a comprehensive and updated summary of current evidence on the use of vasopressors and inotropes in AMI-CS and ADHF-CS, including a discussion of specific scenarios, such as right ventricular CS (RV-CS).

1. Background

Cardiogenic shock (CS) is a result of sudden decrease in cardiac function, resulting in a low output state that may evolve into multiorgan hypoperfusion, failure and death [1–3]. The current understanding of CS emphasizes its heterogeneity and spectrum-like nature, encompassing a wide range of clinical presentations.

Due to the myriads of etiologies and clinical phenotypes, the diagnosis and management of CS pose a significant challenge. Numerous imperfect strategies have been identified to tackle this complex state; however, it remains a devastating condition with high mortality rates. Proving robust therapeutic benefit has been difficult due to the inevitable issues brought by the wide variability in CS presentation and the ethical nuances that arise from comparing treatments in a life-threatening situation, resulting in lack of large-scale randomized trials. Evidence regarding the use of inotropic agents in CS is not the exception.

The management of CS in 2024 demands granular knowledge of the tools that the modern cardiologists carry to treat this deadly condition. Therefore, in the amidst of all these fast-paced changes and advances, we are faced with the need to revisit the role of traditional initial therapies in the contemporary management of CS. The use of inotropes and vasopressors is usually the first line of treatment in about 90 % of patients with CS [8–10,81]. Inotropes are agents that are intended to increase cardiac output by enhancing myocardial contractility, while vasopressors increase the vascular tone to rapidly restore blood pressure.

The following content is aimed at providing consolidated, comprehensive and updated evidence of the use of inotropes and vasopressors in the current management of CS.

2. Methods

2.1. Search methods and study selection

A literature search was performed to identify all articles published in English that discussed use of inotropes in cardiogenic shock. A Boolean search of PubMed, Google Scholar, and Cochrane Library was performed

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using the phrases "Cardiogenic shock", "inotropes", "vasopressors", "management of acute myocardial infarction-CS", "management of acute heart failure-CS", "milrinone", "dobutamine", "dopamine", "norepinephrine", "epinephrine", and "levosimendan". The reference lists of included articles were manually reviewed to identify additional articles.

All articles were included if they discussed use of inotropic agents in CS in adults. We excluded articles that pertained non-human research, pediatric population, perioperative period, cardiac surgery, chronic advanced heart failure, chronic use of inotropes, post-heart transplant, transplant rejection, hypothermia and post-cardiac arrest population.

The literature search and screening for eligibility were performed by four of the authors independently.

2.2. Definitions

CS is broadly defined as a state of end-organ hypoperfusion resulting from decreased cardiac output (CO). CS is a heterogeneous entity and definitions both for clinical and research purposes are imperfect. For this review, we will apply the definition of CS proposed in the SHOCK trial [1], which includes the following elements: hypotension (systolic blood pressure of $<$90 mmHg for at least 30 min or the need for supportive measures to maintain a systolic blood pressure of $\geq$90 mmHg), end-organ hypoperfusion (cool extremities or a urine output of $<$30 mL per hour, and a heart rate of $\geq$60 beats per minute), cardiac index (CI) $<$ 2.2 L/min/m^2 (body surface area) and a pulmonary-capillary wedge pressure $\geq$ 15 mmHg, determined to be secondary to cardiac dysfunction. However, we acknowledge the difficulty in defining this entity both for clinical and research purposes.

The term "inotropes" broadly refers to agents that increase myocardial contractility, thereby increasing cardiac output. For practical purposes, these include dobutamine, dopamine, milrinone and levosimendan. The term "vasopressor" refers to an agent with vasoconstrictive effects that increase mean blood pressure (MAP), such as vasopressin and phenylephrine. Norepinephrine and epinephrine are understood as having dual properties of vasopressor and, to a less extent, inotrope ("inopressors"). Finally, "inodilators" are a group of agents with combined inotropic and vasodilatory properties, including dobutamine, milrinone and levosimendan. Phenylephrine is very rarely used in the management of CS due to negative effects on cardiac contractility and will be excluded from this review. It is worth emphasizing that despite the mechanistic distinction into these 3 drug groups, the in-vivo effects are more complex than mere receptor-effector interactions.

3. Discussion

3.1. Epidemiology of CS

3.1.1. Current trends in incidence and prevalence of CS

CS has been recognized as the most severe form of acute heart failure, with a variety of etiologies and carrying a very high mortality. The most frequent cause of CS is acute myocardial infarction (AMI) with left ventricular (LV) dysfunction [1–3,12]. Several studies have reported an incidence rate of 5–10 % in patients presenting with ST-elevation myocardial infarction (STEMI) and 2.5 % in non-STEMI patients which translates to 40,000 to 50,000 patients per year [1–7].

In recent years, the proportion of CS related to AMI (AMI-CS) has decreased to nearly 30 %, while CS secondary to acute decompensated heart failure (ADHF-CS) has increased to rates as high as 50 % of CS admissions [7]. Several multicenter cohort studies have also reported an increasing prevalence of non-AMI-CS cases [7–10]. The decline in the incidence of AMI-CS has been attributed to the increased rate of primary percutaneous coronary intervention (PCI) for AMI [11].

Unfortunately, the overall rate of CS hospitalizations has increased in the recent years. A study using the National Inpatient Sample (NIS) data reported a tripled increase in CS hospitalizations from 2004 to 2018 (122 per 100,000 to 408 per 100,000 in 2018) [4]. A recent retrospective study from Mayo Clinic echoed similar trends with a remarkable 4-fold increase in CS hospitalizations from 5.7 % between 2007 and 2009 to 19.4 % between 2016 and 2018 [10].

3.1.2. Outcomes: Mortality and morbidity rates

CS carries a poor prognosis and remains the leading cause of death in patients with AMI despite revolutionary efforts in management. Before the introduction of the concept of early revascularization by the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial about two decades ago, mortality of CS was close to 80 % despite optimal treatment [1,5].

The ubiquitous adoption of PCI drastically decreased mortality rates of AMI-CS to roughly 50 % [9] The European Card Shock trial and the American registry reported overall CS in-hospital mortality of 31–39 % [9,29]. Consistently, several cohort studies reported improvement in the post-hospitalization mortality for AMI-CS to 30–40 % [6,13], and this trend has also been observed in multicenter CICU studies [14].

Recent findings from the NIS (from 2004 to 2018) showed reduced in-hospital mortality in both AMI-CS (9 % decline) and non-AMI CS (15 % decline) [5]. This consistently declining mortality trend was observed across ethnic groups, genders, different regions of the United States and hospitals of varying sizes. However, a higher mortality rate was observed among women in certain age groups in both AMI-CS (age group 45–64 years old) and non-AMI CS (age group 20 to 44 years old) [5]. Mortality is also higher in AMI-CS as compared to ADHF [15,16]. Finally, there seems to be significantly higher mortality in patients with AMI-CS that develop shock $>$48 h after a MI as compared to those patients that develop early shock post MI [28].

All-in-all, despite the advancements in the management of AMI and CS, and the declining mortality rates, the 1-year mortality in CS patients remain outstandingly high at 58 % [17] and 1 in every 3 CS patient does not survive hospitalization [9]. There is still significant improvement to be made in the management of these patients.

3.2. Risk stratification in CS: A paradigm change and prompt for intervention

There have been numerous attempts at risk stratifying patients with CS. The first attempt at classifying patients with CS and establishing prognosis was proposed by Killip and Kimball in the 1960s [6]. Their system was based on bedside assessment of the initial presentation of patients with acute coronary syndrome and 47 of 250 patients were recognized as AMI-CS, with higher mortality compared to the absence of shock [6]. This initial system evolved into the Forrester-Diamond classification of AMI-CS into hemodynamic phenotypes, correlating clinical presentation with invasive hemodynamic findings through placement of a pulmonary artery catheter. Patients recognized as "cold and wet" (hypoperfusion and pulmonary congestion) were found to have higher mortality [53].

In the more modern days of coronary revascularization in AMI, two risk scores, the IABP-SHOCK II [54] (AMI-CS) and the CardShock [29] (AMI-CS and non-AMI-CS), were developed to evaluate short term mortality. Unfortunately, both scores included multiple variables that are not readily available at time of presentation, and they only showed modest prognostic accuracy upon validation in real life cohorts [29,52]. Table 1 provides a summary of the classification systems that have been proposed over time.

In 2019, the Society for Cardiovascular Angiography and Interventions (SCAI) released a 5-stage classification system (plus cardiac arrest being an ($_A$)Modifier) for evaluating the severity and clinical management of CS. This classification has been endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) [18,19]. This system moved from the classic "wet and cold" stereotypical CS and broadened the definition of CS to a

Table 1
Classification systems proposed for cardiogenic shock over the decades.

Classification system	Type of CS	Variables Included	Main Predictor Outcome	Year
Killip and Kimball [6]	AMI-CS (47 of 250 patients)	Physical exam	In-hospital mortality	1967 (Landmark)
Forrester and Diamond [53]	AMI-CS	Correlation between physical exam and pulmonary artery catheter hemodynamics (Filling pressures and CI)	In-hospital mortality	1977
CardShock score [29]	AMI-CS Non-AMI-CS	Age, confusion (presentation), previous MI or CABG, ACS, LVEF, lactate levels and creatinine (eGFR)	In-hospital and 90-day mortality	2015
IABP-SHOCK II score [54]	AMI-CS undergoing PCI	Age, prior stroke, admission glucose, creatinine and lactate levels, impaired post-PCI coronary flow	30-day mortality	2017
Zweck's Clinical Phenotypes [55]	AMI-CS Non-AMI-CS	Age, comorbidities, blood pressure, invasive hemodynamics (filling pressures, CO/CI), heart rate, hemoglobin, lactate levels, transaminases, creatinine (eGFR). Used machine learning in cluster analysis	In-hospital mortality	2021
SCAI SHOCK classification [18,20]	AMI-CS ADHF-CS Cardiac intensive care unit Out-of-hospital cardiac arrest	Physical exam, blood pressure, heart rate, lactate levels, creatinine (eGFR), BNP, transaminases and pH. May include invasive hemodynamics	In-hospital mortality and 30-day mortality	Presented in 2019 [18] Updated in 2022 with extensive validation [20]

AMI-CS indicates acute myocardial infarction-related cardiogenic shock; ADHF-CS, acute decompensated heart failure-related cardiogenic shock; CO, cardiac output; CI, cardiac index; MI, myocardial infarction; CABG, coronary artery bypass grafting; ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; and BNP, B-natriuretic peptide.

dynamic process.

In 2022, an update to the 2019 consensus was published with incorporation of data from validation studies that confirmed the correlation of the SCAI SHOCK staging system with mortality in all clinical subgroups, including patients with AMI-CS and ADHF-CS [20]. Fig. 1 shows an adapted summary of the most updated version of the SCAI SHOCK classification. One of the most remarkable features of this system is that it allows for recognition of patients in pre-shock state (stages A-B), who carry different prognosis when compared to patients in stages C—D [21]. As delineated in Fig. 1, stage C is the pivotal moment in the continuum of disease for CS patients, when the first intervention (pharmacologic and/or mechanical), beyond fluid resuscitation, must be

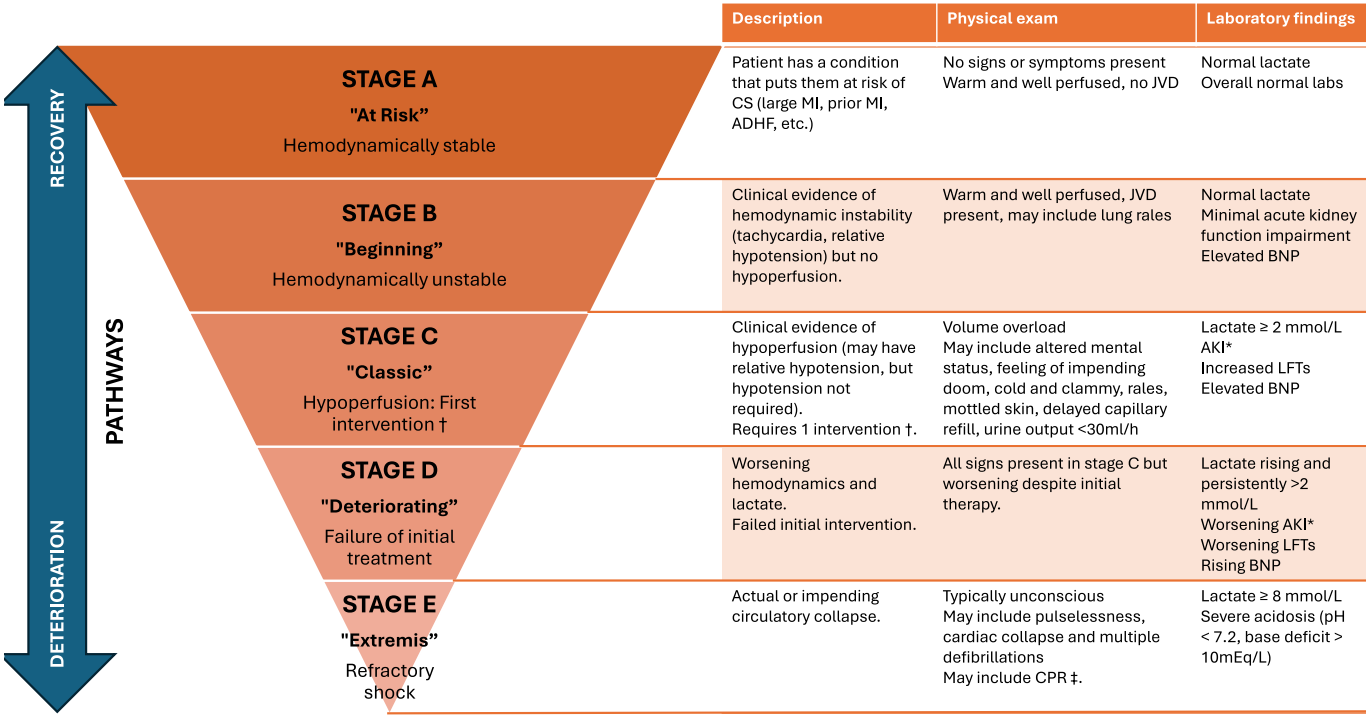


Fig. 1. Society for Cardiovascular Angiography and Interventions (SCAI) SHOCK stages [Adapted from SCAI updated consensus 2021]. After the first publication of this staging system, several trials have validated this classification and have demonstrated the clinical utility in diagnosis and prognosis. Moreover, serial evaluation of the patient with cardiogenic shock helps define the pathways to deterioration and/or recovery, showing the importance of this classification in monitoring and defining course as well as assisting medical decision making.

CS, Cardiogenic shock; ADHF, acute decompensated heart failure, BNP, B-natriuretic peptide; AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; JVD, jugular vein distention; LFTs, liver function tests.

*Defined as creatinine increase to 1.5 x baseline (or 0.3 mg/dL) or > 50 % drop in glomerular filtration rate (GFR).

† Intervention (pharmacological or mechanical) beyond volume resuscitation.

‡ CPR is A-modifier.

implemented. In this regard, the authors make a strong recommendation to monitor hemodynamics invasively in this scenario [20], although discussing the role of invasive hemodynamic monitoring in CS is outside the scope of this review.

Additionally, it is important to notice that patients may need some time in stage C prior to reassessing their trajectory, as the therapeutic intervention is what differentiates stage C from D [20]. Understandably, this "waiting time" may pose a true challenge for the clinical team and strategies to better define how long it is acceptable to wait and what measures to implement in the interim would grant further research.

Along with the above staging, SCAI also proposed a 3-axis prognostic model with enhancing factors that includes shock severity, Zweck's phenotypes of CS [55], and risk modifiers (age, systemic inflammatory response, presence/reversibility of organ failure, comorbidities, frailty, and evidence of anoxic encephalopathy -specifically in the setting of cardiac arrest-). The authors emphasize the need to differentiate "high risk" patients due to severe shock and hemodynamic instability as opposed to "high risk" patients due to non-modifiable risk factors (age, comorbidities, etc.), as these populations do carry different prognosis [20].

The SCAI SHOCK classification is perhaps the most robust attempt at providing clarity to the management of CS. However imperfect, the novelty of this categorization lies on the realistic inclusion of several clinical presentations, allowing clinicians to recognize the variability in presentation and the dynamic changes, while facilitating early diagnosis and treatment initiation and modification.

3.3. Etiology, pathophysiology, hemodynamics and rationale for the use of pharmacologic support

3.3.1. Etiology of CS

Different pathologies may result in CS and their simultaneous treatment is as important as supporting the ventricular function. The most common causes of CS are undoubtedly AMI and ADHF [17]. Less frequent etiologies include myocarditis (multiple etiologies), Takotsubo syndrome, post-partum cardiomyopathy, severe valvular disease, arrhythmias, post-cardiotomy, myocardial contusion, cardiac masses, pulmonary embolism, acute heart transplant rejection, medications (beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, opiates, etc.), among others [17,23]. The specific management of each etiology is outside the scope of this review.

3.3.2. Pathophysiology of CS

In general, CS stems from low CO triggering mechanisms that are initially compensatory and ultimately maladaptive. The hypotension from the cardiac insult and inflammation results in catecholamine surge with vasoconstriction and redistribution of 50 % of the total blood volume from the splanchnic vessels back to the general circulation [23]. There is impairment of macro and microcirculation [22]. There is also activation of the renin-angiotensin-aldosterone system (RAAS) with further vasoconstriction and increase in the renal tubular sodium reabsorption with impaired diuretic efficiency that exacerbate the volume overload [23]. In addition, the high filling pressures result in hypoxia and worsening ventricular ischemia, perpetuating the deleterious cycle [23]. At some point, the severe hypoperfusion overwhelms these compensatory mechanisms causing end-organ damage, acidosis, decreased catecholamine sensitivity and inflammation with release of cytokines, nitric oxide and accumulation of cardiotoxic reactive oxygen

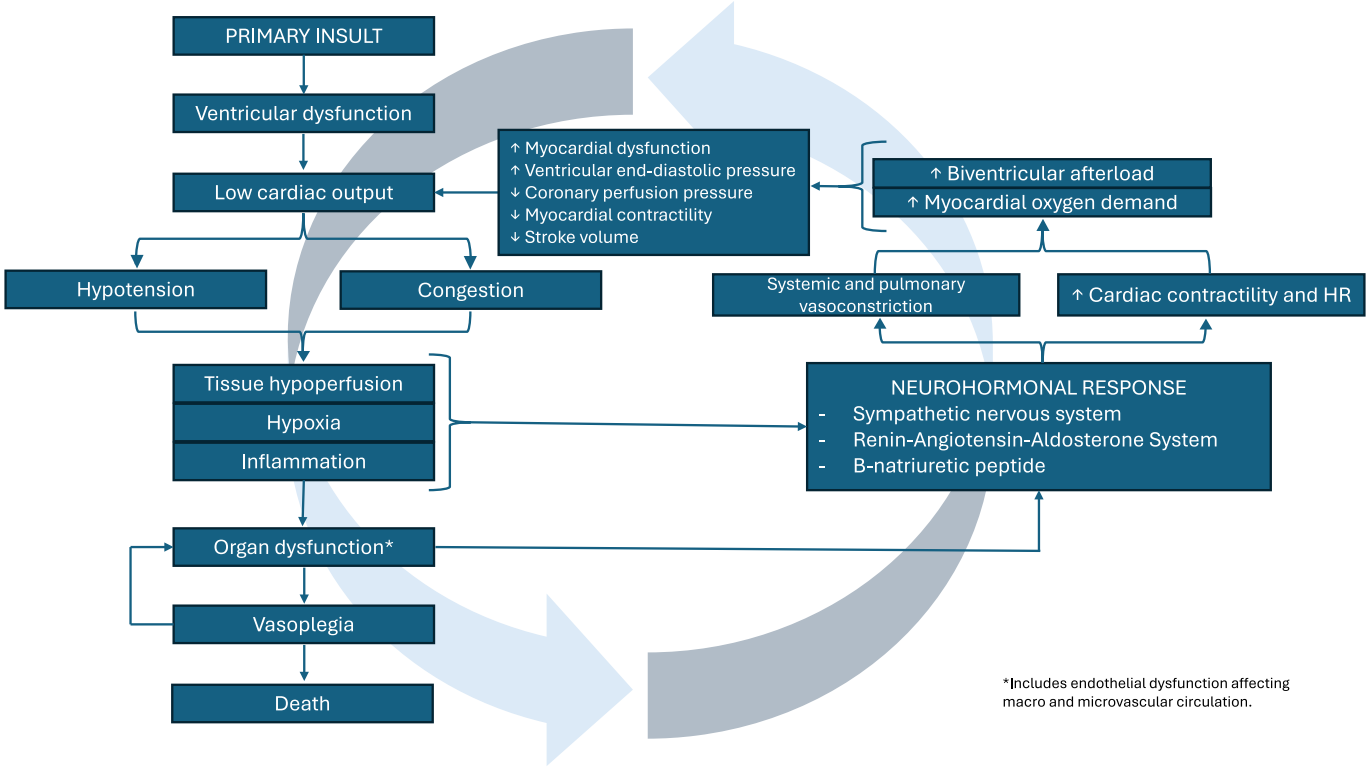


Fig. 2. Simplified pathophysiology of cardiogenic shock (CS). Several intertwined mechanisms participate in the development of CS after an acute drop in myocardial contractility of any etiology that causes low cardiac output (CO), hypotension and congestion. There is a severe imbalance in the oxygen needs and consumption that stimulates neurohormonal mechanisms resulting in vasoconstriction. This increase in vascular tone continues to worsen the myocardial dysfunction in a vicious cycle. Additionally, there is reactive inflammatory response that causes significant hypotension, aggravating the cycle and perpetuating the pathologic neurohormonal response.

species [3,56]. The final pathway is refractory CS with vasoplegia, potentially leading to demise [56]. Fig. 2 summarizes the mechanisms involved in the development of CS.

There are physiopathologic differences between AMI-CS and ADHF-CS that play a fundamental role in tailoring CS treatment. In AMI-CS, a sudden ventricular contractility impairment decreases effective stroke volume, CO, and blood pressure, while increasing pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP) [22]. AMI-CS typically involves the loss of function of a large portion of myocardium (usually >40 %) [24–26], with large areas of necrosis that result in cytokines release and systemic inflammatory response syndrome, that has been recognized as a significant predictor of 30-day mortality [27]. Risk factors for development of CS in the context of AMI include older age, anterior MI, diabetes mellitus, multivessel coronary artery disease, prior MI or angina, prior diagnosis of heart failure, STEMI, and presence of bundle branch block [28]. In AMI-CS, the insult and the maladaptive response strike abruptly, resulting in only mildly to moderately reduced LV ejection fraction with disproportionate hemodynamic impairment [8]. Despite being outside the scope of this review, it is worth emphasizing that patients with AMI who are critically ill should undergo urgent echocardiogram to screen for mechanical complications, which are culprit of additional hemodynamic deterioration [56].

Conversely, in ADHF-CS, chronic heart failure progresses to CS when the already impaired ventricular function critically drops CO due to heightened demand from disease progression or because of a specific trigger (infections, medication non-adherence, dietary indiscretions, etc.) [22]. Patients with ADHF-CS typically have preexistent intense upregulation of vasoconstrictor substances such as angiotensin, endothelin-1 and catecholamines, that create strikingly different hemodynamic and neurohormonal conditions as compared to patients with AMI-CS [3,23]. These patients typically have lower LV ejection fraction and have more tolerance to the changes that occur at the time of the acute on chronic event [8]. ADHF-CS is also associated with significantly higher SVR and a trend towards lower CI compared to AMI-CS [14]. Finally, not only adrenergic receptors can be desensitized and downregulated in chronic HF [94], but also many of these patients use chronic beta-blocking agents that add an additional layer to the complexity in management of ADHF-CS [72].

3.3.3. *Hemodynamic changes in CS*

Hemodynamic changes observed in CS are complex, with the only consistent conditions being abnormally low CI and the absence of hypovolemia (normal or high intracardiac filling pressures). Classic CS is characterized by decreased CO and CI, increased systemic vascular resistance (SVR), increased pulmonary capillary wedge pressure (PCWP), and increased central venous pressure (CVP). However, this description only applies to the subset of patients presenting with the classic “cold and wet” CS state, which excludes about one-third of CS patients [57].

The first framework for understanding hemodynamics in CS was proposed by Forrester and Diamond in the 1970s and has been expanded over the years [3,53]. This framework, supported by invasive hemodynamic parameters, categorizes CS according to peripheral circulation and volume status [3,53], and includes the following categories (See Table 2):

A. **Cold and Wet**: Classic CS, presenting with decreased CI, increased SVR, and increased PCWP. This is the most frequent form of CS [3,57].
B. **Cold and Dry**: Euvolemic CS, presenting with decreased CI, increased SVR, and normal PCWP. This type is more common among ADHF-CS, but about one-quarter of AMI-CS may present this way [3,57]. These patients are usually responsive to diuretics [3].
C. **Warm and Wet**: Vasodilatory CS or mixed shock, presenting with decreased CI, decreased or normal SVR, and increased PCWP. This phenotype is often seen in patients with AMI-CS who have a severe systemic inflammatory response, associated with a higher risk of sepsis and mortality [3,27].
D. **Warm and Dry**: Not considered a category of CS, as these patients typically have increased CI and fit into distributive or vasodilatory shock rather than CS [3].

Table 2
Hemodynamic presentations in cardiogenic shock with hypotension. Adapted from van Diepen et al. [3].

Hypotension → ↓		Volume status	
		Wet	Dry
Peripheral circulation	Cold	Classic CS -Low CI -High SVR -High PCWP	Euvolemic CS -Low CI -High SVR -Normal PCWP
	Warm	Vasodilatory CS or mixed CS -Low CI -Low /Normal SVR -High PCWP	Vasodilatory shock (not CS) -High/Normal CI -Low SVR -Low PCWP

CI indicates cardiac index; PCWP, pulmonary capillary wedge pressure; and SVR, systemic vascular resistance.

Beyond direct measurements, advanced hemodynamics can clarify diagnosis, establish prognosis, and guide treatment. Key advanced parameters derived from pulmonary artery catheter measurements for assessing RV function include pulmonary vascular resistance (PVR), RV stroke work, RV stroke work index, CVP/PCWP ratio, and pulmonary artery pulsatility index (PAPi) [58]. For left ventricular (LV) function, important advanced hemodynamic parameters include CO by the Fick method (also directly measurable via thermodilution), CI, aortic pulsatility index (API), LV stroke work, and LV stroke work index [58]. LV stroke work and LV stroke work index multiplied by heart rate yield cardiac power output (CPO) and cardiac power index, respectively. API is calculated as (systolic−diastolic blood pressure)/PCWP, and accounts for both loading conditions and cardiac efficiency [59,61].

As such, advanced hemodynamics help classify CS into LV-dominant, RV-dominant, or biventricular CS [58] (See Table 3):

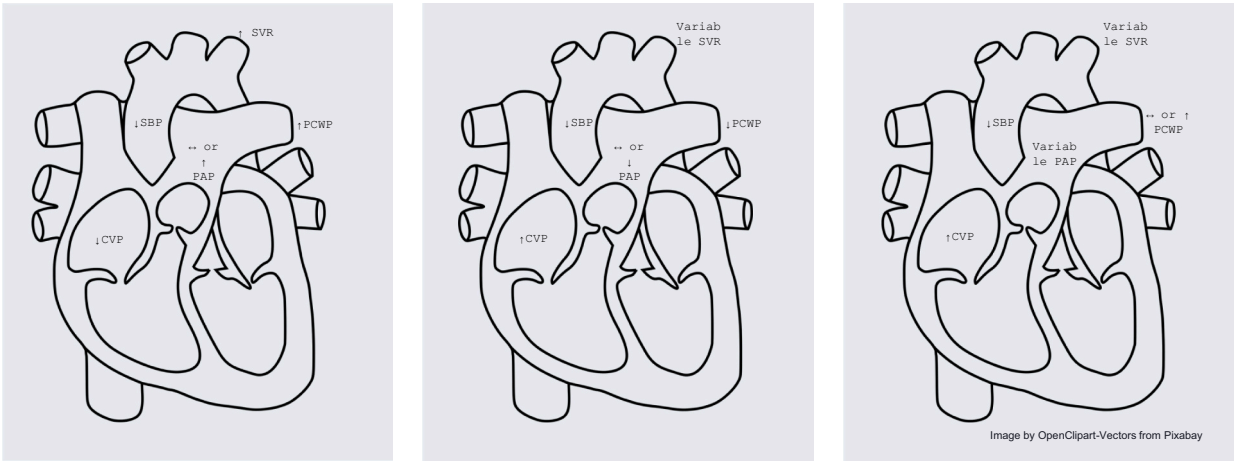
A. **LV-dominant CS**: Characterized by high PCWP and normal or reduced CVP in the setting of reduced LV function [58]. Interestingly, about 5 % of patients with AMI-CS involving the LV has been recognized as a unique subgroup of patients with peripheral hypoperfusion without hypotension [63], with potential of going unrecognized until a more advanced SCAI stage.
B. **RV-dominant CS**: Characterized by elevated CVP, normal to low pulmonary artery pressure, normal or low PCWP, and relatively preserved LV function [58]. RV-CS is rare, constituting 5–10 % of AMI-CS cases [62,98].
C. **Biventricular shock**: Characterized by hypotension, elevated CVP, normal or elevated PCWP, and reduced LV function [58]. Research by Lala et al. suggests that biventricular CS is present in 40 % of patients initially suspected of having LV-dominant CS based on clinical assessments alone [62].

Notably, CPO is a strong hemodynamic predictor of outcomes in AMI-CS but may be less precise for ADHF-CS patients [59–61]. Conversely, API appears to more accurately reflect the clinical state of ADHF-CS patients [59–61].

3.3.4. *Rationale for the use of vasopressors and inotropic agents in CS*

As emphasized by most expert consensus and guidelines, the management of CS should start as early as possible, with several treatments started in parallel. The first goal in the management of CS involves etiology-targeted therapy, which includes early coronary artery

Table 3
Hemodynamic parameters and presentation of cardiogenic shock according to the affected ventricle.



CVP (mmHg)	<14	>14	>14
PAP (mmHg)	Normal or high	Normal or low (Except patients with chronic PAH)	Variable
PCWP (mmHg)	>18	<18	Variable
CVP/PCWP	<0.86	>0.86	>0.86
PAPi (PAS-PAD)/ CVP	>1.5	<1.5	<1.5
CI (L/min/ m^2)	<2.2	<2.2	<2.2
SVR (dynes-s/cm^5)	>1400 (in general)	Variable	Variable
CPO	<0.6	<0.6	<0.6

CPO indicates cardiac power output; CVP, central venous pressure; LV, left ventricle; PAD, pulmonary artery diastolic pressure; PAP, pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PAS, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; and SVR, systemic vascular resistance.

revascularization, valvular disease management, arrhythmia control, etc. [22]. The second goal is stabilizing hemodynamics and enhance tissue perfusion by increasing mean arterial pressure (MAP), reducing venous and pulmonary congestion, and supporting the cardiac pump function [22]. The management of specific etiologies as well as use of measures used for congestion relief in CS are outside the scope of this review.

The use of vasopressors and inotropic agents in CS lacks robust randomized controlled trials and most of the evidence has been generated from observational data and small randomized trials or extrapolated from other types of shock.

In cases of CS with hypotension, early administration of vasopressors such as norepinephrine is recommended to preserve perfusion in critical organs (ESC class IIb/B) [29–31,64]. There were 2 small, randomized trials that compared vasopressors (norepinephrine-dobutamine vs epinephrine [66]; and norepinephrine vs epinephrine [36]), which showed that for the same hemodynamic efficacy, epinephrine was associated with higher heart rates, higher incidence of arrhythmias, increase in lactic acid, and higher incidence of refractory shock [36,66]. In a cohort study, De Backer et al. observed a reduction in mortality with norepinephrine compared to dopamine [35]. However, this finding was based on a limited subgroup analysis of patients with CS within a cohort that included all types of shock [35]. Additionally, norepinephrine-induced increase in blood pressure in patients with AMI-CS is associated with an increase in CI without an increase in heart rate and with increased SvO2 and reduced lactic acid [65]. Finally, an analysis of the European CardShock registry showed that epinephrine was independently associated with higher 90-day mortality [67]. These data are consistent with an individual-level meta-analysis of 2583 patients with CS that showed a 3-fold increase in the risk of death with epinephrine compared with norepinephrine [37], suggesting that norepinephrine could be considered as a first-line vasopressor in CS.

The administration of vasopressors to augment perfusion is associated with increase in LV afterload, negatively affecting myocardial contractility. Therefore, guidelines suggest the use of a combination with an inotrope (ACC class I/B-NR, ESC class IIb) [29–31,64]. Although CS guidelines advocate for initial inotropic and vasopressor dual therapy in CS for supportive care, substantial heterogeneity is found in real-world registries. Survey-based studies reported norepinephrine use varying from 53 % in the FRENSHOCK registry [51,52], 60 % in the Altshock-2 registry [43], to 90 % and 85 % in the American and European registry, respectively [9,29]. In the same way, dobutamine was used in about 80 % of the patients included in the FRENSHOCK registry, but only 40 % of patients in the Altshock-2 registry, 60 % of the patients in the American registry, and 65 % of the patients in the European registry [9,29,43,51].

There is no strong evidence to support definite benefit of one inotrope over other, consequently practice guidelines do not recommend the use of one specific agent as first-line, although dopamine alone has been associated to higher mortality and should be avoided [30,31,64,68–70]. Due to excessive vasodilation and hypotension with comparable hemodynamic efficacy [32], levosimendan and milrinone are usually reserved as second-line agents, although only the latter is available for use in the USA. Notably, levosimendan can be particularly beneficial for patients on chronic beta-blocker therapy [33,71,72]. Given the risk of increasing myocardial oxygen demand, ischemic burden, and malignant arrhythmias, all inotropes should be used at the lowest possible doses for the shortest duration [23,30,31,69].

Table 4 provides a summary of the randomized trials pertaining the use of vasopressors and inotropic agents in CS.

Table 4
Summary of the randomized controlled trials focused on vasopressors and inotropes used in cardiogenic shock.

Trial	Year	Strategies Compared	Trial design	Patient Population	Center location	Included AMI-CS	Included ADHF-CS	Primary Efficacy Outcome	Key points
Francis GS et al. [106]	1982	Dobutamine vs dopamine	Single-blind (investigators aware), crossover, randomized	13 patients with CS	Single-Center, USA	Yes	Yes	Hemodynamic effects at different doses of each infusion	No difference in heart rate, MAP, SVR, stroke work index, or mean right atrial pressure. Dobutamine improved the CI more than dopamine at 5 μg/kg/min. Dopamine increased left ventricular filling pressure more than dobutamine at 5 μg/kg/min and at 10 μg/kg/min
LIDO trial [104]	2002	Levosimendan vs dobutamine	Double-blind, double-dummy, randomized 1:1	203 patients with CS	26 centers in Austria, Denmark, Finland, France, Germany, Hungary, Italy, Switzerland, the Netherlands, Sweden, and the United Kingdom	Yes	Yes	Proportions of patients with hemodynamic improvement (>30 % increase in CO and > 25 % decrease in PCWP) at the end of the 24 h infusion period	Levosimendan improved hemodynamic performance more effectively than dobutamine. Additionally, there was lower all-cause mortality in the levosimendan group at 180 days (was analyzed after breaking the code by Sweden regulations)
LINCS study [109]	2003	L-NAME (N^G-Nitro-L-Arginine-Methyl Ester) plus supportive care vs supportive care alone	Open-label, randomized 1:1	30 patients with early refractory AMI-CS	Single-center in Israel	Yes	No	All-cause mortality at 30 days	All-cause mortality at 30 days was lower in the L-NAME group
Aranda JM Jr., et al. [112]	2003	Dobutamine vs milrinone	Unblinded, randomized 1:1	36 patients with ADHF-CS awaiting heart transplant (Excluded patients that needed mechanical support)	Single-Center in USA	No	Yes	Occurrence of hemodynamic decompensation (assessed by periodic right heart catheterization), occurrence of ventricular arrhythmias requiring increased antiarrhythmic therapy, and need for additional vasodilator or inotropic therapy	No difference in hemodynamic stability, occurrence of ventricular arrhythmias and need for additional vasoactive agent was observed
Garcia-Gonzalez MJ et al. [107]	2006	Levosimendan vs dobutamine	Open-label, randomized 1:1	22 patients with AMI-CS (STEMI), following revascularization	Single-Center in Spain	Yes	No	30 % or greater increase in CPO after 24 h of therapy	Levosimendan increased the CPO significantly more than dobutamine
SURVIVE Trial [105]	2007	Levosimendan vs dobutamine	Double-blind, randomized 1:1	1327 patients with severe acute decompensated HF, including those with CS	75 centers in Austria, Finland, France, Germany, Israel, Latvia, Poland, Russia, and the United Kingdom	No	Yes	All-cause mortality at 180 days	No significant difference in mortality, but levosimendan reduced BNP levels and improved short-term hemodynamics
TRIUMPH trial [89]	2007	Tilarginine acetate vs placebo	Double-blind, randomized 1:1	398 patients with AMI and refractory CS (already on high doses of vasoactive agents) following revascularization	130 centers in North America and Europe (8 countries)	Yes	No	All-cause mortality at 30 days	No difference in 30-day and 6-month all-cause mortality, nor in shock duration or resolution. Trial terminated early due to futility

(*continued on next page*)

Table 4 (*continued*)

Trial	Year	Strategies Compared	Trial design	Patient Population	Center location	Included AMI-CS	Included ADHF-CS	Primary Efficacy Outcome	Key points
SHOCK-2 trial [111]	2007	N^G-monomethyl-L-arginine (l-NMMA) vs placebo	Phase II, double-blind, randomized (4 different doses of investigation drug and placebo)	79 patients with AMI and refractory CS (already on vasoactive agents and 78 had IABP), following revascularization	22 centers in the USA, Canada, Germany, Israel, Austria, and Denmark	Yes	No	Change in MAP at 2 h after initiation of study drug	L-NMMA resulted in modest increases in MAP at 15 min compared with placebo but there were no differences at 2 h
CAT study [108]	2008	Epinephrine vs norepinephrine	Double-blind, randomized 1:1	280 patients with shock, including 128 with "acute circulatory collapse" and 27 AMI-CS	4 centers in Australia	Yes	Yes	Time to achieve a clinician-prescribed MAP goal for >24 h without vasopressors, also expressed as the number of vasoactive drug-free days (from randomization). Secondary outcome: All-cause mortality at 28 and 90 days.	No difference in the time to achievement of a target MAP and number of vasopressor-free days between the epinephrine and norepinephrine in the overall population or in the "acute circulatory collapse" subgroup (a priori subgroup). No difference in mortality. Epinephrine was associated with development of transient but significant lactic acidosis, hyperglycemia and tachycardia
Samimi-Fard S et al. [101]	2008	Levosimendan vs dobutamine	Open-label, randomized 1:1	22 patients with STEMI (post revascularization) complicated by CS	Single-center in Spain	Yes	No	Cardiac death at 12 months	No difference in long-term survival in STEMI patients revascularized by PCI complicated by CS
Fuhrmann JT et al. [103]	2008	Levosimendan vs enoximone	Open-label, randomized 1:1	32 patients with refractory CS (already on vasoactive agents) following revascularization	Single-Center in Germany	Yes	No	All-cause mortality at 30 days	Levosimendan improved survival when compared to enoximone in patients with refractory AMI-CS following revascularization and standard therapy
SOAP II Trial [35]	2010	Dopamine vs norepinephrine	Double-blind, randomized 1:1	1679 patients with shock, including 280 with CS	8 centers in Belgium, Austria and Spain	Yes	Yes	All-cause mortality at 28 days	No difference in terms of survival. Compared to norepinephrine, dopamine was associated with increased arrhythmias.
Levy B et al. [66]	2011	Combined norepinephrine-dobutamine vs epinephrine	Open-label, randomized 1:1	30 patients with CS that failed initial dopamine	Single-Center in France	No	Yes	Hemodynamic and perfusion effects upon reaching and maintaining target MAP 65–70 mmHg	Both arms of study increased BP, CO, CI, and renal function. However, epinephrine caused transient increased lactic acidosis and higher incidence of arrhythmias
LEAF trial [102]	2013	Levosimendan vs placebo	Double-blind, randomized 1:1	61 patients with AMI-HF, including 9 with AMI-CS	Single-center in Norway	Yes	No	Change in wall motion score index from baseline to day 5 measured by echocardiography	Levosimendan improved contractility in post-ischemic myocardium in patients with PCI-treated STEMI complicated by HF, without increasing the incidence of arrhythmias

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Table 4 (*continued*)

Trial	Year	Strategies Compared	Trial design	Patient Population	Center location	Included AMI-CS	Included ADHF-CS	Primary Efficacy Outcome	Key points
OPTIMA CC Trial [36]	2018	Epinephrine vs norepinephrine	Double-blind, randomized 1:1	57 patients with AMI-CS	9 centers in France	Yes	No	Change in cardiac index and incidence of refractory shock within 72 h	Patients treated with epinephrine had higher rates of refractory shock and lactic acidosis. Effects of blood pressure and cardiac index were similar in both groups
DOREMI (CAPITAL) Trial [32]	2021	Milrinone vs. Dobutamine	Double-blind, randomized 1:1	192 patients with CS	Single-center in Canada	Yes	Yes	Composite of in-hospital death (all-cause), resuscitated cardiac arrest, receipt of cardiac transplant or mechanical circulatory support, non-fatal myocardial infarction, cerebrovascular event, or initiation of renal replacement therapy	No significant differences in individual components of the primary outcome or other secondary outcomes
SEISMiC [110]	2022	Istaroxime vs placebo	Phase IIa, double-blind, randomized 1:1	60 patients with ADHF pre-shock (SCAI B CS)	9 centers in USA, Italy, Russia, Romania and Poland	No	Yes	Change in SBP from baseline, start of study drug infusion, through 6 h	Istaroxime improved SBP, CI and some echocardiography measures (left atrial area, left-ventricular end-systolic volume), and was well tolerated

3.4. Pharmacology of inotropic and vasopressor agents in CS

Despite the limited prospective data, inotropes and vasopressors are largely used in cardiac critical care for the management of CS, likely driven by the urgency to preserve coronary and end-organ perfusion and the wide availability of these medications amid a life-threatening situation. Table 5 provides a comprehensive summary of the hemodynamic effects, doses, adverse effects and monitoring required for the main inotropes and vasopressors available for clinical use in CS.

According to the main mechanisms of action, the agents that are available for parenteral use in CS can be divided into the following categories: sympathomimetics, phosphodiesterase (PDE)-3 inhibitors, calcium sensitizers, vasopressin derivates, and guanylate cyclase and nitric oxide (NO) synthase inhibitors. Figs. 3 and 4 are diagrams of the mechanisms of action of these agents in cardiomyocytes and vascular smooth muscle cells, respectively.

3.4.1. Sympathomimetics (calcitropes)

These agents, including dobutamine, dopamine, epinephrine and norepinephrine, stimulate different adrenoreceptors, including β1-, β2- and α1-receptors [79]. The stimulation of the β1 receptor (to some degree also β2) in cardiomyocytes activates a signaling cascade that results in increased intracellular calcium and enhanced actin-myosin interaction, increasing inotropy and chronotropy [73,77,79]. The activation of α1-adrenergic receptors in the vascular smooth muscle cells increases the vascular tone [73,79], whereas activating β2 receptors in the vascular smooth muscle cells results in vasodilation [79,80]. Dopamine has dose dependent properties, and at low doses stimulates dopaminergic receptors located in selective territories, such as renal vasculature, causing vasodilation [77]. Sympathomimetic agents have different affinities for different receptors and may stimulate more than one kind of receptor simultaneously, resulting in a certain effect that biologically may also have reflex responses by the autonomic nervous system [80]. Finally, phenylephrine is a pure α1-agonist with potentially adverse effects on cardiac contractility by increasing afterload, and is not recommended in the management of CS [78], thus it will not be discussed in this review.

Figs. 3 and 4 summarize the mechanism of action of the inotropes and vasopressors that are clinically available for management of CS.

3.4.2. Phosphodiesterase-3 inhibitors (calcitropes)

Phosphodiesterase (PDE)-3 is the enzyme responsible for breaking down intracellular cAMP to inactive 5-AMP. By inhibiting PDE-3 the intra-cardiomyocyte cAMP levels increase causing a surge of intracellular calcium and enhancement of the interaction actin-myosin, resulting in increased contractility as well as acceleration of myocardial relaxation [73]. Peripherally, these agents cause systemic and pulmonary vasodilation as well as venodilation by increasing cAMP in the vascular smooth muscle cells [77,82]. The outcomes of these effects are decreased SVR and PVR, decreased filling pressures and increased CO [82]. The only available agent for clinical use in CS in the USA is milrinone. Enoximone is another PDE-3 inhibitor with limited availability world-wide, and we will consequently not include this agent in our review. Due to their mechanism of action independent from β-adrenergic receptors, PDE-3 inhibitors are among the preferred agents in patients utilizing betablockers [30,31,72].

3.4.3. Calcium-sensitizers (myotropes)

Increase the sensitivity of troponin C to calcium, facilitating the interaction actin-myosin without increasing intracellular calcium and, theoretically, without causing increase myocardial oxygen consumption [77]. These agents also stimulate the ATP-sensitive potassium channels in the vascular smooth muscle cells causing vasodilation [77]. Notably, by stimulation of the ATP-sensitive potassium channels in mitochondria, this class of inotropes has additional anti-oxidative and anti-inflammatory effects, protecting renal, hepatic, neural and myocardial

Table 5
Pharmacology, hemodynamic effects, adverse effects and monitoring features of inotropes and vasopressors clinically available for the management of cardiogenic shock.

Agent	Mechanism of action	Hemodynamic Effects					Dosage and administration	Half-life	Arrhythmogenesis	Adverse effects and monitoring
		BP	HR	Contractility	SVR	PVR				
Dobutamine	β1 > β2 > α1-adrenergic receptors, increasing cAMP and enhancing calcium influx	↑	↑	↑↑	↓ (except high doses)	↓ or N	2.5–20 μg/kg/min IV infusion. No bolus	2–5 min	Intermediate risk of inducing tachyarrhythmias (increased myocardial excitability)	Adverse Effects: Tachyarrhythmias, hypotension, headache, eosinophilic myocarditis, blood eosinophilia, hypokalemia, myoclonus Monitoring: ECG, BP, urine output, intravascular volume status, creatinine, electrolytes, CBC
Milrinone	Inhibits phosphodiesterase III, increasing cAMP and enhancing calcium sensitivity	V	↑	↑	↓	↓	0.125–0.75 μg/kg/min IV infusion	2–3 h	Lower reported risk of tachyarrhythmias compared to catecholamines, but still present	Adverse Effects: Hypotension, arrhythmias, headache, thrombocytopenia, hypokalemia, drug accumulation in renal failure Monitoring: ECG, BP, urinary output, intravascular volume, creatinine, electrolytes, CBC
Isoproterenol	β1 > β2-adrenergic agonist, increasing cAMP and enhancing calcium influx	↑	↑↑	↑	↓	↓	2–20 μg/min IV infusion. No bolus	2.5–5 min	Higher risk of tachyarrhythmias	Adverse effects: Hypotension, hyperglycemia, myocardial ischemia. Contains sulfites Monitoring: ECG, BP, electrolytes, blood glucose
Norepinephrine	α1 > β1 > β2-adrenergic agonist, increasing cAMP and enhancing calcium influx	↑	V	↑	↑↑	N or ↓ (In acute PH)	0.05–0.4 μg/kg/min IV infusion. No bolus	2–3 min	Generally low risk but may exacerbate existing arrhythmias or cause bradycardia due to reflex mechanisms	Adverse Effects: Hypertension, reflex bradycardia, tissue necrosis with extravasation, headache Monitoring: BP, peripheral perfusion, intravascular volume status
Epinephrine	β1 = α1 > β2-adrenergic receptors, increasing cAMP and enhancing calcium influx	↑	↑↑	↑↑	↑	↑ or N	0.01–0.5 μg/kg/min IV infusion. Bolus: 1 mg IV every 3–5 min during resuscitation	2–5 min	Intermediate risk of tachyarrhythmias in patients with underlying cardiac disease (especially ischemic)	Adverse Effects: Tachyarrhythmias, myocardial ischemia, hyperglycemia, headache, anxiety, pulmonary edema, cerebral hemorrhage, limb ischemia Monitoring: ECG, BP, blood glucose, lactic acid, intravascular volume status
Dopamine	Dose-dependent effects Low doses stimulate dopaminergic receptors (renal vasodilation)	N or ↓	N or ↑	N	↓	N/A	No bolus Low doses: 0.5–3 μg/kg/min	2–5 min	Intermediate risk of tachyarrhythmias (higher doses)	Adverse Effects: Tachycardia, arrhythmias, myocardial ischemia Monitoring: ECG, BP, HR, urine output, intravascular volume status
	Moderate doses stimulate β1 > β2-adrenergic receptors (increased contractility)	↑	↑↑	↑↑	↑	N/A	5–10 μg/kg/min			
	High doses stimulate α1-adrenergic receptors (vasoconstriction)	↑↑	↑	↑	↑↑	N/A	>10 μg/kg/min (rarely used)			

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Table 5 (*continued*)

Agent	Mechanism of action	Hemodynamic Effects					Dosage and administration	Half-life	Arrhythmogenesis	Adverse effects and monitoring
		BP	HR	Contractility	SVR	PVR				
Levosimendan	Calcium sensitizer; augments contractility by binding to troponin C Opens ATP-sensitive potassium channels (vasodilation)	↓	N or ↑	↑	↓	↓	0.05–0.2 μg/kg/min IV infusion	1 h Active metabolites have a half-life >80 h	Generally low proarrhythmic risk	Adverse Effects: Hypotension, headaches, hypokalemia Monitoring: BP, ECG, electrolytes Not FDA approved
Vasopressin	Stimulates V_{1a} receptors, causing vasoconstriction Stimulates V_2 receptors, causing water retention	↑	N or ↓	N	↑↑	↓	0.01–0.04 units/min IV infusion	6–30 min	Minimal proarrhythmic effects	Adverse Effects: Hyponatremia, ischemia, decreased CO at doses >0.04 U/min, splanchnic vasoconstriction, skin necrosis, thrombocytopenia Monitoring: BP, HR, fluid input and output, serum and urinary sodium and osmolality, peripheral perfusion
Phenylephrine	α1-adrenergic receptors stimulation, causing vasoconstriction	↑↑	↓	N or ↓	↑↑	N or ↑	0.1–10 μg/kg/min IV infusion	5 min	Bradycardia	Adverse Effects: Reflex bradycardia, tissue necrosis with extravasation, cold extremities Monitoring: BP, ECG, peripheral perfusion (skin and urinary output), creatinine
Methylene Blue	Inhibits nitric oxide mediated cGMP production, resulting in increased vasoconstriction	↑↑	N or ↑	N	↑↑	↑	Bolus 1–2 mg/kg (over 15 min to 6 h); continuous infusion 0.25–2 mg/kg/h up to 48 h However, doses vary per institutional protocols.	Not well-defined 5–6.5 h	Low risk of tachyarrhythmias	Adverse Effects: Serotonin syndrome, paradoxical methemoglobinemia and hemolytic anemia (in glucose-6-phosphate dehydrogenase deficiency) Monitoring: BP, ECG, pulse oximeter, CBC, arterial or venous blood gases, methemoglobin, creatinine

ATP indicates adenosine triphosphate; BP, blood pressure; cAMP, cyclic adenosine monophosphate; CBC, complete blood count; cGMP, cyclic guanosine monophosphate; CO, cardiac output; ECG, electrocardiogram; HR, heart rate; N, normal; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; and V, variable.

cells from ischemia/reperfusion injury [77]. At high doses, levosimendan also inhibits PDE-3. One of the main limitations to the use of levosimendan is the extremely long half-life, with its active metabolite half-life being approximately 80 h, which is further prolonged in the not uncommon scenario of kidney failure [87]. The only clinically available agent is levosimendan, however it is not available in the USA.

3.4.4. *Vasopressin derivates*

By stimulating the Vasopressin-$_{1a}$ (V_{1a}) receptors, coupled to phospholipase C, vasopressin increases vascular tone and limits endothelial permeability [77]. V_{1a} receptors are highly present in the systemic vasculature (particularly abundant in the mesenteric circulation), as opposed to the pulmonary vascular tree, causing differential raise in vascular resistance [73]. This effect is particularly desirable for patients that have isolated RV-CS and for those who have high PVR [73]. In addition, the V_{1a} receptors are present in the efferent arterioles of the renal glomeruli, increasing the glomerular filtration pressure [73,74].

Vasopressin also stimulates V2 receptors, which are coupled to adenylyl cyclase and located in the kidneys. These receptors are responsible for the antidiuretic effect of vasopressin, achieved by promoting the insertion of aquaporins (water channels) into the luminal membrane of the renal collecting duct cells [83].

Despite the limited prospective data regarding the use of vasopressin in CS, there is at least one registry that documented its use as second-line vasopressor in patients with CS [75]. The absence of chronotropic effect makes this agent particularly advantageous in patients who are at high risk for arrhythmias [73,74]. Finally, a recent observational study demonstrated that vasopressin was associated to lower in-hospital mortality in CS [76], which would grant further prospective research.

3.4.5. *Guanylate cyclase and nitric oxide synthase inhibitors*

Methylene blue is a commonly used dye that is also utilized in the treatment of methemoglobinemia, and that has demonstrated some benefits in the treatment of vasoplegic shock [38,44,84–86]. Methylene blue inhibits guanylate cyclase and the inducible isoform of nitric oxide synthase, resulting in decreased levels of cyclic-GMP (c-GMP), and decreased levels of nitric oxide (NO) and NO-derived reactive nitrogen species, causing vasoconstriction [84,85]. Limited observational data and case series showed improvement of BP in refractory CS and suggest that methylene blue could have a role in the management of CS with

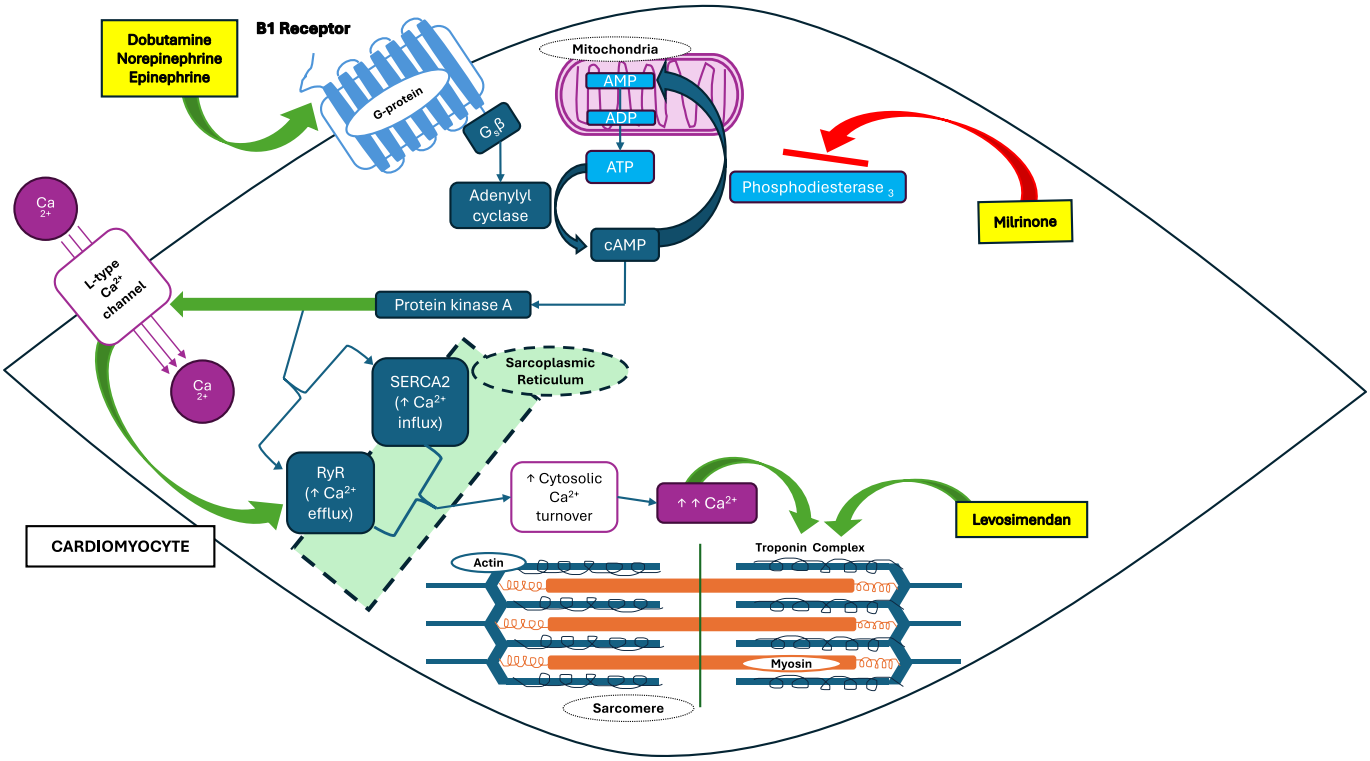

Fig. 3. Mechanisms of action of catecholamines, milrinone and levosimendan in cardiomyocytes. Through different mechanisms, catecholamines and milrinone cause increased levels of cytosolic calcium (thus considered calcitropes), resulting in increased actin-myosin interaction and enhanced contractility and relaxation. Levosimendan does not affect the levels of calcium but increases the myofilaments sensitivity to calcium by binding to troponin C, promoting the actin-myosin interaction, which improves myocardial contractility and relaxation.
AMP indicates adenosine monophosphate; ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; Ca^{2+}, calcium ion; RyR, ryanodine receptor; SERCA, sarcoplasmic reticulum Ca^{2+} ATPase.

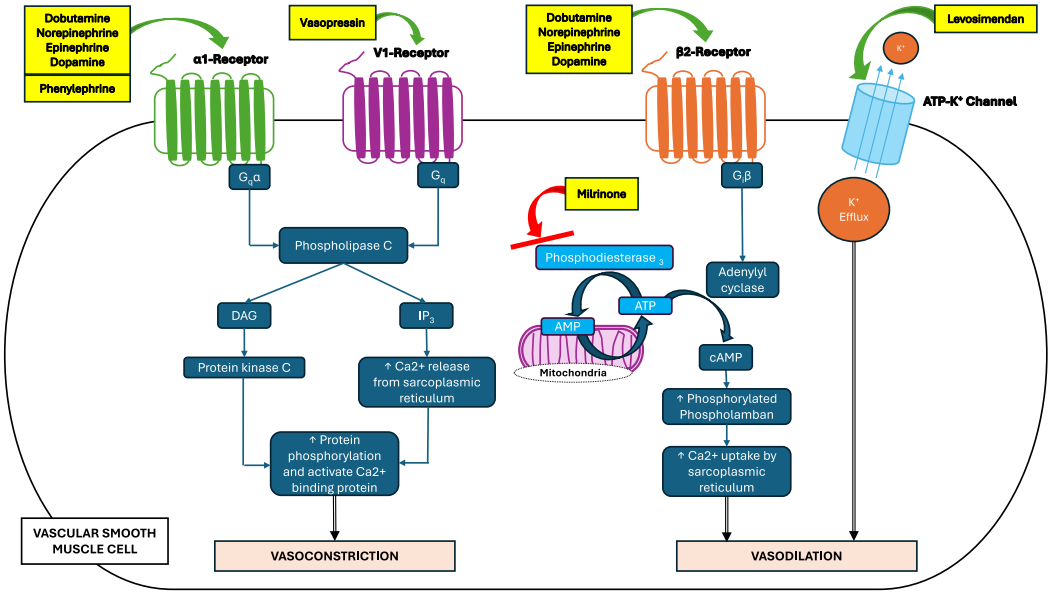

Fig. 4. Mechanisms of action of catecholamines, milrinone, levosimendan and vasopressin in vascular smooth muscle cells. By interacting with the β2-receptors, catecholamines induce phospholamban-mediated uptake of calcium by the sarcoplasmic reticulum via adenylyl cyclase. Milrinone inhibits the phosphodiesterase-3, which increases cAMP, promoting calcium uptake by the sarcoplasmic reticulum with resultant vasodilation. Levosimendan interacts with the ATP-dependent potassium channel, also resulting in vasodilation. Vasoconstriction is caused by the interaction of catecholamines with the α1-adrenergic receptors that activates the phospholipase C cascade. Vasopressin stimulates the V1-receptors causing activation of phospholipase C and subsequent vasoconstriction.
AMP indicates adenosine monophosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; Ca^{2+}, calcium ion; DAG, diacylglycerol; IP_3, inositol 1, 4, 5-triphosphate; and K^+, potassium ion.

severe systemic inflammatory response and advanced stages of CS [84–86]. However, no definite benefit can be established for the use of methylene blue in CS due to the scarcity of data.

Tilarginine, another NO synthase inhibitor, failed to demonstrate improvements in the duration of shock and in the mortality in patients with refractory AMI-CS despite revascularization [89].

3.5. Differential use of inotropes and vasopressors in AMI-CS vs ADHF CS

3.5.1. Acute Myocardial Infarction Cardiogenic Shock (AMI-CS)

As previously discussed, there is a paucity of data specific to the use of vasoactive agents in the treatment of CS. For this reason, much of the current recommendations are based on extrapolation of data from trials studying "all comers" in shock, small sample-size randomized trials, metanalyses, and expert opinion.

Although not the focus of this review, it is important to note that revascularization is the first-line treatment for AMI-CS [1], and that specifically for CS of this etiology, mechanical support can be considered early, as evidenced by the DanGer Shock Trial which found that the routine use of percutaneous left ventricle assist device (Impella) along with standard care in the treatment of CS from STEMI led to a lower risk of death from any cause at 180 days vs standard care alone [34].

Norepinephrine is typically considered the first line for the treatment of AMI-CS, especially when severe hypotension is present, as it has a balanced profile of β1- and α1-adrenergic activity and has been shown to have equivalent positive outcomes in shock compared to dopamine, but with significantly reduced risk of arrhythmia [35]. Epinephrine, in comparison, also has mixed β1 and α1 action, however it is also more arrhythmogenic than norepinephrine and can induce myocardial ischemia, therefore it is judiciously reserved as a second line agent [36,37].

Another vasoactive agent that is usually avoided in CS is phenylephrine which has primarily α1 activity, thus increasing afterload and worsening the CS physiology [38]. By contrast, vasopressin is a reasonable adjunct treatment for CS with hypotension refractory to norepinephrine alone. Vasopressin maintains its efficacy in acidotic environments, has a synergistic effect with norepinephrine- increasing the vascular sensitivity to this first line agent-, has lower risk of arrhythmia, and at low dose causes pulmonary vasodilation, which is helpful for reducing RV afterload [39,40].

Inotropes like dobutamine and milrinone have been shown to be equally efficacious for the treatment of cardiogenic shock, specifically when there is a low flow state as defined as a stroke volume index of <35 mL/m^2, or in patients with significant hypervolemia [32]. These agents must be used with caution in the presence of hypotension, as they can cause significant vasodilation worsening shock physiology in the absence of norepinephrine [32]. In patients with adequately treated hypotension, or hypotension refractory to vasoactive agents, these inotropes can improve cardiac output and diuresis [38,43].

Specific pharmacologic protocols for AMI-CS include initiating norepinephrine with the intention of maintaining MAP above 65 mmHg to preserve end-organ perfusion, adding vasopressin for persistent hypotension in cardiogenic shock or to augment the effects of norepinephrine, and then considering the addition of dobutamine or milrinone if stroke volume index is <35 mL/m^2, or if the patient is hypervolemic and requires diuresis to improve hemodynamics which can be facilitated by increasing cardiac output [32,38]. An alternative regimen for AMI-CS in the presence of only moderate hypotension is dopamine and dobutamine in combination [41], but if hypotension persists or becomes severe norepinephrine is still the first line agent [35,88]. It is important to note that the target MAP is still a matter of debate and that targeting MAP above 65 mmHg has been extrapolated from septic shock data and based on expert opinion, since targeting higher MAPs has not been consistently beneficial [45,64,65,73,78]. It is vital to recognize that in this context, clinical perfusion is likely to serve as a more reliable guide for treatment than MAPs. Caution should be exercised when considering an increase in vasopressor doses, as higher doses of these agents have been universally associated with increased mortality in cardiogenic shock [91–93]. However, it should be noted that this association may also reflect more advanced stages of the disease.

3.5.2. Acute Decompensated Heart Failure Cardiogenic Shock (ADHF-CS)

Treatment of ADHF-CS entails using the same agents as CS secondary to other etiologies with some additional considerations. Compared to AMI-CS, the pathophysiology of chronic heart failure causing CS is predominantly related to poor CO and reduced stroke volume index, hypervolemia, and importantly chronic hypoperfusion and systemic compensation resulting in increased SVR, pulmonary hypertension, and renal dysfunction [42]. As discussed before, the chronic nature of this disease process, combined with the benefits of goal directed medical therapy and systemic compensation, results in CS presenting more subtly and insidiously in this patient population [43].

The leading goals of pharmacologic therapy in ADHF-CS are to support CO, preserve pulmonary artery vasodilation (to reduce RV afterload), and facilitate effective diuresis to relieve the underlying congestion despite chronic renal dysfunction [30]. For this reason, in this patient population, it may be reasonable to cautiously initiate an inotrope (dobutamine or milrinone), as first line to improve cardiac output and augment diuresis [38,43]. However, if MAP falls below 65 mmHg, it is vital that additional vasoactive agents (norepinephrine, vasopressin, or both) be included in management [43]. Although no difference has been found in terms of short-term mortality or other relevant clinical outcomes between dobutamine and milrinone [32], due to the longer half-life, milrinone is typically reserved as a second line agent, especially in patients with kidney failure [32,90].

Furthermore, vasopressin can be considered early on in patients with RV failure as the pulmonary vasodilation caused by this agent can significantly reduce RV afterload [39,40]. If pharmacologic therapy alone fails to correct the decompensation, escalation to mechanical support can be considered, which should be tailored to the specific features of the patient's condition [43].

3.6. Use of inotropes and vasoactive agents in CS with LV failure vs isolated RV failure

3.6.1. Pharmacological strategies in LV failure CS

LV-CS occurs when the LV cannot provide effective circulation and systemic support, carrying high morbidity and mortality [38]. When acute LV failure occurs, we are often met with the challenge of deciding on the best pharmacological and mechanical treatments to support patients. Appropriate pharmacological vasopressor and inotrope selection is key to maximizing outcomes in patients with LV failure with CS.

As discussed in previous section, in CS with associated hypotension the first choice is typically a vasopressor agent such as norepinephrine, epinephrine or dopamine. The premise to use a vasoconstrictor is attempting to preserve organ perfusion. Nevertheless, single-agent vasoconstrictor is meant to be used for the shortest time possible, as these medications logically result in worsening CO and flow by increase in afterload. The SOAP-II (Sepsis Occurrence in Acutely Ill Patient) trial compared mortality outcomes with the use of dopamine vs norepinephrine in shock of all causes, which included 280 patients with CS [35]. This study showed increased mortality in CS treated with dopamine compared to norepinephrine, however increased arrhythmic events were also seen in patients treated with dopamine [35]. The OptimaCC trial compared epinephrine vs norepinephrine for AMI-CS, showing increased rates of refractory shock in the epinephrine group without difference in mortality [36]. No differences in MAP, CI or stroke volume were seen between the groups. Those treated with epinephrine were associated with worse metabolic acidosis, increases in HR and cardiac double product. This study was terminated early due to increased rates of refractory CS in the epinephrine group [36]. Additionally, in patients with refractory hypotension and severe metabolic

acidosis vasopressin and methylene blue were found to be effective in catecholamine refractory vasoplegia and CS [38,44]. Overall, the AHA Scientific Statement, ACC and ESC guidelines on the management of LV-CS recommend the use of norepinephrine as first-line treatments for CS [31,32,45].

Once hypotension has been addressed, pharmacological therapies to improve contractility can be considered, including inodilators such as dobutamine and milrinone [38]. Other options are epinephrine and dopamine, or combination of agents. As outlined earlier, levosimendan has also been studied however but is not available for use in the USA [38]. The guidelines do not favor the use of a specific inotrope due to lack of strong evidence, and the choice of agent is left at the healthcare providers discretion [30,31].

No clinical trial has compared head-to-head all the inotropic and vasopressor agents in CS. Therefore, with scarce available evidence, the choice of pharmacologic agent varies significantly between institutions, and is mainly directed by evidence from limited trials, clinician experience, presumed relative risk of tachyarrhythmia, presence of underlying ischemia, and access to medication. Table 4 summarizes the randomized controlled trials focused on inotropic and vasopressor support in patients with CS.

3.6.2. Approach to RV failure CS

The management of RV-CS is an area of active research and, as expected, focuses on identifying and addressing the underlying etiologies of RV-CS, and optimizing volume, myocardial contractility and afterload. In RV failure the volume load has the potential to distend the RV and compromise the LV filling pressures and the LV CO [95,96]. Nevertheless, these patients may also be preload dependent [96]. Therefore, the key initial element in the management of RV-CS consists of carefully assessing volume status to determine if the patient would benefit from decongestion with parenteral diuretics as opposed to intravenous fluid resuscitation [46] (see Table 3). There are several agents (loop diuretics, thiazides, carbonic anhydrase inhibitors, etc.) and strategies (ultrafiltration, etc.) that may be implemented to decongest hypervolemic patients and optimize the preload, however these are outside the scope of this review.

Pharmacological vasoactive therapies for contractility augmentation and afterload reduction in isolated RV-CS have not been studied in dedicated randomized trials. Thus, data has been extrapolated from LV-CS and from observational registries [96]. Norepinephrine remains the first line inopressor [46,79,97], and further escalation of inotropic agents would include utilizing milrinone and dobutamine [30,31,94]. Milrinone carries the theoretical benefit of causing decreased PVR and improving the RV-arterial coupling, however there are no dedicated studies to confirm this benefit and a subgroup analysis of the DOREMI trial of patients with RV-CS did not show this benefit either [32]. In patients receiving chronic betablockers, dobutamine may result in pulmonary vasoconstriction due to α1-receptors stimulation not counteracted by the stimulation of β2-receptors, which is detrimental in RV-CS [72].

As addressed previously, if hypotension persists despite norepinephrine, vasopressin may be considered as it may lower PVR while increasing SVR, leading to improved renal and coronary artery perfusion while reducing the risk of RV myocardial ischemia [46]. Further research is needed.

Despite not being within the focus of this review, it is worthwhile highlighting a few important points in the management of RV-CS. First, the treatment of hypoxia and acidosis is imperative in the successful management of RV-CS due to the direct effect these conditions have in PVR, worsening RV afterload [94–96]. Positive pressure to improve oxygenation should be used cautiously, with minimal effective tidal volume and lowed positive end-expiratory pressure possible to avoid decreasing preload [94]. Finally, even though pulmonary vasodilators (inhaled/parenteral epoprostenol and nitric oxide) have a role in decreasing PVR in patients with pulmonary arterial hypertension [46,96], because isolated RV-CS is rare and is frequently associated with some degree of LV failure and pulmonary edema, they are not preferred agents and may be harmful in the setting of LV disease [96].

3.7. Use of peripheral inotropes in cardiogenic shock

CS will often require rapid initiation and titration of vasoactive agents to optimize tissue and vital organ perfusion. As such, we are often pressed to initiate support through a peripheral venous route to avoid worsening hemodynamics or clinical deterioration. Here we will provide a review of administration routes of inotropes in CS.

Central administration using a central venous catheter (CVC; in the internal jugular, subclavian or femoral veins) has been the long-time recommended and preferred route of administration as this allows for reliable delivery of the inotropic agents and will help to diminish the risk of causing skin tissue damage through extravasation [47].

Peripheral administration is an alternative mode of inotrope delivery, typically utilized via a peripheral IV line (PIV) that can be quickly established to allow prompt administration of a vasoactive medication. This route avoids the risk of theoretically more serious CVC placement related complications including pneumothorax, excessive bleeding, carotid/femoral artery unintentional thrombosis, or infection. However, its use is limited by the risk of extravasation, phlebitis and tissue necrosis, plus the inability to infuse higher doses and longer duration of vasoactive agents.

3.7.1. Comparative outcomes for peripheral vs central inotrope infusion

There have been mixed results on efficacy and safety of the administration route of vasoactive agents in CS, and most of the data is derived from observational studies in shock of all cause.

In a retrospective cohort of 212 patients receiving IV vasopressor support in a mixed medical and surgical intensive care unit (ICU), divided into 3 groups: PIV alone, PIV followed by CVC, and CVC alone. There were no differences in rates of major complications (bloodstream infection, skin necrosis, and gangrene) in PIV compared to CVC [47]. Minor complications such as leakage, extravasation, and access site erythema occurred in 51 % of the PIV group, although the report of complications was not consistently analyzed. In this study, duration of peripheral vasopressor infusion was not associated with an increased risk of complications [47].

Another retrospective study of 202 patients receiving vasopressors (norepinephrine and phenylephrine) through PIV reported an overall incidence of extravasation of only 4 %. All the events were managed conservatively and none required surgical management [48].

Additionally, a prospective single-center study of 139 patients (120 patients with CS) compared safety and outcomes of vasopressors administered through PIV vs CVC in patients with shock. About 108 (78 %) had vasoactive agents delivered via PIV and 31 (22 %) via CVC, with minimal rate of extravasation and phlebitis in the overall cohort that was non-significant between the groups, and only 1 episode of bleeding in the CVC site that was managed conservatively [49]. The length of stay was shorter for patients with PIV [49], however this may have been because the patients that received CVC were actually sicker.

Cardenas-Garcia et al. worked in a multidisciplinary effort to develop and implement a protocol for administration of vasoactive agents via PIV. Their observational prospective cohort included 734 patients of a medical ICU that received vasoactive medications via PIV. They found that extravasation of PIV occurred in only 19 patients (2 %) without any tissue injury following treatment [50]; 49 patients (6.7 %) required insertion of 2 or more PIV due to time out at 72 h of the initial or subsequent PIV, per protocol [50]. One major noticeable difference in this cohort compared to others is that most of the PIVs were actual basilic or cephalic large bore accesses (18- or 20-gauge) [50], which may have helped decrease the incidence of local complications. Other authors have reported the successful management of peripherally infused norepinephrine in medical ICU patients with low rate of local

complications and showed reduction in the number of CVCs inserted [99].

Loubani et al. published a systematic review of patients with shock that had received IV vasoactive agents via PIV and developed local tissue injury [100]. The authors encountered that most data were derived from case reports and observational cohorts, including 318 local tissue injury (204) and extravasation (114) events. Interestingly, 85 % of these patients with local injuries were receiving vasopressors in PIVs that were located distal to the antecubital or popliteal fossa, and although a minority of data reported the catheter size, most of the patients that suffered a complication had 22-gauge PIVs [100].

Overall, there remains a significant gap in knowledge regarding the optimal route of administration for vasopressors and inotropes in CS. While short-term infusions of up to 48–72 h through a large-bore PIV accompanied by close monitoring of the infusion site appear to be safe, there is no supporting evidence to confirm this practice. One potential challenge in utilizing PIVs for patients with CS is the elevated SVR, which may complicate both the insertion and maintenance of a PIV line. Future research should aim to refine protocols for peripheral administration, reduce complications and better define its role in the management of CS.

4. Conclusion

In conclusion, CS remains a complex and multifaceted condition with high mortality rates despite advancements in medical management. The heterogeneity of CS, coupled with the challenges in diagnosis and treatment, underscores the need for a nuanced approach to patient care. The use of inotropes and vasopressors continues to be a cornerstone in the initial management of CS, providing critical support to maintain cardiac output and blood pressure. However, the scarcity of high-quality data from randomized trials limits our ability to establish robust guidelines, often relying on limited data and expert opinion.

The recent advances in the SCAI classification and the work by Zweck et al. [55] using machine learning to define CS phenotypes represent significant steps forward. These developments hold promise for generating better quality data and improving our understanding of CS. Additionally, standardizing the quantification of vasopressors and integrating this into the staging system should be a priority for future prospective trials. By addressing these gaps, we can hope to refine therapeutic strategies and ultimately improve outcomes for patients suffering from this life-threatening condition.

As we move forward, a deeper understanding of the pathophysiology of CS and the development of more targeted interventions will be essential in improving outcomes for patients suffering from this life-threatening condition.

CRediT authorship contribution statement

Ana Florencia Becerra: Conceptualization, Data curation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Udochukwu Amanamba:** Data curation, Writing – original draft, Writing – review & editing. **Jonathan E. Lopez:** Data curation, Writing – original draft. **Noah J. Blaker:** Data curation, Writing – original draft, Writing – review & editing. **David E. Winchester:** Conceptualization, Data curation, Methodology, Project administration, Supervision, Visualization, Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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