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Review

The medical treatment of cardiogenic shock

Mickael Lescroart [1,2,3], Benjamin Pequignot [1,2,3], Dany Janah [1,2,3], Bruno Levy [1,2,3,*]

[1] Service de Médecine Intensive et Réanimation Brabois, CHRU Nancy, Pôle Cardio-Médico-Chirurgical, Vandoeuvre-les-Nancy 54511, France
[2] INSERM U1116, Faculté de Médecine, Vandoeuvre-les-Nancy 54511, France
[3] Université de Lorraine, Vandoeuvre-les-Nancy 54000, France

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ABSTRACT

Cardiogenic shock (CS) is a leading cause of mortality worldwide. CS presentation and management in the current era have been widely depicted in epidemiological studies. Its treatment is codified and relies on medical care and extracorporeal life support (ECLS) in the bridge to recovery, chronic mechanical device therapy, or transplantation. Recent improvements have changed the landscape of CS. The present analysis aims to review current medical treatments of CS in light of recent literature, including addressing excitation–contraction coupling and specific physiology on applied hemodynamics. Inotropism, vasopressor use, and immunomodulation are discussed as pre-clinical and clinical studies have focused on new therapeutic options to improve patient outcomes. Certain underlying conditions of CS, such as hypertrophic or Takotsubo cardiomyopathy, warrant specifically tailored management that will be overviewed in this review.

Background

Cardiogenic shock (CS) is a major worldwide concern occurring in 5–7% of patients presenting with acute myocardial infarction (AMI), with its incidence increasing as life expectancy rises.[1] CS is usually defined as a state of organ hypoperfusion related to low cardiac output with normal or elevated filling pressure.[2] While the prognosis of chronic heart failure (HF) has improved over the decades, the prognosis of CS remains poor.[3,4] The management of CS first relies on inotropic agents and vasopressor use to restore oxygen delivery (DO_2) and maintain normal ventricular-arterial coupling.[4] When medical therapy is ineffective, extracorporeal life support (ECLS) should be proposed as rescue therapy in the bridge to recovery, transplantation, or chronic mechanical support. Pre-clinical studies and clinical trials have recently assessed additional therapies to improve outcomes in critically ill patients with CS. This work aims to review current treatments for CS management in light of the recent literature.

Basic Principles for Applied Hemodynamics

A better understanding of excitation–contraction coupling has provided new insights for the development of target treatments for inotropy.[5] Briefly, each action potential drives calcium entry into cardiac myocytes via L-type Calcium ion (Ca^{2+}) channels (LTCC), triggering a greater Ca^{2+} release from the sarcoplasmic reticulum (SR). Calcium binding troponin C facilitates actin–myosin interactions and cardiomyocyte contraction. Thereafter, Ca^{2+} diffuses away from troponin C, initiating diastolic relaxation. The Ca^{2+} released from the SR is recaptured by the SR Ca^{2+} ATPase (SERCA), while the amount of Ca^{2+} that enters the cell via LTCCs is exported by the Sodium ion (Na^+)/Ca^{2+}-exchanger (NCX). Stimulation of β1-adrenergic receptors (β1-ARs) leads to coupling to G-proteins (G_s), activation of adenylyl cyclase (AC), and cAMP production. Intracellular cAMP activates LTCCS, enhances Ca^{2+} release by the SR after binding specific ryanodine receptors (RyRs), and decreases troponin calcium affinity driving positive inotropic and lusitropic effects. During HF, SERCA expression decreases, Ca^{2+} efflux is impaired, and $[Na]_{IC}$ increases, paving the way for failure of underlying compensatory mechanisms (i.e., positive force–frequency relationship and Starling effect). The mechanism of excitation–contraction coupling is illustrated in Figure 1.

The 21st century has also provided significant enhancement in applied hemodynamics. Guyton[6] first stated in the 1950s that cardiac output mainly relied on the output of systemic venous return, right atrial pressure, and mean systemic pres-

* Corresponding author: Bruno Levy, Medical Intensive Care Unit, University Hospital of Nancy, Brabois, Rue du Morvan, Vandoeuvre-Lès-Nancy 54500, France.
E-mail address: blevy5463@gmail.com (B. Levy).

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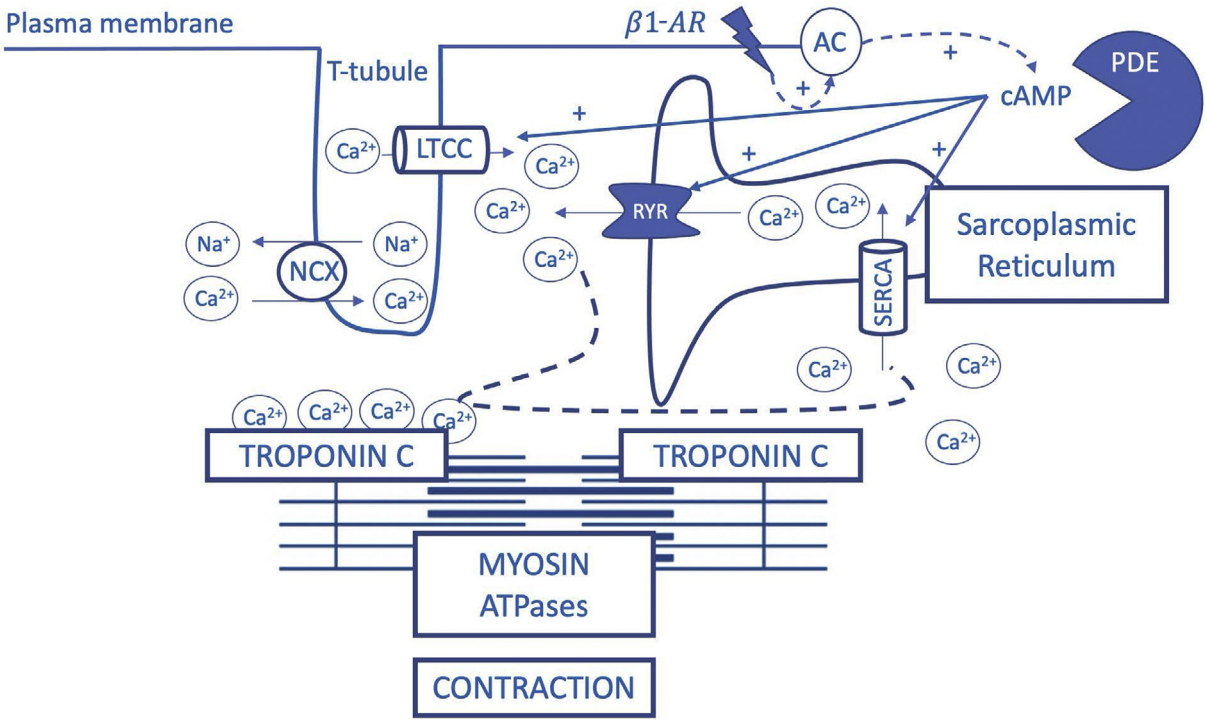

Figure 1. Excitation–contraction coupling.
β1-AR: β1 adrenergic receptors; AC: Adenylate cyclase; Ca^{2+}: Calcium ion; LTCC: L-type Ca^{2+} channels; Na^{+}: Sodium ion; NCX: Na^{+}/Ca^{2+}-exchanger; PDE: Phosphodiesterase; RyR: Ryanodine receptor; SERCA: SR Ca^{2+} ATPase; T-tubule: Transversal tubule.

sure (i.e., the residual pressure within the circuitry at zero flow). In the 1990s, Sunagawa et al.[7] developed the concept of ventricular-arterial coupling between the left ventricle and the arterial tree, each defined by its own elastic properties. The end-systolic/arterial elastance (Ees/Ea) ratio (Ees for the left ventricle and Ea for the arterial tree) shows optimal coupling for Ea = Ees/2. In this model, a lower inotropism is represented by a lower Ees, and the adaptation will be left ventricular (LV) dilatation, thus optimizing cardiomyocyte contraction according to Starling's law (as a result of an immediately increased sensitivity of troponin C to calcium) and the Anrep effect (caused by a delayed increase of the intracellular calcium pool). The Windkessel effect converts a pulsatile flow generated by a water hand pump into a continuous flow. This model partly accounts for the property of the aortic tree to release, during diastole, the pressure energy accumulated in its walls during the previous ventricular ejection phase, thus partly dampening the pulse pressure generated at the aortic root by the previous ventricular ejection.[8]

When all of these adaptative mechanisms are overwhelmed, patients may develop CS. Sympathetic activation shifts blood from the unstressed splanchnic circulation to low-capacitance vessels, with long-lasting systemic hypoperfusion driving organ damage, inflammation, and vasoplegia.[9] Restoring vascular tone with norepinephrine (not solely focusing on low cardiac output syndrome [LOCS]) improves survival in ischemic CS.

Epidemiology and Definition of CS

CS encompasses a heterogeneous population of patients. The evolving definition of CS over the last decades is depicted in Table 1. Briefly, CS is considered when organ damage results from LOCS. The European Card Shock study and the American registry reported similar in-hospital mortality rates ranging from 31% to 39%.[10,11] Although international guidelines advocate inotropic and vasopressor bi-therapy in CS, substantial heterogeneity is found in surveys with norepinephrine use varying from 53% in the FRENSHOCK study to 92% and 85% in the American and European registry, respectively.[12] Recent efforts by the Society for Cardiovascular Angiography and Interventions (SCAI) have been directed toward a more uniform CS definition with a classification scheme similar to the INTERMACS HF classification.[13] Based on this new definition, there are five categories, ranging from at-risk, pre-shock to extreme CS labeled as A–E. Medical therapy remains central to improving tissue DO_2 and myocardial recovery.

Medical Therapy

Inotropic agents are still required to treat patients with low cardiac output with grade IIb-C recommendations for the European Society of Cardiology (ESC).[16] Management of CS was summarized in an international expert consensus statement published in 2015.[2] The aforementioned epidemiological studies highlight that medical treatment of CS mainly relies on dobutamine and norepinephrine in the current era. Three catecholamines have been used to date: epinephrine, dobutamine, and dopamine targeting β-AR, α-ARs, and D1- and D2-receptors. One approach when considering medical management is to classify drugs according to their inotropic and vasoactive effects. Inotropic, inopressor, and inodilator therapies may be considered. It should be noted that inopressors have failed to improve outcomes in CS while inotropes and inodilators are still considered in our clinical practices.

Table 1
Definition of cardiogenic shock over trials.

Trials	Definitions of CS
SHOCK Trial, 1999[14]	Clinical criteria: SBP <90 mmHg and end organ hypoperfusion AND Hemodynamic criteria: CI <2.2 L/min/m^2 AND PCWP ≥15 mmHg
IABP-SHOCK II, 2012[15]	SBP <90 mm Hg or catecholamines AND Clinical pulmonary congestion AND Impaired end-organ perfusion
CARDSHOCK, 2015[10]	Acute cardiac cause AND Sustained SBP <90 mmHg or catecholamines + hypoperfusions signs (lactate >2.0 mmol/L or oliguria or skin mottling)
FRENSHOCK, 2022[12]	SBP <90 mmHg or CI <2.0 L/min/m^2 (TTE or right catheterization) AND Elevated R/L heart pressure defined by clinic, radiology, biology (BNP), TTE or invasive monitoring AND Clinical/biological hypoperfusion

CI: Cardiac index; CS: Cardiogenic shock; ESC: European Society of Cardiology; HF: Heart failure; IABP-SHOCK II: Intra-Aortic Balloon Pump in Cardiogenic Shock II; LV: Left ventricular; MI: Myocardial infarction; PCWP: Pulmonary capillary wedge pressure; SBP: Systolic blood pressure; SHOCK: Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock trial; TTE: Transthoracic echocardiography.

Dobutamine, an inotropic agent

Dobutamine is a synthetic catecholamine derived from isoprosterenol, developed to reduce chronotropic, arrhythmogenic, and vascular side effects.[17] The affinity of dobutamine for β2-AR is 10-fold lower than for β1-ARs and, in particular, its agonistic efficacy for β2-ARs and α1-ARs is much weaker than for β1-ARs. The cardiovascular effect of dobutamine has been assessed in a dose-ranging study, which revealed a dose-dependent inotropic and lusitropic action.[18] Although dobutamine is the most frequently used inotropic agent,[18] only small comparative trials support its use in clinical practice. A recent expert statement recommended avoiding high doses (>20 μg/kg/min) since these are associated with excessive tachycardia and an increase in metabolism (thermogenic effect, increased glycolysis), which may impair oxygen balance. Ultimately, dobutamine also improves mitochondrial function in non-infarcted myocardium, improving oxygen utilization efficiency.[19] Of note, catecholamines drive the down-regulation of cardiac β-ARs and tachyphylaxis has been observed as early as 3 days after exposure.[20]

Inotropic-vasodilator agents could be considered as an alternative to dobutamine

Levosimendan has been proposed for decades as an alternative to dobutamine in the treatment of CS. The active metabolite OR 1896 (after acetylation in the colon and liver) targets the Ca^{2+}-binding sites in the N-terminal region of troponin C (cTNC), improving myofilament shortening[21] without impairing diastolic relaxation or increasing myocardial oxygen consumption (MVO_2). With a longer half-life reaching 75–80 h, OR 1896 can improve inotropism for 7–9 days after infusion.[22] Levosimendan reduces peripheral vascular resistance by inhibiting K^+-channels in vascular smooth muscle, inducing arterial and venous vasodilatation,[23] and is a potent and selective phosphodiesterase 3 (PDE3)-inhibitor. PDE inhibitors (iPDE) increase contractility by increasing $[cAMP]_{IC}$. In the human myocardium, only iPDE3 improves contractility while iPDE4 rather increases atrial arrhythmias. Pre-exposure to β-adrenergic stimulation modulates the mechanism for inotropy: under β-adrenergic stimulation, levosimendan is a Ca^{2+}-sensitizer under β-blockade therapy, conversely inhibits PDE3. In the initial dose-ranging studies, levosimendan was found to improve hemodynamics and reduce pulmonary capillary wedge pressures (PCWP) to a greater extent than dobutamine when a loading dose of 6–24 μg/kg/min was followed by an infusion dose of 0.05–0.2 μg/kg/min. The RUSSLAN trial addressed its safety and found no difference between levosimendan *vs.* placebo for clinically relevant hypotension or myocardial ischemia[24]. The LIDO study first compared the Ca^{2+}-sensitizer to dobutamine and suggested a benefit for levosimendan assessed by days alive and out-of-hospital criteria[25]. However, these results were not replicated in either the SURVIVE or REVIVE trials[26,27]. There was moreover no improvement in the targeted cardiac surgery population in the CHEETAH or LEVO–CTS studies[28,29]. Levosimendan remains to date a drug of interest for β-blocker intoxication, adrenergic cardiomyopathy, or weaning VA-ECMO. iPDE3 also drives systemic and pulmonary vasodilation that may reduce right ventricular afterload, although there are concerns raised for end-organ and coronary perfusion pressure. iPDE5 has been proposed for the treatment of right ventricular HF after LV assistance device therapy or after heart transplantation for right ventricular primary graft dysfunction, although remains with marginal indication.[30–32] Milrinone is a bipyridine derivative synthetized after chemical modification of amrinone, another inotropic drug. Its plasma half-life averages 100 min and the duration of inotropic action is 60 min. Eighty percent of the drug may be recovered intact in the urine after 24 h. Dose ranging studies found that intravenous doses of 12.5 μg/kg were efficient to improve CO by 30% and reduce PCWP by 20%, while clinically relevant hypotension was observed for doses >75.0 μg/kg.[33] iPDE3 milrinone was also assessed in randomized clinical trials. In 2021, the DOREMI trial compared milrinone *vs.* dobutamine (96 patients in each group) in CS and showed no improvement in outcome.[34]. To date, milrinone remains marginally used by clinicians, with the FRENSHOCK registry reporting only 1.8% of CS patients having been

treated with milrinone. According to international guidelines on CS management, milrinone could be considered in instances of right ventricular-related CS.[2]

Dopamine is an endogenous catecholamine that exerts its dose-dependent effects on the cardiovascular system via its interaction with four different receptors: dopaminergic types 1 and 2 and adrenergic $\alpha-1$ and $\beta-1$. Its use has been discouraged after the ROSE-AHF[35] and DAD-HF[36] trials found no clinical benefit while De Backer et al.[37] reported frequent atrial and ventricular arrhythmias with dopamine.

Time for vasopressors in cardiac ICUs

Vasopressor therapy is used for improving tissue perfusion in 50–90% of patients presenting with CS.[38] Advanced CS is associated with low vascular resistance due to the activation of inflammatory pathways,[39] with patients often meeting SIRS criteria.[40] Vasopressors are introduced to maintain mean arterial pressure (MAP) >65 mmHg as well as tissue perfusion pressure. However, the use of vasopressor treatment at bedside remains difficult due to a logical increase in LV afterload with an obstacle to LV ejection as a result of its use.

Vasopressors act on vascular myocyte $\alpha 1$-adrenergic receptors to increase cytosolic calcium availability, resulting in vasoconstriction and an increase in vascular resistance and MAP.[41] Norepinephrine is the most widely used vasopressor in CS.[12] Hemodynamic effects of norepinephrine are vasoconstriction and an increase in MAP, albeit with a weak increase in heart rate due to a low β-adrenergic effect. At low infusion rates, norepinephrine increases cardiac output with a $\beta 1$-adrenergic action.[42] Epinephrine is an $\alpha 1$ and $\beta 1$ agonist, which has stronger $\beta 2$ stimulation than norepinephrine. At low dose, epinephrine increases cardiac output due to its $\beta 1$-adrenergic effect. At high dose, the vasoconstrictive action of epinephrine is limited by a $\beta 2$-adrenergic activity, and results in paradoxical effects on MAP. It has been reported that in patients free of any β-blocking agent, the net effect of adding epinephrine on top of norepinephrine on MAP could be essentially unchanged.[43] Epinephrine increases cardiac oxygen consumption,[44] while vasopressin stimulates V1a-receptor activation, producing vasoconstriction. One interesting effect of vasopressin consists in reducing catecholamine requirements in patients with shock. Vasopressin is used in salvage therapy in vasoplegic shock and post-cardiotomy vasoplegia, although no large clinical trials have studied the effect of vasopressin as a vasoconstrictor in CS.[45] Phenylephrine is an $\alpha 1$ agonist without β-adrenergic effect, which is not recommended in states of shock.[16]

One randomized trial in 2010 compared dopamine and norepinephrine as first line vasopressor therapy in shock. Of 1679 patients, there was no significant difference between the two groups in the rate of death at 28 days; however, there were a greater number of arrhythmic events among patients treated with dopamine than among those treated with norepinephrine. A subgroup analysis showed that dopamine, *vs.* norepinephrine, was associated with an increased rate of death at 28 days among patients with CS.[37]

Whether epinephrine or norepinephrine-dobutamine should be preferred to improve survival has been intensely debated in the literature. In 2011, Levy et al.[46] compared the infusion of norepinephrine-dobutamine *vs.* epinephrine on hemodynamics among 30 patients in CS. The authors concluded that epinephrine was as effective as norepinephrine-dobutamine on global hemodynamic parameters, although epinephrine was associated with more lactic acidosis, higher heart rate and arrhythmia, and inadequate gastric mucosa perfusion.[46] In 2018, the nationwide OptimaCC randomized clinical trial conducted in nine French ICUs compared epinephrine *vs.* dobutamine + norepinephrine among 57 patients in ischemic CS and confirmed experimental results whereby epinephrine was associated with a higher incidence of refractory shock.[47] It should be noted that patients under VA-ECMO were excluded. Although mortality and cardiac index (CI) were similar in both groups, epinephrine was hindered by a decreased lactate clearance, prolonged acidosis, increased heart rate, and more frequent refractory shocks. These results were consistent with those reported in the literature. In a meta-analysis including 2583 patients from 16 studies, Léopold et al.[48] found that epinephrine in CS was associated with a 3.33 (2.88–3.94) higher risk for short term mortality. Only one subgroup analysis, i.e., patients under ECLS, did not find an excessive risk for short term mortality and should be considered for further studies.[48]

Regarding the pathophysiology of low systemic resistance in CS, and in line with the results of the main clinical trials, the ESC guidelines recommend the use of norepinephrine as a first-line vasopressor in CS to maintain MAP >65 mmHg by analogy with septic shock,[49] with a IIb-B recommendation.[50] Considering potential side effects, vasopressors must be used to obtain optimal organ perfusion, with reduced prescription duration.

While catecholamines are the cornerstones for relieving patients from multiple organ failure, diuretics could also potentially be considered for treating congestive symptoms, particularly pulmonary edema. β-blockers should be discontinued as soon as the diagnosis of CS is confirmed.[2] When β-blocker therapy is responsible for refractory CS in response to standard dobutamine, clinicians should consider non-adrenergic inotropic drugs (i.e., levosimendan and milrinone) and glucagon infusion to stimulate adenylate cyclase and cAMP production independently of $\beta 1$-adrenergic stimulation.[51] Non-catecholamine supportive therapy has only been scarcely explored in the literature and available data are not sufficient to provide clear-cut recommendations.

Finally, medical therapy of CS has barely changed over the past decade and primarily relies on inotropic drugs (dobutamine should be preferred) and vasopressor agents (norepinephrine should be preferred). Levosimendan may be considered for treating β-blocker intoxication or adrenergic cardiomyopathy, or for weaning VA-ECMO, and milrinone (iPDE-III) for right ventricular-related CS. In determining the best timing for initiating inotropic or vasopressor agents, the severity of hypotension needs to be considered. In severe hypotension, inotropic and vasopressor agents should be initiated simultaneously to enhance cardiac output and restore optimal coronary perfusion pressure.

When CS Deserves Specific Therapy?

The above-described catecholamine-based management of CS has mainly been validated in an ischemic shock population. While these guidelines could potentially be exported to other CS, two conditions deserve specific mention since standard amine infusion could worsen the outcome: namely, Takotsubo

syndrome (TTS) and obstructive hypertrophic cardiomyopathy (HCM).

TTS

TTS was first described in 1990, and is defined as an acute and reversible LV dysfunction associated with LV wall motion abnormalities that are not limited to an epicardial artery territory. These LV kinetic disorders typically concern the LV apex with an apical ballooning and basal hyperkinesis,[52] in the absence of culprit epicardial coronary artery disease.[53]

This syndrome is due to an increase in circulating catecholamines sufficient to trigger stress cardiomyopathy in predisposed patients, followed by impaired microvascular perfusion, myocardial inflammation, and electrophysiological abnormalities.

There are no randomized clinical trials to support specific treatment for stress cardiomyopathy. Regular echocardiographic monitoring is needed. In patients with hemodynamically significant left ventricular outflow tract obstruction (LVOTO) >40 mmHg, β-blockers may be considered. As to the pathophysiology of TTS, cessation of sympathomimetic drugs appears to be necessary.

In patients with acute failure symptoms and altered LVEF, levosimendan, a non-catecholamine inotrope that does not increase oxygen consumption, can accelerate recovery.[54] In instances of CS and absence of access to emergency mechanical support, levosimendan is probably preferable to conventional inotropes or vasopressors.[55]

In patients with severe CS, the use of inotropes or vasopressors should be avoided.[56] These drugs can further activate catecholamine pathways and worsen the clinical prognosis.[57] At a stage of end-organ dysfunction, options include mechanical support such as temporary LV assist devices and extracorporeal membrane oxygenation (ECMO) in the "bridge to recovery" with a high probability for full recovery,[58,59] although no evidence currently exists. A possible alternative is the combined use of short half-life selective β1-blockers such as landiolol with a post-receptor inotrope such as levosimendan or milrinone plus a vasopressor in situations of hypotension.

HCM

HCM is the most frequent inherited cardiomyopathy, and is diagnosed in transthoracic echocardiography (TTE) as a wall thickness >15 mm in one or more LV myocardial segments, and unexplained by loading conditions.[60] Sixty percent of cases involve an autosomic dominant gene mutation targeting sarcomere proteins, while non-genetic etiologies are metabolic disorders, mitochondrial diseases, infiltrative diseases with amyloidosis, or neuromuscular disease.[61]

Critical care physicians should track LVOTO, defined by an LV outflow tract gradient ≥30 mmHg at rest or ≥50 mmHg provoked and mitral regurgitation due to systolic anterior motion (SAM).[62] Identification of LVOTO and SAM is crucial for medical management as catecholamine infusion increases inotropism, LVOTO, and SAM and subsequently worsens the condition.[62]

Large randomized trials are currently lacking in HCM. Objectives or treatments are aimed at reducing symptoms and halting disease progression. LVOTO should be treated with β-blockers (atenolol, propranolol) and fluid loading, which improve LV filling. Propranolol has exhibited beneficial effects in this indication.[63] If β-blockers are contraindicated, verapamil can be considered. Disopyramide, which is a class IA antiarrhythmic with negative inotropic properties, can be used if β-blockers are not sufficient, together with QT monitoring.[64] Digoxin should be avoided due to inotropic effects.[65] If medical treatments fail and the patient remains symptomatic with LVOTO >50 mmHg and NYHA dyspnea III or IV, septal alcohol ablation or surgical myomectomy are potential alternatives.[60] CS without LVOTO must be treated with the usual drugs.

There is a lack of data on patients with HCM developing CS. Due to LVOTO and microvascular ischemia, some patients present with features suggesting acute coronary syndrome, with normal coronary angiograms. A small study on 14 HCM patients in CS with LVOTO showed improvement after β-blocker infusion with metoprolol or esmolol, with phenylephrine to support blood pressure, thereby reducing SAM and LVOTO gradients.[66]

This counterintuitive medical management in obstructive HCM should be kept in mind by critical care physicians who should track LVOTO and SAM, to avoid catecholamine infusion and perform fluid loading.

Post Shock Management

Expert guidelines currently rely on sparse literature. The best timing to initiate cardioprotective drug titration after CS remains unclear and should be individualized. New SGLT2 inhibitors are not burdened by hypotension and could be initiated after catecholamine removal. However, the benefit of early introduction of iSGLT2 after CS has yet to be established. Recent publications suggest empaglifozin and dapaglifozin could be introduced early after MI.[67] For the other cardioprotective drugs, the rule should be: "start low, go slow." Although current guidelines suggest that only targeting doses of cardioprotective drugs are effective, low drug doses for HF with reduced ejection fraction yield substantial benefits in reducing morbidity and mortality. Clinicians should remember that the addition of a new drug class yields benefits that are greater in magnitude than up-titration of existing drug classes.[68] Experts recommend that β-blockers should be introduced only several days after IV drug discontinuation. In patients with troublesome hypotension (i.e., systolic arterial pressure <100 mmHg), mineralocorticoid antagonists (MRA) and iSGLT2 should first be introduced.[68] Whether the patient could be considered for heart transplantation or ventricular assistance device implantation should be assessed early as it may help to stratify the need for VA-ECMO.

Perspectives for CS

The prognosis of CS has scarcely improved over the past decade and its management, aside from catecholamine therapy, has remained broadly similar. New treatments targeting inflammation, vasoplegia, or inotropism are currently proposed to improve the outcome. Table 2 summarizes target populations as well as main results of recently published major clinical trials.

Immunomodulation has failed to improve outcomes in CS to date. In 2007, the TRIUMPH trial assessed the non-selective NOS inhibitor L-N-monomethylarginine (L-NMMA) in myocardial in-

Table 2
Perspective treatment for cardiogenic shock.

Treatment	Pathophysiology and benefits	Study population	Main results
Adrecizumab ACCOST HH[70]	Endovascular chelation of adrenomedullin to enhance its vascular and myocardial protective effects	CS defined as low SBP + clinical pulmonary congestion + organ dysfunction (lactate, oliguria, altered mental status, clammy skin and limbs) Exclusion criteria: cardiac arrest with CPR >60 min, sustained bradycardia or tachycardia.	On day-30, number of days free from any CV support (vasopressor, inotropes, mechanical circulatory support) Failed to improve CV support free survival days.
OM ATOMIC HF[74,75]	Cardiac myosin activator. Increases systolic ejection time and inotropism without increasing MVO_2	Elevated BNP/NTBNP and reduced LVEF and dyspnea refractory to IV loop diuretics Exclusion criteria: eGFR <20 mL/min/m^2, stenotic valvular disease, recent AMI (<30 day), uncontrolled blood pressure	Primary outcome: dyspnea relief after OM infusion *vs.* placebo. Only the highest dose (targeting blood concentration ≈ 310 ng/mL) improved dyspnea relief at 48 h
iDPP3	Increased DPP3 found in CS DPP3 injection in murine models induces myocardial depression Murine model of isuprel induced heart failure, injection of iDPP3 resolve cardiac function	Pre-clinical studies only	–
Istaroxime SEISMIC trial[79]	Positive stimulation of SERCA Ca^{2+} re-uptake and Na/K ATPase plasmatic membrane pump Increases inotropism and lusitropism without increased heart rate.	SCAI stage B pre-CS: acute HF + LVEF <40% + SBP <75–90 mmHg Exclusion criteria: recent AMI < 3 months; IV drugs; venous lactate >2 mmol/L; eGFR <30 mL/min/m^2; Tp° >38 °C; recent stroke.	Primary outcome: AUC of SBP along the first 6 h of infusion was significantly higher in the Istaroxime group TTE ΔCO improvement: +0.2 L/min/m^2 Adverse events: nausea, vomiting

ΔCO: Cardiac output variations; AMI: Acute myocardial infarction; AUC: Area under the curve; BNP: Type natriuretic peptide; CPR: Cardiopulmonary resuscitation; CS: Cardiogenic shock; CV: Cardiovascular; eGFR: Estimated glomerular filtration rate; iDPP3: Dipeptidyl peptidase 3 inhibitor; IV: Intravenous; LVEF: Left ventricular ejection fraction; MVO_2: Myocardial oxygen consumption; NTBNP: N-terminal pro B-type natriuretic peptide; OM: Omecamtiv mecarbil; SBP: Systolic blood pressure; SCAI: Society for Cardiovascular Angiography and Interventions; SERCA: Sarcoendoplasmic reticulum calcium ATPase; Tp: Temperature; TTE: Transthoracic echocardiography.

farction CS (MI-CS) and found no improvement for the primary endpoint of 30-day all-cause mortality.[69] Adrenomedullin blood concentration has been identified as a risk factor for mortality in CS.[70] Circulating adrenomedullin binding to endovascular receptors improves vascular function while interstitial adrenomedullin drives inflammation and capillary leakage. Adrecizumab binds to adrenomedullin and prolongs its vascular half-life but does not act as an inhibiting antibody. In the ACCOST-HH trial, 77 patients (51%) were randomly assigned to adrecizumab and 73 (49%) to placebo. Mortality did not differ between groups at 30 days (hazard ratio[HR]=0.99, 95% confidence interval [CI]: 0.60–1.65; *P*=0.98) or 90 days (HR=1.10, 95% CI: 0.68–1.77; *P*=0.70).[70] Whether non-specific anti-inflammatory therapy could benefit CS patients remains unknown. The ongoing "low dose corticosteroids for CS in Adult patients" (COCCA) trial is designed to assess the hemodynamic effects of early low-dose corticosteroid therapy (with hydrocortisone and fludrocortisone) on CS reversal, as defined by catecholamine-free days at day 7, while 28- and 90-day overall survival will be analyzed as secondary outcomes.[71]

Current treatments targeting inotropism raise myocyte calcium concentrations and increase myocardial contractility but at the cost of increased heart rate and oxygen consumption. Omecamtiv mecarbil (OM) is a selective cardiac myosin activator accelerating the transition rate of myosin into the strongly actin-bound force-generating state and generating an increased systolic ejection time (SET) without increasing heart rate or MVO_2.[5] Nagy et al.[72] found that OM improved isometric force in response to increasing Ca^{2+} contraction in an in vitro experimental study. Bakkehaug et al.[73] reported an improvement in ejection fraction under OM in an ischemic porcine model of acute HF. Large clinical trials have assessed the outcomes for OM in chronic and acute HF.[74] Although OM failed to improve exercise capacity at 20 weeks in the METEORIC–HF trial, GALACTIC–HF randomized 8256 patients with reduced ejection fraction to OM (using pharmacokinetic-guided doses of 25 mg, 37.5 mg, or 50 mg twice daily) or placebo and found a lower incidence of a composite of heart-failure event or death from cardiovascular causes (37% *vs.* 39%, respectively).[74,75] The ATOMIC-AHF trial specifically assessed OM in acute HF and found a dose-dependent improvement for dyspnea.[76]

Recently, dipeptidyl peptidase 3 (DPP3) has been proposed as a new biomarker in CS.[77] DPP3 is a metallopeptidase involved in cleavage of proteins such as angiotensin II (ATII). Deniau et al.[78] recently reported that DPP3 should be not only a biomarker but also, more importantly, a causal myocardial depressant agent and could represent a bio-target in CS. In a murine model of isoproterenol-induced HF, the DPP3 inhibitor procizumab restored normal hemodynamics while DPP3 infusion resulted in a profound negative inotropic action in healthy mice. In a previous pre-clinical study, DPP3 infusion affected hemodynamics only in ATII-infused mice. While the mechanism for myocardial improvement remains unknown, DPP3 inhibitor and its therapeutic potential will be of interest in coming years.

Istaroxime, a new molecule targeting both inotropism (Na^+/K^+ ATPase pump activation) and lusitropism (through diastolic Ca^{2+} reuptake in the SERCA), has been developed. Animal models confirmed this favorable mechanism with a dose-dependent cardiac unloading and inotropism effect, while not hampered by an increased heart rate. The HORIZON–HF trial assessed the effects of istaroxime in a randomized controlled trial in non-shock patients hospitalized with acute HF: unlike dobutamine or milrinone, this agent was found to decrease heart rate, shorten the QTC interval, and demonstrated no pro-arrhythmic effects.[79] The phase II SEISMIC trial recently validated the safety and efficacy of istaroxime in a pre-CS population.[80] Further studies are needed to implement istaroxime in clinical practice.

Similarly, ATII infusion has been proposed in refractory CS. Under VA-ECMO, the significant proportion of blood bypass-

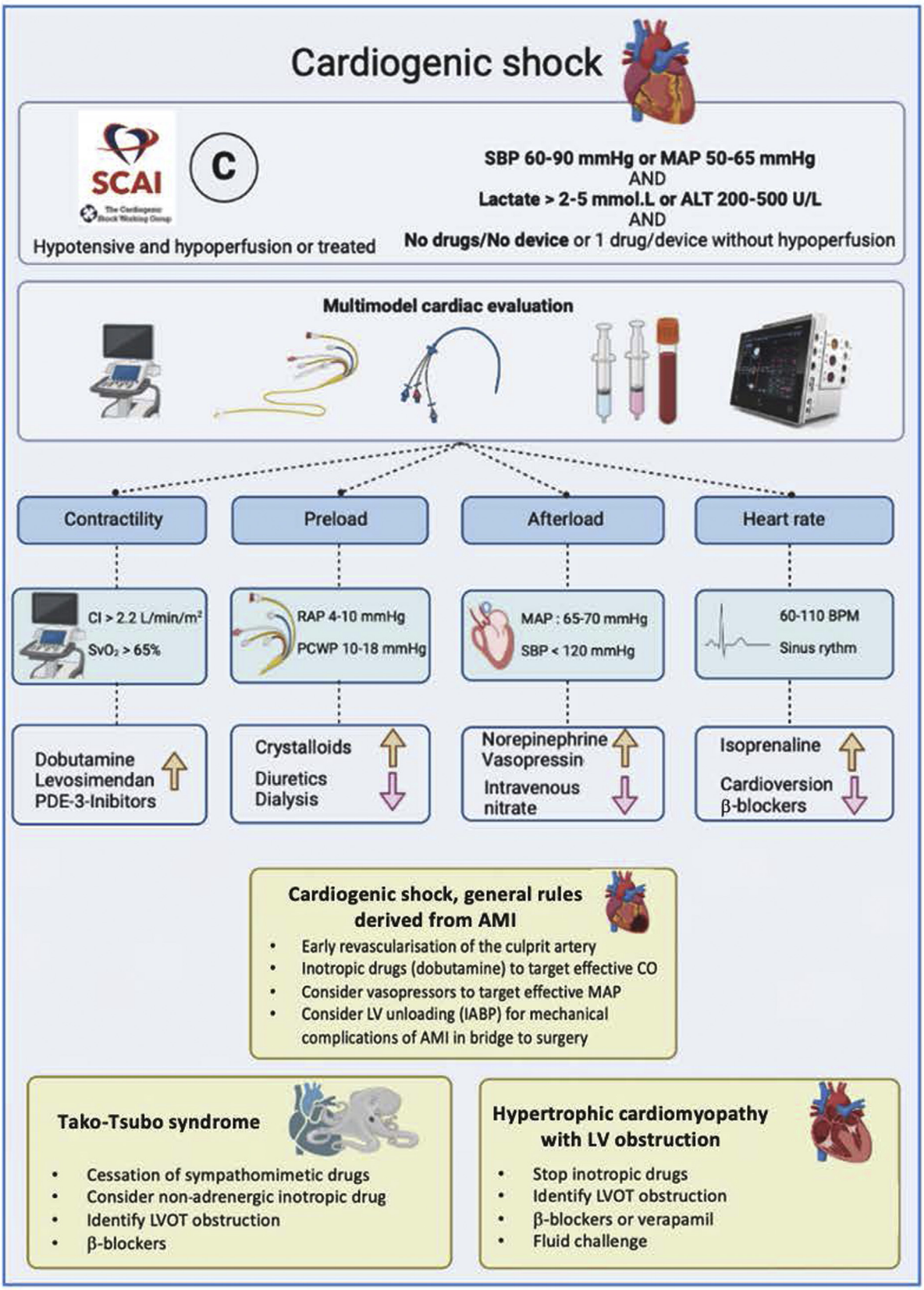

Figure 2. Central illustration. Definition, monitoring, and medical treatment of CS.
ALT: Alanine aminotransferase; AMI: Acute myocardial infarction; BPM: Beats per minute; CI: Cardiac index; CMP: Cardiomyopathy; CO: Cardiac output; CS: Cardiogenic shock; IABP: Intra-Aortic balloon pump; LV: Left ventricle; LVOT: Left ventricular outflow tract; MAP: Mean arterial pressure; PCWP: Pulmonary capillary wedge pressure; PDE-3: Phosphodiesterase 3; RAP: Right atrial pressure; SBP: Systolic blood pressure; $ScvO_2$: Venous blood oxygen saturation.

ing the lung contributes to ATII deficiency.[81] A systematic review reported that ATII improved systolic blood pressure and cardiac output in 38 patients with CS or cardiac arrests.[81] In the ATHOS-3 trial, ATII effectively increased blood pressure in patients with vasodilatory shock not responding to high doses of conventional vasopressors.[82] Osterman et al.[83] further reported that five patients with septic myocardial dysfunction requiring VA-ECMO hemodynamically improved following ATII infusion. However, ATII infusion remains controversial as its pro-coagulant effect may burden the outcome in cardiovascular patients.[84] Further studies are also needed to support clinical practice.

Temperature management has been proposed since target-temperature therapy can improve outcomes in cardiac arrest. However, randomized hypothermia *vs.* normothermia failed to improve survival and neurological outcomes at 6 months after cardiac arrest. Whether mild hypothermia could benefit CS patients has been assessed in the SHOCK COOL trial.[85] In this RCT involving 40 patients with CS after MI, mild therapeutic hypothermia failed to show a substantial beneficial effect on cardiac power index at 24 h. In line with these results, HYPO ECMO randomized early moderate hypothermia (33–34 ˚C; *n*=168) for 24 h *vs.* strict normothermia (36–37 ˚C; *n*=166) and found no significant improvement for 30-day survival, although it did provide insights suggesting that hypothermia under ECMO could be safely administered, without any increase in the rate of complications (e.g., incidence of bleeding).[86] There is currently no evidence supporting hypothermia in CS.

Conclusions

Other than catecholamine management, only a few changes have been reported in the landscape of medical management of CS over the past decade.

Dobutamine should first be considered to restore CO. Vasopressors (norepinephrine) may then be used to restore end-organ perfusion pressure targeting MAP >65 mmHg. When confronted with low MAP, dobutamine and norepinephrine should be introduced concomitantly. For right ventricular-related CS, inotropic drugs reducing RV afterload could be considered (milrinone, levosimendan). For TTS, clinicians should first consider using catecholamine-free therapy based on iPDE. Caution is required in obstructive hypertrophic cardiomyopathies since any increase in inotropism could result in LVOTO augmentation and worsen hemodynamics. The central illustration (Figure 2) provides a summary of these treatment approaches.

In the era of mechanical devices, medical therapy remains a cornerstone for myocardial recovery. New therapeutics are currently being assessed in ongoing trials.

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Conflict of Interest

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