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Myocardial Recovery in Cardiogenic Shock

REVIEW

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ABSTRACT

The overarching goal of cardiogenic shock (CS) therapy is ensuring long-term survival. In recent years, increasing emphasis has been placed on analyzing mechanisms to improve outcomes in CS. This includes averting in-hospital mortality, modifying the disease process by promoting heart recovery while avoiding multiorgan failure, and circumventing complications related to both CS and treatment strategies deployed to treat CS. Heart replacement therapies represent a viable strategy for long-term survival but are restricted to a small, select percentage of patients. In this review we focus on pathophysiology of the shock state, with an emphasis on addressing reversible etiologies contributing to the decompensated state, optimizing physiological factors for recovery, and identifying therapeutic targets to promote recovery. We also review the known predictors of myocardial recovery, regardless of the etiology of CS. Lastly, we highlight the current gaps in knowledge in this field and support additional high-quality studies focusing on myocardial recovery in CS.

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INTRODUCTION

Cardiogenic shock (CS) is a complex and heterogenous syndrome characterized by cardiac dysfunction and systemic hypoperfusion, and it is associated with high morbidity and mortality.[1] In recent years, major efforts including randomized clinical trials, large registry analyses, and development of interdisciplinary shock teams have been undertaken to improve patient survival.[2-4] Current guidelines suggest the use of inotropic agents, vasopressors, and temporary mechanical circulatory support (tMCS) devices to improve patient hemodynamics.[1,5,6] Even so, minimal data is available to support these therapies for improving outcomes, including myocardial recovery and survival, among CS patients.

When assessing outcomes in CS, patients are often divided into two categories at the time of hospital discharge: mortality or survival—the latter reported as either heart replacement therapy (HRT) or native heart survival.[7] In contemporary publications, HRT is defined as patients who were discharged with a durable left ventricular assist device (LVAD) or underwent heart transplant (HT) during hospitalization. Native heart survival (NHS) is defined as those who were successfully discharged without HRT, while the mortality cohort is comprised of patients who died during their index hospitalization. Survival and, ideally, NHS is the ultimate goal for patients with CS. While survival from index hospitalization is the key first step to allow for long-term myocardial recovery, defining NHS in the context of CS is not well established.

For those with chronic or end-stage heart failure (HF) presenting with acute on chronic HF (ACHF), heart replacement therapy is an ideal but limited option for a select patient population. Clinical experience has shown that the process of reverse remodeling in chronic HF can be facilitated through guideline-directed medical therapy (GDMT) as well as myocardial unloading. Depending on the underlying etiology and duration of HF, recovery of a myocardium inflicted with CS requires time and interventions, including cardiac unloading, revascularization, and stabilization of arrhythmias. This is especially true for CS related to myocardial infarction (MI-CS) or from an acute pathology resulting in decompensated heart failure (ADHF) or post-cardiotomy CS. Hence, every effort should be made to assess for and promote myocardial recovery and NHS in this patient population. In this review, we focus on mechanisms of promoting myocardial recovery in CS regardless of underlying etiology. We also review known predictors of myocardial recovery and the role of specific interventions as well as future directions in the field.

DEFINING MYOCARDIAL RECOVERY IN CARDIOGENIC SHOCK

By definition, myocardial recovery in HF with reduced ejection fraction entails a return to both normal structure and function of the myocardium, which rarely occurs in the majority of HF syndromes in the short term.[8] Instead, most patients with HF enter a "remission" phase of reverse remodeling. This phase results from partial reversal of the cardiac myocyte and extracellular matrix abnormalities, leading to improvement in left ventricular (LV) geometry and contractile performance. The degree of recovery is determined in part by the reversibility of underlying etiology as well as the extent of underlying myocyte and extracellular matrix derangements.[9]

In the context of CS, myocardial recovery can be defined as a reversal of the pathological state of the myocardium, with significant improvement in heart structure and function sufficient to allow hospital discharge and sustained remission from hospitalizations. However, nuances of myocardial recovery distinct from those in chronic HF are not well defined and are the subject of ongoing work.[10]

IMPACT OF CS ETIOLOGY ON MYOCARDIAL RECOVERY

The reverse remodeling in myocardial recovery is not simply a reversal of the pathophysiologic process that led to the shock state. Rather, it reflects a new process resulting in a less pathological state. Although most existing trials in CS focus on MI-CS, both MI-CS and HF-CS are now well recognized as distinct clinical entities with divergent profiles and outcomes.[3] A key distinction is that MI-CS usually begins with hypotension progressing to hypoperfusion and resulting in congestion, whereas HF-CS presents with ADHF and congestion leading to hypoperfusion and hypotension.[11] Of note, advanced stages of CS from either etiology are characterized by significant systemic inflammatory response and cytokine surge leading to vasoplegia.[12]

PREDICTORS OF MYOCARDIAL RECOVERY IN MI-CS

In patients with acute MI-CS, various clinical factors have been associated with increased likelihood of myocardial recovery (Table 1). The residual severity of baseline coronary artery disease also has been a predictor of worse outcomes, sometimes described as the "double jeopardy" phenomenon in patients presenting with acute MI-CS that are found to have concomitant noninfarct-related chronic total occlusions (CTO). These patients usually suffer larger infarct size when the

	HF-CS	MI-CS
Imaging/EKG	• Absence of left bundle branch block (+) • LVEF[80] • End-systolic and end-diastolic volumes (+) • Improvement in valvular regurgitation (+)	• Presence of viable myocardial segments (+) • LVEF[80] • Chronic total occlusion in non-infarct related artery [14] • Infarct related artery supplying large area[13]
Hemodynamics	• PAPi – predictor of RV failure	• Baseline SBP(1) • Cardiac power output (CPO) - strongest independent parameter of in-hospital mortality[81] • PAPi – predictor of RV failure • Shock index (HR/SBP)[82]
Biomarkers	• Lactate[28] • NT-proBNP, BNP[20] • IL-6[19] • Soluble ST2[21] • Dipeptidyl peptidase 3[23] • Adrenomedullin[22]	• Lactate[28] • Cardiac troponins[24] • Solube ST2[21] • Dipeptidyl peptidase 3[23] • Adrenomedullin[22] • Angiopoietin-2[83] • Cardiogenic Shock 4 Proteins (CS4P) complex- liver fatty acid-binding protein (L-FABP), beta-2-micro- globulin (B2M), fructose-bisphosphate aldolase B (ALDOB), and SerpinG1 (IC1)[24]
Miscellaneous	• Female sex (+) • Non-ischemic etiology (+) • Younger age (+)	

Table 1 Predictors of recovery and outcomes in cardiogenic shock. EKG: electrocardiography; HF-CS: heart failure cardiogenic shock; MI-CS: myocardial infarction cardiogenic shock; LVEF: left ventricular ejection fraction; PAPi: pulmonary artery pulsatility index; (+) predictor of better outcome, (-) predictor of worse outcome

previously developed collaterals from patent donor vessels to myocardial areas subtended by the CTO become suddenly occluded in the setting of an acute MI. A key factor is the anatomical location of the acute infarct artery: compared to inferior MI, anterior MIs place a large area of the myocardium at risk and have a higher likelihood of progression to worse myocardial function, which is associated with increased 30-day mortality.[13] The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial showed that the presence of a CTO in a noninfarct-related artery was an independent predictor of increased mortality.[14]

Viability testing, often used to predict whether revascularization of ischemic segments will lead to myocardial recovery, is often not possible in a state of CS. Results from the largest clinical trials in ischemic cardiomyopathy—STITCH (Surgical Treatment for Ischemic Heart Failure) and REVIVED-BCIS (Revascularization for Ischemic Ventricular Dysfunction)—have indicated that the presence of viable myocardial segments suggests a higher likelihood of improved LV function.[15,16] However, preoperative viability analysis did not identify patients who benefit from surgical revascularization, and myocardial viability did not correlate with improved survival.

Several hemodynamic parameters have been identified as predictors of mortality in patients with MI-CS. In the SHOCK (Should we Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial registry of MI-CS, cardiac power output was identified as the strongest independent parameter of in-hospital mortality.[17] In addition, pulmonary artery pulsatility index was found to be a valuable hemodynamic assessment of right ventricular (RV) failure in both patients with MI-CS and RV failure after durable LVAD.[18] Invasive hemodynamic assessments using pulmonary artery catheters has been suggested to improve prognostication in patients with CS and to identify patients that will likely benefit from tMCS strategies, although this approach has not been validated in randomized clinical trials.

The biomarkers B-type natriuretic peptide (BNP), N-terminal (NT)-proBNP, and interleukin-6 play complementary roles in predicting outcomes in MI-CS, but their utility is hindered by complex relationships with several variables.[19,20] While soluble ST2 (sST2) shares the same limitations, a combination of sST2 and NT-proBNP demonstrates good discrimination for 30- and 90-day mortality in MI-CS.[21] Novel biomarkers such as dipeptidyl peptidase 3 and adrenomedullin have been investigated in the PREPARE CardShock (PRospective REgistry of PAtients in REfractory cardiogenic shock) registry with positive results.[22,23] Angiopoietin-2 is another potential biomarker whose serum concentrations were independently associated with mortality in a substudy of the IABP-SHOCK II (Intra-Aortic Balloon Pump in Cardiogenic Shock II) trial. Rueda et al. described the Cardiogenic Shock 4 Proteins (CS4P) score, which may aid in risk stratification in MI-CS.[24] However, the use of these novel biomarkers is limited to the research setting for now.

PREDICTORS OF MYOCARDIAL RECOVERY IN HF-CS

Despite poorer initial hemodynamics, HF-CS patients have a more favorable in-hospital course with less need for vasopressor or mechanical support. This is partly because HF-CS is characterized by a prolonged evolution that permits compensatory mechanisms to support pump function at the expense of increased filling pressures and adverse remodeling. Typically, an acute event (eg, tachyarrhythmias, volume overload, or valvular disease) precipitates decompensation, ultimately resulting in a shock state. Recovery from the shock state in these patients hinges on identifying and then reversing this acute trigger. One specific cause of HF-CS that merits special mention is acute myocarditis, which has a better chance of recovery compared to acute-on-chronic HF from other causes.[25] Although limited data are available to support specific therapies directed at the causes of myocarditis, prompt recognition and diagnosis of acute myocarditis, along with the initiation of immunosuppressive therapy when appropriate, as well as hemodynamic support with inotropes and MCS are key to maximizing the chance of recovery.[25] Moreover, the duration of HF is an important predictor of myocardial recovery, with acute HF-CS, such as that due to acute myocarditis, having a much better prognosis compared to acute-on-chronic HF-CS.

Clinical parameters extrapolated from chronic HF observational studies have suggested that female sex, nonischemic etiology, younger age, and absence of left bundle branch block may predict reverse LV remodeling and recovery of LVEF.[26] Identifying patients with improvements in end-systolic and end-diastolic volumes, the absence of RV dysfunction, and improved valvular regurgitation all predict increased reverse LV remodeling.[27]

Biomarkers such as troponin, NT-proBNP, and BNP have consistently been utilized in clinical practice for prognostication purposes in HF-CS patients. These measures are particularly helpful in prognostication when applied at presentation, but their ability to predict myocardial recovery in HF-CS is not well understood. However, early lactate clearance is associated with better survival in CS, and this evidence supports serially trending lactate until it normalizes.[28] As noted earlier, it is unclear whether IL-6, sST2, dipeptidyl peptidase 3, and adrenomedullin have differing predictive abilities with HF-CS and MI-CS.[19,21–23] The hemometabolic derangements that occur in HF-CS affect the amounts of circulating biomarkers, and serial measurements are required over time as these multiple confounding factors likely limit their ability to remain specific to intrinsic myocardial properties.

STRATEGIES TO PROMOTE MYOCARDIAL RECOVERY IN CARDIOGENIC SHOCK

As stated, promoting NHS by promoting myocardial recovery is key to improving survival in CS, and various strategies can be used in clinical practice to accomplish this (Figure 1).

ROLE OF REVASCULARIZATION

The SHOCK trial (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) demonstrated that early revascularization for acute MI-CS improved overall survival at 6 months.[29] The STICH trial randomized patients with coronary artery disease and LVEF ≤ 35% who were also receiving GDMT to surgical revascularization or GDMT alone.[15] It showed a 16% reduction in total mortality with bypass surgery compared to medical therapy. In addition, a prespecified subgroup-analysis of STICH showed that mortality was significantly reduced with surgical revascularization in patients who had at least two of the three following anatomical variables: (1) three vessel disease; (2) severe LV dysfunction (LVEF < 27%); or (3) high-end systolic LV volume (> 79 mL/m^2), whereas a benefit of surgical revascularization was not observed in patients without three-vessel disease.[30] On the other hand, REVIVED-BCIS2 failed to show survival benefit with multivessel percutaneous coronary intervention among patients with severe ischemic cardiomyopathy.[16]

LEFT VENTRICULAR UNLOADING WITH TEMPORARY MCS

The goals of LV unloading in CS are myocardial protection by optimizing the balance between oxygen demand and supply, augmented end-organ perfusion, and weaning of vasopressors to mitigate mesenteric and peripheral vasoconstriction. The use of intra-aortic balloon pump (IABC) did not reduce morality in patients with MI-CS, and its routine use for CS is not recommended by the 2014 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines. However, IABC may still have a role in treatment for chronic HF patients who present with ADHF and CS.[31]

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a robust MCS for treatment of Society for Cardiovascular Angiography and Intervention (SCAI) stage D-E CS, which provides optimal end-organ perfusion and reverses vasopressor requirement. Because of its inherent physiologic feature of increasing LV afterload, it may cause LV distention and pulmonary edema, mitigating against myocardial recovery. More recently, the ECLS-SHOCK (Extracorporeal Life Support in Infarct-Related Cardiogenic Shock) trial failed to show survival benefit of VA-ECMO support over medical therapy alone in acute MI-CS. The

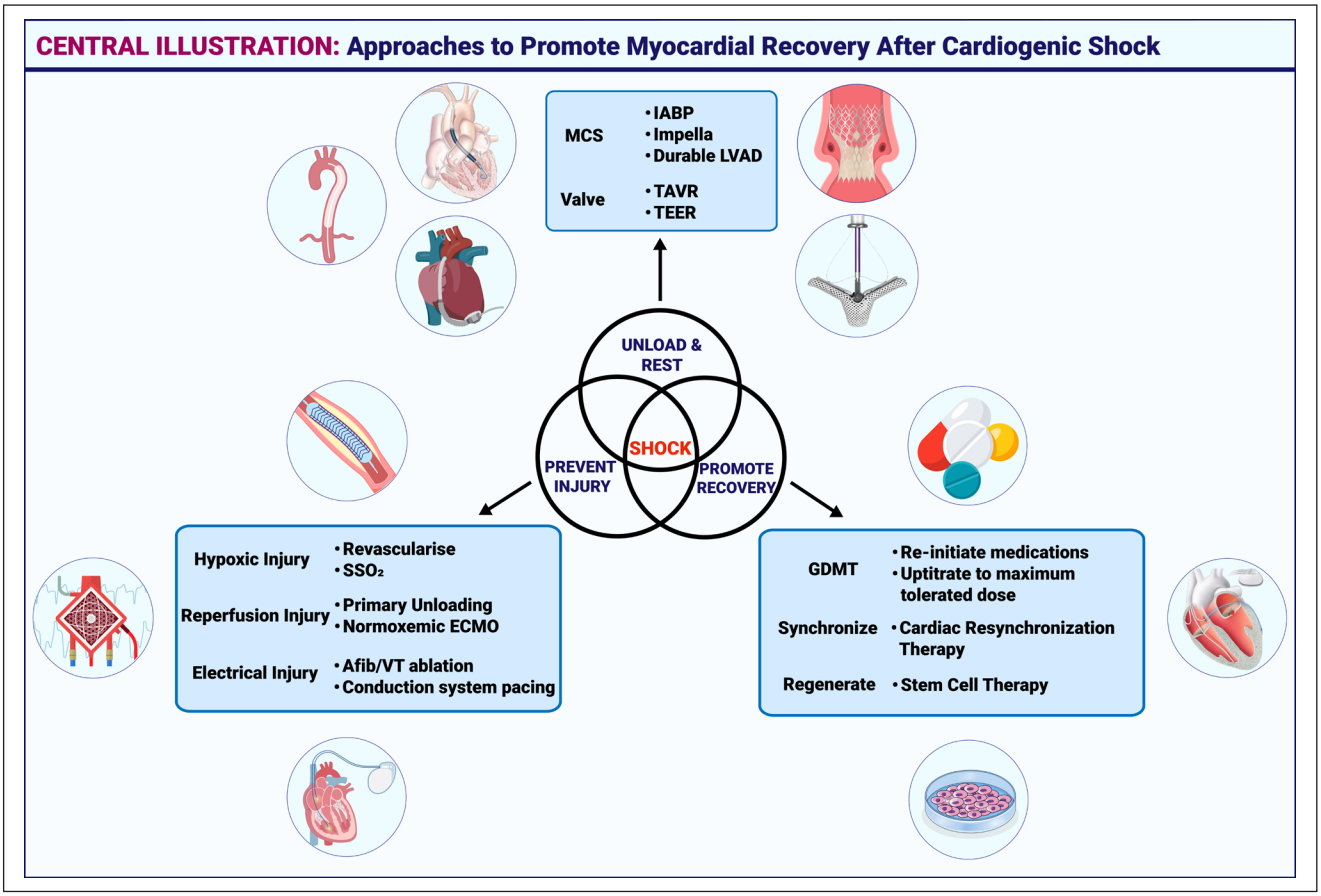

Figure 1 Approaches to promote myocardial recovery after cardiogenic shock. MCS: myocardial cardiogenic shock; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; TAVR: transcatheter aortic valve replacement; TEER: transcatheter edge-to-edge repair; SSO_2: super-saturated oxygen; ECMO: extracorporeal membrane oxygenation; VT: ventricular tachycardia; GDMT: guideline-directed medical therapy

authors speculate that device-related complications such as bleeding, limb ischemia, and LV distention with a lack of mandated LV unloading offset the potential benefits.[32]

Transvalvular unloading is a strategy that improves myocardial energy substrate utilization and preserves mitochondrial function, limiting ischemic injury.[33,34] The Impella (Abiomed) catheter is a transvalvular microaxial flow pump that is placed either percutaneously or surgically. Particularly, Impella 5.5 can generate up to 6.2 L/min of flow, increasing coronary flow and unloading the LV vigorously. Combining Impella with VA-ECMO provides robust hemodynamic support without LV distention, and improved survival has been shown with the addition of Impella to VA-ECMO in the setting of refractory CS compared to VA-ECMO alone.[35] Although no randomized prospective trials have shown Impella 5.5 support in CS, some case series have shown successful bridging to advanced HF options and LV recovery.[36] Indeed, the DanGer (Danish-German) shock trial showed lower mortality in acute MI-CS patients supported with Impella CP for LV unloading.[2]

Although the STICH trial showed survival benefit of surgical revascularization for ischemic cardiomyopathy over medical therapy, those patients with reduced LVEF are at high risk of post-cardiotomy shock. Pathophysiological mechanisms associated with post-cardiotomy shock are multifactorial and include inflammatory response resulting in vasoplegia, tissue ischemia caused by use of vasoactive agents as a treatment for vasoplegia, and suboptimal myocardial protection with aortic cross-clamping. To offset some of these pathophysiologic mechanisms and reverse the vicious spiral in high-risk cardiac surgery, early initiation of tMCS plays an important role. Currently, the ongoing IMpella-Protected cArdiaC Surgery Trial (IMPACT) is a prospective single-armed trial aiming to demonstrate the safety and efficacy of the preemptive use of Impella 5.5 in high-risk cardiac surgery patients with severe LV dysfunction.[37]

For those who need longer-term LV unloading, implantation of durable LVAD should be considered. Contemporary LVAD (HeartMate 3) has been shown to have improved hemocompatibility with a lower risk of pump thrombosis and nondisabling stroke than its predecessors.[38] Myocardial recovery has been reported in a small subset of LVAD patients, and surgical explant is performed for eligible patients.[39-42] LVAD explant for myocardial recovery in the setting of chronic unloading can be promoted in select patients with the use of GDMT.[7,43] With follow-up extending

to 10 years post explant, the outcomes of these patients post explant remain encouraging, including freedom from recurrent HF or need for advanced therapies.[44,45]

ADDRESSING VALVULAR PATHOLOGIES IN CS

For CS in the setting of aortic stenosis, percutaneous procedures are a reasonable option for patients who are too unstable for surgical intervention. Balloon aortic valvuloplasty (BAV) may be considered in hemodynamically unstable patients with critical aortic stenosis as a bridge to surgical aortic valve replacement or to transcatheter aortic valve replacement (TAVR). However, it may cause or worsen aortic regurgitation. The more definitive TAVR appears to be the optimal strategy, although it requires scrupulous preprocedural assessment of aortic root anatomy to minimize periprocedural or post-procedure complications. A recent study showed a high success rate with better short-term survival in emergent TAVR compared with emergent BAV followed by elective TAVR.[46]

A multicenter, collaborative, patient-level analysis showed that MitraClip® (Abbott Vascular) was a safe and effective therapeutic device to treat patients with significant MR and CS who were not surgical candidates. Specifically, successful device implantation was achieved in 88.7% and associated with a decreased risk of mortality.[47] For severe mitral stenosis complicated by CS, percutaneous balloon mitral valvuloplasty can be considered if the anatomy is favorable (Wilkins score 8).[48]

ROLE OF GDMT IN MYOCARDIAL RECOVERY IN CS

In patients with chronic HF, use of GDMT has been associated with reduced 1-year mortality and rates of hospitalization. Moreover, there is a clear trend of improved outcomes with the use of monotherapy, dual therapy, or triple therapy compared to no GDMT.[49,50] However, patients in CS may require discontinuation of some or all of their GDMT medications, which has been linked to worse outcomes even in the absence of CS. Evidence from studies such as OPTIMIZE-HF as well as subsequent meta-analyses have demonstrated that stopping beta blockers post-hospitalization is associated with higher mortality rates (HR 0.60; 95% CI, 0.37-0.99, P = .044).[51,52] Similarly, findings from Get With The Guidelines-Heart Failure and the COACH (Comparison of Outcomes and Access to Care for Heart Failure) study have indicated adverse outcomes upon discontinuing ACEi/ARB and MRAs.[53,54]

These data suggest the importance of resuming GDMT in CS patients when feasible. Strategies such as transvalvular unloading to maintain hemodynamics may facilitate the continuation of GDMT either partially or fully in the setting of CS. It is also important not to withhold oral GDMT for transient reductions in blood pressure or mild worsening of renal function, especially for patients in the recovery phase of CS. The strategy of combining GDMT with durable MCS was investigated in the RESTAGE-HF (Remission from Stage D Heart Failure) study, where over 50% of patients receiving aggressive GDMT had an LVAD explant within 18 months, with an impressive 90% 1-year survival post-explant.[7,44] The Impella BTR (Bridge-to-Recovery) Early Feasibility Study aims to evaluate the safety of the Impella 5.5 and its feasibility in supporting patients for up to 28 days, until they either recover or receive alternative treatment.[10] Initiating GDMT while patients are supported with the Impella 5.5 may increase their chances of recovery; however, this remains to be studied.

ELECTROPHYSIOLOGY OPTIMIZATION AND MYOCARDIAL RECOVERY

Effective arrhythmia management is essential in promoting myocardial recovery after CS. The use of antiarrhythmic therapies with negative chronotropic or inotropic effects such as beta-blockers or calcium channel blockers may be challenging in CS, but it is possible if hemodynamics are supported by a tMCS device. Alternatives include amiodarone or DC-cardioversion with close clinical monitoring. If these strategies fail, consideration should be given to restoring sinus rhythm as early as possible during the recovery phase, before substantial substrate modification occurs. This approach is backed by contemporary trials such as CASTLE-HTx (Catheter Ablation for Atrial Fibrillation in Patients with End-Stage Heart Failure and Eligibility for Heart Transplantation), which demonstrated a mortality benefit with catheter ablation (HR 0.29; 95% CI, 0.12-0.72) for atrial fibrillation in end-stage HF.[55] Moreover, patients with persistent systolic dysfunction during the recovery period should be evaluated for cardiac resynchronization therapy (CRT) or CRT-defibrillator (CRT-D), recommendations supported by multiple randomized controlled trials and systematic reviews.[56,57] However, CRT remains underutilized, possibly due to the misconception that LV dilation indicates nonresponsiveness. While there is growing interest in conduction system pacing, including His bundle pacing and left bundle branch area pacing, the current evidence for CRT is substantially stronger than that available for conduction system pacing.[58]

NOVEL THERAPEUTIC STRATEGIES PROMOTING MYOCARDIAL RECOVERY IN CS

The ongoing exploration of CS pathophysiology reveals potential therapeutic targets to mitigate injury and promote recovery. Microcirculatory dysfunction, as a sign of distal perfusion in shock state and detected via orthogonal polarization spectral imaging, is an adverse prognostic factor in CS due to reduced erythrocyte deformability and

impaired response to reactive hyperemia.[59-62] Strategies addressing microcirculatory dysfunction may limit myocardial damage and allow promotion of recovery. MI-CS patients are at risk of reperfusion injury, linked partly to mitochondrial permeability transition, which is influenced by factors such as mitochondrial membrane potential, matrix calcium, reactive oxygen species, and pH.[63] Super-saturated oxygen (SSO_2) therapy delivers localized hyperbaric levels of oxygen to treat ischemic myocardium and has demonstrated improvements in microvascular flow, reducing infarct size, and increasing the likelihood of reverse LV remodeling in patients with AMI.[64] The ISO-SHOCK (Incorporating SuperSaturated Oxygen in Shock) trial is currently ongoing to evaluate outcomes of SSO_2 therapy in AMI-CS patients.

Reperfusion-induced cardiolipin level reduction, affecting inner mitochondrial membrane structure and electron transport chain function, is being explored as a therapeutic target in VA-ECMO for MI-CS.[65] Furthermore, reducing systemic inflammation may benefit CS, as elevated interleukin-1β, 6, 7, 8, and 10 levels correlate with poorer outcomes.[12]

Another area of research on myocardial recovery post-MI-CS explores the regeneration of infarcted myocardium. Promising approaches involve the use of extracellular matrix-based biomaterials, administered via open chest surgery or minimally invasive catheters.[66] Small animal studies have demonstrated functional improvement following the delivery of embryonic stem cells (ESCs) or induced pluripotent stem cells.[67] Direct intramyocardial injection of ESCs in myocardial infarction animal models has shown significant LV function improvement at 4 weeks post-injection.[68,69] In HF-CS patients receiving LVADs, ongoing research focuses on promoting myocardial recovery.[7] Strategies such as ramp testing with invasive hemodynamic measurements aim to optimize LVAD unloading, while titration of pump speed enables patients to tolerate more intense GDMT.[70,71] Moreover, after LVAD implantation, there has been an observed decrease in MMP-1 and MMP-9, and an increase in the metalloprotease inhibitors TIMP-2 and TIMP-4 as well as the ratio of mutated collagen to total collagen, indicating extracellular matrix repair.[72]

LACUNAE IN KNOWLEDGE AND FUTURE DIRECTIONS

Despite recent progress in clinical research to manage CS and promote recovery, the field lacks evidence from randomized controlled trials to guide care effectively. Significant unknowns persist in risk stratification for CS, although a revised classification of CS proposed and validated by the Cardiogenic Shock Working Group offers a promising framework.[3,73] Machine learning approaches to classification and risk stratification also have been proposed, with integration of these algorithms into electronic health records potentially enhancing real-time decision-making capabilities.[74]

The notion that myocardial injury, and hence recovery, is binary has been debunked by clear evidence demonstrating myocardial recovery in various scenarios. However, the exact mechanisms and drivers behind this process remain poorly understood. Preclinical studies investigating the biological signature of CS and myocardial recovery face challenges, particularly in studying changes to myocardial cells under mechanical and biochemical stress using traditional tissue culture methods. The utilization of living animal or human cardiac tissue holds promise in overcoming this obstacle.[75]

Evidence regarding treatment methods to promote myocardial recovery after CS is largely limited to observational studies, with a notable scarcity of randomized clinical trials in this field. Recent findings on complete hemodynamic profiling suggest potential benefits in improving CS outcomes. However, hemodynamic predictors of myocardial recovery, especially in HF-CS, are not well established.[76] The ongoing PACCS (Pulmonary Artery Catheter in Cardiogenic Shock) trial aims to provide further clarity on this issue.[77] Investigative approaches such as upfront unloading and delayed reperfusion in STEMI are being explored in trials such as STEMI DTU (Door-To-Unload in STEMI Pilot Trial), but their efficacy in reducing infarct size in MI-CS remains uncertain.[78] Animal models suggest that ECMO may increase infarct size in MI-CS, with potential mitigation by EC-Pella; however, the translation of these findings to clinical practice is yet to be elucidated.[78,79] Moreover, trials like RESTAGE HF have primarily focused on traditional GDMT medications in improving outcomes in LVAD patients, leaving the role of newer GDMT medications such as ARNi, SGLT-2 inhibitors, and ivabradine unexplored.[44]

In addition, several other aspects of CS management require further investigation to elucidate their impact. First and foremost, we need a consensus on the definition of myocardial recovery in the context of CS that allows for optimal patient outcomes beyond survival at hospital discharge. These include determining the optimal timing and patient selection for percutaneous interventions, MCS, or cardiac transplantation as well as exploring interventional approaches to managing recurrent, life-threatening ventricular tachyarrhythmias while on MCS. Additionally, assessing the potential of conduction system pacing in preventing pacing-induced cardiomyopathy in

CS and evaluating the safety and efficacy of percutaneous or surgical interventions for tricuspid regurgitation are crucial areas of research. It is hoped that advancements in these areas will enhance CS management and promote myocardial recovery. Overall, the field of myocardial recovery after CS offers numerous avenues for exploration and discovery. Despite current knowledge gaps and the ongoing need for further investigation, the future holds promise with continued advancements in this rapidly evolving domain.

KEY POINTS

- Myocardial recovery in cardiogenic shock involves reversing the pathological state of the myocardium, leading to significant improvements in cardiac structure and function and ultimately promoting patient survival.
- Predicting myocardial recovery after cardiogenic shock involves a multifaceted approach, including the use of imaging modalities, hemodynamic parameters, and biomarkers.
- Left ventricular unloading with temporary mechanical circulatory support, revascularization, addressing valvular pathologies, optimizing guideline-directed medical therapy, and managing arrhythmias are essential to facilitate myocardial recovery after cardiogenic shock.
- Despite current gaps in knowledge, ongoing research is exploring novel therapeutic strategies to further enhance myocardial recovery outcomes in cardiogenic shock patients.

COMPETING INTERESTS

The authors have no competing interests to declare.

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