Hemodynamics of Cardiogenic Shock

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KEYWORDS
- Cardiogenic shock
- Hypoperfusion
- Hemodynamic
- Pressure-volume loops
- Right heart catheterization

KEY POINTS
- Treatment of cardiogenic shock remains a clinical challenge.
- Greater understanding of the pathophysiology of cardiogenic shock from different causes and of the available treatment strategies is leading to new treatment concepts.
- If the left ventricular dysfunction is based on ischemia or infarction, changes in myocardial perfusion occurring at different stages of the process can play pivotal roles.
- It is important that clinicians appreciate and understand the physiologic meaning of these measurements and take them into account when treating patients with cardiogenic shock.

INTRODUCTION
Cardiogenic shock (CS) represents an advanced state of morbidity along the pathophysiologic pathway of end-organ hypoperfusion caused by reduced cardiac output (CO) and blood pressure (Table 1). Acute coronary syndromes (ACSs) remain the most common cause of CS, with an estimated 100 to 120,000 patients in the United States and Europe subsequently having CS after ACS each year. The spectrum of hypoperfusion states caused by low CO ranges from pre-CS to refractory CS and can be characterized by an array of hemodynamic parameters. This review provides the foundation for a hemodynamic understanding of CS including the use of hemodynamic monitoring for diagnosis and treatment, the cardiac and vascular determinants of CS, and a hemodynamic approach to risk stratification and management of CS.

DEFINITIONS
The spectrum of CS can be divided into pre-CS, CS, and refractory CS—whereby each state is characterized by increasing levels of tissue hypoperfusion and poorer response to treatment but have in common an underlying reduction in CO. Although several different parameters have been used to define CS, the most widely used definitions focus on hemodynamic parameters based on blood pressure and cardiac index (CI). Abnormalities of central venous pressure, pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR) are typically involved but not always included in CS definitions owing to variability in measurement, and serum lactate is often included to provide objective evidence of end-organ hypoperfusion. For each of these parameters, it is well recognized that there is a continuum ranging from the completely normal condition to a state of refractory CS. Current management strategies rely on this continuum, in particular by drawing attention to patients who are on the verge of significant end-organ dysfunction development in whom early intervention can be particularly effective.

In this regard, the state of pre-CS, also referred to as nonhypotensive cardiogenic shock, has been...
discussed and defined as clinical evidence of peripheral hypoperfusion with systolic blood pressure (SBP) more than 90 mm Hg without vasopressor circulatory support. Compared with patients with CS, patients with pre-CS had similar CI, left ventricular ejection fraction (LVEF), and PCWP but higher SVR (1753 ± 675 vs 1389 ± 689 dyn/cm/sec *P* = 0.07).3 Notably, patients with pre-CS are often difficult to identify because of subtle signs of hypoperfusion; however, proper diagnosis can be important because of high rates of in-hospital mortality (as high as 43%).3

CS has been defined clinically as (1) SBP less than 90 mm Hg for greater than 30 minutes or use of vasopressors to achieve those levels; (2) evidence of pulmonary edema or elevated left ventricle (LV) filling pressures (LV end diastolic pressure or PCWP); (3) evidence of organ hypoperfusion including at least one of the following: (a) change in mental status; (b) cold, clammy skin; (c) oliguria; (d) increased serum lactate.4,5 Finally, refractory-CS can be defined as CS unresponsive to medical or mechanical support.

The use of invasive hemodynamic measurements is important for definitive diagnosis and for characterizing the extent and site of the cardiac pathologic condition through the measurement of right-sided filling pressures, pulmonary pressures, wedge pressures, and CO.

### ETIOLOGY

A multitude of processes can lead to CS. CS can occur acutely in a patient without prior cardiac history or progressively in a patient with longstanding chronic heart failure. The most prevalent etiology of CS remains ACS (including ST-segment elevation myocardial infarction [MI] and non–ST-segment elevation acute coronary system), which accounts for nearly 80% of cases. Despite advances in treatment and revascularization, CS remains the most lethal complication of MI, with mortality rates ranging from 38% to 65% in different cohorts.6–8 CS in ACS results most commonly from myocardial dysfunction caused by ischemia or infarct but can also be caused by mechanical...
Complications including acute mitral regurgitation from papillary muscle rupture, ventricular septal rupture, and free wall rupture. Non-ACS causes of CS, although less frequent, can result from abnormalities or as a consequence of a primary cardiac, valvular, electrical, or pericardial abnormality\(^4,9\) including decompen-
sated valvular disease, acute myocarditis, left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy, cardiomyopathy, pericardial tamponade, arrhythmias, mechan-
ical (traumatic) injury to the heart, postcardiot-
omy syndrome, uncontrolled arrhythmia, and progression of congenital lesions. The preva-
ience of these various non-ACS causes of CS has been estimated as follows: progression of chronic heart failure (11%), valvular and other mechanical causes (6%), stress-induced/ Takotsubo cardiomyopathy (2%), and myocard-
itis (2%).\(^10\) Among heart failure patients, CS was the presenting clinical feature of 7.7% of patients with either new-onset heart failure or decompensated chronic heart failure patients.\(^11\)

**DIAGNOSIS AND EVALUATION OF CARDIOGENIC SHOCK PATIENTS**

Although physical examination and laboratory, electrocardiographic, and echocardiographic testing remain the mainstay in the initial evalua-
tion of a patient suspected of having CS, increasing emphasis on hemodynamic evalua-
tion has the potential for earlier recognition and more appropriate management of CS with subsequent improvement on outcomes. The initial clinical evaluation in CS is difficult in unsta-
able patients owing to rapidly changing hemody-
namics and the frequent contribution of multiple comorbid processes.\(^12\) Traditional signs of heart failure, including pulmonary congestion and ju-
gular venous distention, may be misleading in a patient with right ventricular (RV) failure, pul-
monary embolism, chronically compensated heart failure, arrhythmias, and mechanical com-
lications—thus reducing the specificity of these signs to diagnose CS. Invasive hemodynamic assessment using pulmonary artery catheteriza-
tion (PAC) provides an important adjunct in the diagnosis and continuous evaluation of a patient with CS. This technique allows bedside direct and indirect measurement of major determi-
nants of cardiac performance (such as preload, afterload, and CO) supplying additional data to support clinical decision making.\(^13\) Right heart catheterization additionally offers information regarding fluid status and right heart filling pres-
ures, adequacy of oxygen delivery, and the
degree of pulmonary vascular resistance. These hemodynamic data in turn can guide the therapeu-
tic choices through volume optimization, va-
sodiators, vasopressors, and inotropes as appropriate and the critical decision regarding whether to provide mechanical circulatory sup-
port (MCS). In fact, invasive hemodynamic mea-
surements are often necessary for the proper selection, timing, and settings of medical and mechanical support. Finally, hemodynamic changes throughout treatment course and follow-up have shown prognostic importance.\(^14,15\)

The use of invasive hemodynamic assessment is in decline,\(^16\) primarily because of data from studies such as the ESCAPE trial,\(^17\) in which an overall neutral impact of PAC-guided therapy was seen in heart failure patients compared with therapy guided by clinical evaluation alone. However, this study was limited by several po-
tential confounders, including the possibility that the neutral results actually reflected a nega-
tion of the benefit of aggressive reduction in filling pressures by the harmful effects of thera-
pies such as inotropes that were used based on the hemodynamic profile extracted from the use of PAC. In fact, high-volume centers in the ESCAPE trial along with patients in CS may have shown outcome benefit with PAC compared with non-PAC use. Other studies have examined the use of PAC in the treatment of ACS patients, finding associations with PAC use and increased 30-day mortality, although CS patients have shown a notable exception whereby the harmful effect of PAC was dimin-
ished.\(^18–20\) In the retrospective SUPPORT study,\(^20\) although higher mortality rates were observed in intensive care unit patients and related to PAC, it is difficult to determine whether these effects were not simply caused by PAC use in sicker patients compared with non-PAC use. A second study by Murdoch and colleagues\(^21\) confirms this suspicion, as PAC insertion was not predictive of death (odds ratio, 1.08; 95% confidence interval, 0.87–1.33) after correcting for treatment bias, suggesting that higher mortality in PAC-guided patients may be owing to worse baseline condition rather than the effect of hemodynamic measurement or the invasive nature of the procedure.

The debate about the necessity of PAC use is further fueled by findings from studies exam-
inining physician ability to predict hemodynamic findings without the use of PAC compared with invasive measures that showed only half of the estimations were correct.\(^12\) Additionally, in a reported series of patients treated for
circulatory shock, 63% of cases underwent a change in treatment plan after insertion of PAC.\textsuperscript{23} No study yet has used PAC-derived variables to drive treatment protocols to determine whether invasive hemodynamic-guided data result in better outcomes than do data derived from noninvasive methods such as echocardiography.\textsuperscript{24} Although noninvasive measurements are commonly used to gain proxy information regarding hemodynamic changes in critically ill patients, in the setting of CS, these measures are hampered by lack of accuracy and may not identify dynamic changes that can only be assessed invasively.\textsuperscript{25}

Filling pressures are a necessary but often overlooked component of PAC measurements. In a recent analysis of the ESCAPE trial of patients treated for acute decompensated heart failure, last recorded CI was not associated with clinical outcomes, whereas PCWP was associated with long-term morbidity and mortality. These findings argue further that treatment goals should focus not only on improving cardiac function but also hemodynamic assessment and reduction of filling pressures, which can only reliably be achieved through invasive measurement.\textsuperscript{26} This finding has been substantiated by recent literature from patients with mechanical circulatory support (MCS) arguing that direct hemodynamic evaluation of patients with left ventricular assist devices is required for optimization and determination of ventricular-vascular device interactions.\textsuperscript{27}

Invasive hemodynamic measurement is not without risk—including complications, inaccuracies, and interpretation ambiguity. Complications include insertion site hematoma, arterial puncture, arrhythmias, infections, pulmonary infarction, pulmonary hemorrhage, and pulmonary artery puncture.\textsuperscript{28} Inaccuracies in measurement include temporal, positional, and volumetric variation, and interpretation can be different according to patient characteristics and overall clinical contextualization as well as conflicting measurements.\textsuperscript{29} Each of these limitations is heavily influenced by the experience level of the operating physician. With PAC insertion done by junior physicians along with the decline in overall volume of PAC procedures, it is expected that higher rates of complications and misinterpretation may occur.\textsuperscript{29}

**PATHOPHYSIOLOGY AND HEMODYNAMICS**

CS shock stemming from myocardial ischemia and infarction provides a useful model to illustrate the pathophysiologic and hemodynamic effects of CS. Beginning with an incident MI of sufficient size to significantly reduce ventricular chamber contractility, the cascade of events that culminates in CS starts with initial decline of CO and subsequent increase of left and RV diastolic pressures that eventually leads to further decline of coronary perfusion and a resulting cycle of myocardial impairment. End-organ damage develops with pulmonary congestion, tissue hypoxia, and further myocardial ischemia.

Several compensatory mechanisms are activated in response to these hemodynamic changes, including increased sympathetic tone (yielding both positive inotropic and chronotropic effects), activation of the renin angiotensin aldosterone system (yielding increases in preload as a result of fluid retention and afterload as a result of vasoconstriction), and subsequent activation by the natriuretic peptide system that responds to myocardial stretch and attempts to counteract the renin angiotensin aldosterone system through natriuresis, diuresis, and vasodilation.

It can be difficult to clearly ascertain whether certain changes are beneficial or detrimental. One such example is afterload reduction with decreased arterial blood pressure, whereby the unloading of the ventricle has a protective effect while coronary perfusion declines even further, worsening myocardial ischemia and necrosis.\textsuperscript{5} Similarly, the increased sympathetic tone and the release of catecholamines is essential to maintain adequate CO by increasing contractility, but at the same time this increases myocardial oxygen consumption and puts the patient at higher risk of arrhythmias and additional myocardial necrosis.

The following provides a useful model for a hemodynamic understanding of CS by examining the cardiac and vascular determinants of CS.

**Decreased Contractility**

Although impaired contractility is a primary driver of CS owing to ischemia, impaired contractility does not necessarily mean the patient will have CS after an acute ischemic event. Rather, it is the degree of cardiovascular adaptability both before the event and immediately afterward that will determine the hemodynamic outcome and whether the patient will subsequently have CS. Moreover, LVEF is probably not sensitive enough to express the degree of cardiac impairment observed in CS. This finding shown in the SHOCK trial whereby LVEF of CS
patients was approximately 30%, and nearly one-quarter of patients had LVEF greater than 40%, a proportion similar to that reported in other MI trials that included reduced LVEF patients without evidence of CS. Additionally, patients who recovered and had improvement in their functional status showed no change in their LVEF compared with values recorded during the acute phase of CS. Several groups have reported that nearly half of CS nonsurvivors died with a normal CI; despite this, among CS patients, LVEF was found to be a reliable predictor of mortality. Lastly, because CS is a proinflammatory state that has important effects on preload and afterload, the correlation between contractility and CO may be particularly variable in the CS population.

For purposes of illustrating and understanding the pathophysiology of CS, pressure-volume (PV) analysis can be particularly helpful. Fig. 1A depicts the PV loop of a normal person; the loop is contained within the boundaries of the end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR, respectively). With the incident MI, the ESPVR shifts downward and rightward, signifying the abrupt reduction of ventricular contractility (Fig. 1B). This reduction is accompanied by immediate and profound reductions in blood pressure (indexed by the height of the PV loop), stroke volume (SV, indexed by the width of the PV loop) and cardiac output (the product of SV and heart rate). Mild elevations of LV end-diastolic pressure and PCWP may also be seen.

**Autonomic Response to Decreased Contractility**

Decreases in blood pressure are sensed by the baroreceptors, which activate efferent autonomic nerve fiber firing to heart and vascular structures and activate adrenal release of epinephrine. These factors act to increase

![Fig. 1. The pathophysiology of CS illustrated by use of PV loops. (A) Normal state. (B) PV loop shows changes after acute MI (red); (C) PV loop shows changes caused by autonomic response to decreased contractility (blue); (D) PV loop shows changes caused by release of inflammatory mediators (green); (E) PV loop shows manifestation of cardiac remodeling (pink) with changes in both ESPVR and EDPVR relationship. See text for further details. LVD, left ventricular dysfunction; NH, neurohormonal.](#)
heart rate (CO), attempt to increase cardiac contractility, and cause systemic vasoconstriction, which increases SVR and induces vasoconstriction. Venoconstriction plays a critical role in the pathophysiology of CS\textsuperscript{13} and results in a leftward shift of the venous pressure-volume curve, which functionally shifts blood from an unstressed to a stressed compartment (Fig. 2), thus increasing functional circulating blood volume and causing elevations of central venous and pulmonary venous pressures. In aggregate, these effects cause further rightward shifts of the PV loop, increases in blood pressure, and inconsequential effects on cardiac output (increased heart rate tending to increase CO and increased SVR tending to decrease CO) as illustrated in Fig. 1C.

**Inflammatory Response**

An essential consequence of CS, with or without primary myocardial injury is the accompanying inflammatory process, which manifests in release of several inflammatory mediators. From a hemodynamic standpoint this inflammation causes pronounced nitric oxide mediated vasodilation. This has been seen in CS patients initially considered due to impaired myocardial function that have prominent declines in SVR.\textsuperscript{1,12} Among the explanations for this observation are (1) the pronounced cytokine-mediated response seen in CS after acute MI,\textsuperscript{34,35} (2) sepsis or bacteremia (eg, gut bacterial transmigration),\textsuperscript{36} and (3) oxygen free radicals buildup and amplified nitric oxide synthesis as part of ischemia-reperfusion syndrome.\textsuperscript{35,37} Regardless of the mechanism, these inflammatory mediators counteract certain aspects of the neurohormones, resulting in reduction in SVR and the potential for venodilation, both of which can decrease blood pressure (Fig. 1D).

**Remodeling**

Persistent neurohormonal activation and elevated filling pressures drive the process of remodeling,\textsuperscript{38} characterized by progressive increases in LV size and reductions in function. Furthermore, in the setting of infarction, remodeling is mediated by 2 interrelated processes: extension and expansion.\textsuperscript{35} Extension involves areas of the myocardium remote from the primary infarct zone and was explained previously by the CS state affecting myocardial perfusion by (1) infarct-related artery re-occlusion, (2) intracoronary thrombus propagation, or (3) a mismatch between the elevated myocardial oxygen demand and decline in coronary perfusion pressures. Ventricular dysfunction and dilation caused by infarct extension plays a major role in the deterioration of CS.\textsuperscript{39} This finding is particularly evident in patients with prior multi-vessel disease and impaired autoregulation owing to flow limitation in more than 1 myocardial territory in the low pressure state of CS. The second process in infarct evolvement is expansion, whereby areas adjacent to the infarction become ischemic. This process occurs as the cells neighboring the border zone of an infarction are at higher risk for additional ischemic events.\textsuperscript{40} One factor contributing to infarct expansion is a catecholamine-induced increase in myocardial oxygen demand. It is, therefore, not surprising that in a pooled analysis of 10 randomized trials evaluating infarct size by advanced imaging techniques, infarct size was closely related to clinical outcomes after ACS.\textsuperscript{41} Infarct extension, expansion, and, more generally, remodeling, manifest on the pressure-volume diagram as rightward shifts of both the ESPVR and the EDPVR and reflect in the global

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**Fig. 2.** (A) Venous PV relationship (blue) shows functional compartmentalization of blood between unstressed and stressed compartment. (B) With venoconstriction caused by increased neurohormonal activation, leftward shift of the curve increases venous pressure owing to functional shift of blood from unstressed to stressed blood volume despite constant total blood volume. Because of the steepness of the curve, relatively small shifts can cause large increases of venous pressure. Further discussion in Burkhoff and Tyberg.\textsuperscript{33} NH, neurohormonal.
changes in LV size, structure, and function characteristic of chronic heart failure (Fig. 1E).

**Right Ventricular Failure Involvement in Cardiogenic Shock**

The RV has several unique characteristics compared with the LV that are important in understanding the pathway by which RV failure can cause CS on its own or contribute to CS during primary LV dysfunction. First, compared with the LV, the RV differs substantially in terms of size, structure, metabolism, and afterload. Second, the RV has remarkable recovery abilities after RV infarct. Involvement of the RV in CS is less common compared with LV involvement (5% vs ~95%, respectively, in the SHOCK trial) yet patients with RV caused by LV failure have mortality rates similar to those in patients with CS caused by LV failure. Furthermore, patients with CS caused by involvement of both LV and RV have worse outcomes than patients with LV involvement alone.

Most patients with isolated RV failure have suffered inferior or posterior MI and present with CS earlier (>3 hours earlier) compared with LV-failure patients. This finding emphasizes the fact that the RV is prone to rapid decline in function because of its formation and thin walls, and indeed a short time span is needed for transition from stable conditions to development of right heart failure. Elevated right atrial pressures with similar LV filling pressures, CO and CI, are found in patients with RV CS. Finally, because the septal wall is responsible for an important part of the contractile force generated by the RV, septal ischemia involvement of LV infarction can have a marked impact on RV function because of RV-LV interactions.

Fortunately, several studies found an impressive recovery of RV function in survivors of CS caused mainly by RV dysfunction. This observation underscores the importance of early recognition of RV failure as a cause of CS and the need for treatment aimed at prompt relief of RV ischemia. Notably, there are some early promising results seen with the use of temporary mechanical unloading with percutaneous RV assist devices allowing patients to bridge through the period of RV failure.

**MECHANICAL COMPLICATIONS OF ACUTE MYOCARDIAL INFARCT PRESENTING AS CARDIOGENIC SHOCK**

In patients with CS after acute MI (AMI; especially first or nonanterior MI) a high index of suspicion should be kept for mechanical complications as the source of CS rather than LV dysfunction. Mechanical complications include ventricular septal rupture, contained free wall rupture, and papillary muscle rupture. In most of such cases, rapid echocardiographic evaluation will reveal the mechanism of CS, and because prognosis is dismal in mechanical CS, urgent intervention (usually surgical) should be delivered promptly.

**RISK STRATIFICATION AND PROGNOSIS**

The prognosis of CS remains poor despite advances in treatment options and improved understanding of the pathophysiologic mechanisms. Risk stratification models in CS, in principle, allow for early identification and direction of aggressive treatment of those at highest risk. Age, SBP, heart rate, and presenting Killip class were found to be predictive of adverse outcomes in the GUSTO I and III trials. In the PURSUIT cohort, presenting ST depressions, height, and rales on physical examination showed additional prognostic value; however, positive predictive values remained less than 50%. In the TRIUMPH study, which included vasopressor-dependent CS patients after revascularization, only SBP and creatinine clearance were found to be predictive of mortality (variables that have since been validated in the SHOCK-II trial).

A severity score system derived from the SHOCK trial and registry included 2 models for prediction of in-hospital mortality, the first accounting for clinical variables and the second based on invasive hemodynamic data. Both models included age, end-organ hypoperfusion, and anoxic brain damage; the clinical model also included shock on admission, SBP, prior coronary artery bypass grafting, noninferior myocardial infarction, creatinine of $1.9 \text{ mg/dL}$, and the hemodynamic model added stroke work and LVEF less than 28%. The CardShock risk score incorporated common clinical variables for prediction of in-hospital mortality and found the following predictors: ACS as the etiology for CS, age, prior MI, prior coronary artery bypass grafting, confusion, reduced LVEF, and elevated serum lactate level. In a comparison with the SHOCK risk model the authors were able to show superiority in terms of c-statistics for prediction in both the CardShock cohort and in the IABP-SHOCK II cohort.

Finally, cardiac power index may be useful not only as a means of estimating cardiac contractile reserve but also as a strong predictor of mortality in AMI CS. Low initial cardiac power index is considered a predictor of unfavorable outcomes in CS patients (0.6 W/m²) in nonsurvivors.
vs 0.74 in survivors). This index accounts for the fact that in many CS patients, merely improving CO will not promote recovery from shock, as the inflammation-mediated decline of SVR remains prominent. The increase in mean arterial pressure in addition to improved CO serves as evidence of improvement of both the contractility component and recovery of SVR, and might be a useful tool to assess patients’ prognosis and responsiveness to vasopressors.

**MANAGEMENT OF CARDIOGENIC SHOCK**

The initial evaluation of patients presenting with CS should trigger an attempt to address all reversible causes according to the suspected etiology of the condition. For the rarer etiologies of CS other than ischemia, immediate intervention is necessary, as with pericardial tamponade or free wall rupture. As for most CS patients, management of CS resulting from AMI includes the use of drugs such as inotropes and vasopressors, fluid management, and early revascularization. The introduction of early revascularization over the last decades has resulted in a decline in mortality compared with the pre-revascularization era.

Despite the sharp increase of percutaneous coronary intervention rates in CS patients and guideline recommendations for early revascularization in CS, percutaneous coronary intervention rates remain underutilized, with only 50% to 70% of eligible patients receiving intervention.

However, as summarized in Fig. 3 reproduced from Thiele and colleagues, commonly used

**Table 1**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Follow-up</th>
<th>n/N</th>
<th>n/N</th>
<th>Relative Risk 95% CI</th>
<th>Relative Risk 95% CI</th>
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<tr>
<td><strong>Revascularization (PCI/CABG)</strong></td>
<td>1-y</td>
<td>81/152</td>
<td>100/150</td>
<td>0.72 (0.54;0.95)</td>
<td>0.87 (0.66;1.29)</td>
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<td>SHOCK</td>
<td>30 d</td>
<td>22/32</td>
<td>18/23</td>
<td>0.72 (0.54;0.95)</td>
<td>0.87 (0.66;1.29)</td>
</tr>
<tr>
<td>Total</td>
<td>103/184</td>
<td>118/173</td>
<td>0.82 (0.69;0.97)</td>
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<tr>
<td><strong>Vasopressors</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>SOAP II (CS subgroup)</td>
<td>28 d</td>
<td>64/145</td>
<td>50/135</td>
<td>0.75 (0.55;0.93)</td>
<td>0.75 (0.55;0.93)</td>
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<tr>
<td><strong>Inotropes</strong></td>
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<td></td>
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<tr>
<td>Unverzagt et al.</td>
<td>30 d</td>
<td>5/16</td>
<td>10/16</td>
<td>0.33 (0.11;0.97)</td>
<td>0.33 (0.11;0.97)</td>
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<td><strong>Glycoprotein IIb/IIIa-inhibitors</strong></td>
<td>In-hospital</td>
<td>15/40</td>
<td>13/40</td>
<td>1.15 (0.59;2.27)</td>
<td>1.15 (0.59;2.27)</td>
</tr>
<tr>
<td><strong>Nitric oxide synthase inhibitors</strong></td>
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<td></td>
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<td>TRIUMPH</td>
<td>30 d</td>
<td>97/201</td>
<td>76/180</td>
<td>1.14 (0.91;1.45)</td>
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<td>24/59</td>
<td>7/20</td>
<td>1.16 (0.59;2.69)</td>
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<tr>
<td>Cotter et al</td>
<td>30 d</td>
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<td>10/15</td>
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<td>1.05 (0.85;1.29)</td>
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<td><strong>IABP</strong></td>
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<tr>
<td>IABP-SHOCK I</td>
<td>30 d</td>
<td>7/19</td>
<td>6/21</td>
<td>1.28 (0.45;3.72)</td>
<td>1.28 (0.45;3.72)</td>
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<td>IABP-SHOCK II</td>
<td>30 d</td>
<td>119/300</td>
<td>123/298</td>
<td>0.86 (0.79;1.17)</td>
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<td>Total</td>
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<td>0.98 (0.81;1.18)</td>
<td>0.98 (0.81;1.18)</td>
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<td><strong>LVAD</strong></td>
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<td>Thiele et al</td>
<td>30 d</td>
<td>9/21</td>
<td>9/20</td>
<td>0.95 (0.48;1.90)</td>
<td>0.95 (0.48;1.90)</td>
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<td>Burkhoff et al</td>
<td>30 d</td>
<td>9/19</td>
<td>5/14</td>
<td>1.33 (0.57–3.10)</td>
<td>1.33 (0.57–3.10)</td>
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<td>Seyfarth et al</td>
<td>30 d</td>
<td>6/13</td>
<td>6/13</td>
<td>1.00 (0.44–2.29)</td>
<td>1.00 (0.44–2.29)</td>
</tr>
<tr>
<td>Total</td>
<td>24/53</td>
<td>20/47</td>
<td>1.06 (0.68–1.66)</td>
<td>1.06 (0.68–1.66)</td>
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</tbody>
</table>

Fig. 3. Summary for the evidence from randomized, controlled trials studying different treatment modalities in cardiogenic shock patients. CABG, coronary artery bypass grafting; CI, confidence interval; IABP, intra-aortic balloon pump; IABP-SHOCK, intra-aortic balloon pump in shock; LVAD, left-ventricular assist device; PCI, percutaneous coronary intervention; SHOCK, SHould we emergently revascularize occluded coronaries for cardiogenic shock; SMASH, Swiss multicenter trial of angioplasty for SHock; SOAP II, sepsis occurrence in acutely III patients II; TRIUMPH, tilargin acetate injection in a randomized international study in unstable MI patients with cardiogenic shock. (From Thiele H, Ohman EM, Desch S, et al. Management of cardiogenic shock. Eur Heart J 2015;36(20):1223–30; with permission.)
approaches have not shown benefit. Accordingly, guidelines for the management of CS are based on expert opinion. As a result, practice varies significantly from institution to institution and even among physicians in the same institution.

Despite these advances in therapy, however, mortality rates of patients with refractory CS remain unacceptably high. Major efforts are devoted in recent years toward introduction of new approaches, trying to (1) prevent the evolvement of massive cardiac injury after MI with intravenous β-blockers, intramyocardial delivery of miR-29a, intracoronary supersaturated oxygen, and pressure-controlled intermittent coronary sinus occlusion among many other approaches and (2) allowing better treatment once CS is present—as in the development of acute mechanical circulatory support (AMCS) devices. Although these minimally invasive devices have the potential to transform the management and prognosis of many types of CS, ongoing studies are aimed at proving their hemodynamic effectiveness and impact on clinical outcomes. Effective use of AMCS strategies can be done as a bridge to decision, recovery, long-term support devices (such as ventricular assist devices or total artificial hearts), or heart transplantation. Historically, intra-aortic balloon pump was the only device of this class but failed to show significant mortality benefit in the large IABP-SHOCK II trial. Different new generation devices are now in use, in which some are aimed at assisting the function of the LV, whereas others are designed to assist in cases of RV failure. The mechanism of action of each differs substantially, and a comprehensive understanding of the hemodynamics before its insertion and obviously once in use is warranted. A thorough review of this issue was published recently and may help in the consideration of the pros and cons of each device in different clinical scenarios (Fig. 4).

Several key concepts to the management of CS and AMCS should be considered. First, survival of CS patients is time dependent. The introduction of the concept of “time to unload,” rather than just “time to balloon,” accentuates the need to act quickly and use AMCS earlier than is commonly practiced in the current

![Fig. 4. Three modes of AMCS (upper panel) and corresponding PV loops (lower panel) in a cardiogenic shock state with progressively increasing rates of device flow. Although each mode can improve blood pressure and total blood flow, each mode has a different effect on LV because of the different sites from which blood is withdrawn. CGS, cardiogenic shock; LVAD, left ventricular assist device. (From Burkhoff D, Sayer G, Doshi D, et al. Hemodynamics of mechanical circulatory support. J Am Coll Cardiol 2015;66(23):2663–75; with permission.)](image-url)
In fact, reserving the use of AMCS for patients already being treated with 2 or more inotropes might actually be too late, at a stage at which they already suffer irreversible organ dysfunction and metabolic derangements. Instead, using AMCS devices supplementary to aggressive fluid management and early revascularization could improve survival and allow for myocardial recovery, as the cardiac function is replaced by the device at a critical timing of myocardial ischemia, thereby interfering with the vicious cycle of myocardial deterioration.

Current understanding suggests that 3 aspects of treatment should be addressed to potentially improve chances of survival.65

1. Circulatory support—to treat tissue hypoperfusion and avoid accumulation of lactic acid and other metabolic products of anaerobic metabolism.
2. Ventricular unloading—normalizing (or even minimizing as much as possible) filling pressures, in addition to improving CO, has the potential to minimize the remodeling process and favorably impact prognosis; therefore, using and adjusting devices by their effect on PCWP or central venous pressure might be beneficial.
3. Myocardial perfusion—revascularization is essential, and allowing for higher DBP and lower LVEDP may shift the coronary pressure gradient toward increased myocardial perfusion.

Second, when a mechanical support device is used, optimization of its settings can be guided by change in hemodynamics and based on data gathered from right heart catheterization and invasive hemodynamics from PAC.64 With advances in AMCS technology come an increasing role for understanding the fundamental pathophysiology underlying hemodynamic changes and using these to guide intervention. PV loops offer an applicable and generalizable approach to compare hemodynamic status before and after an intervention. Fig. 4 depicts 3 modes of AMCS used in practice. The physiology of these devices differs significantly in how they affect the ventricle, which may potentially impact myocardial recoverability in the setting of an acute myocardial insult; these effects have been detailed previously.64

Third, consider the status of the RV. Specialized devices designed for treatment of RV failure might be valuable in cases of isolated RV failure or combined with LV support in complex cases of biventricular failure.47,66,67 The understanding of the interdependence between the 2 sides of the heart is crucial in many cases, and early identification and treatment of RV failure may help improve survival in many cases.

Finally, as new treatment algorithms in CS are developed that account for early intervention with AMCS,65 future research is necessary to clarify safety and effectiveness. However, it must be recognized that appropriately powered randomized clinical trials of AMCS in CS are extremely difficult to conduct, in large part because of the need for informed consent in an urgent setting. Accordingly, we have advocated the conduct of smaller, well-conducted studies documenting the safety and effects on key physiologic parameters, including hemodynamics, LV function, and metabolic factors (eg, lactate).68 Despite recognition that such parameters do not always correlate with clinical outcomes like mortality and progression to heart failure, it is clear that fundamental differences in hemodynamic effects of the different available devices are not fully appreciated in the clinical setting; such understanding has the potential to affect at least short-term clinical outcomes.

SUMMARY

Treatment of CS remains a clinical challenge. Despite advances in technologies, there is a high mortality rate. However, greater understanding of the pathophysiology of CS from different causes and of the available treatment strategies is leading to new treatment concepts. At a high level, the pathophysiology consists of (1) a primary decrease in LV contractility; followed by (2) autonomic activation with vasoconstriction, salt, and water retention; followed by (3) inflammatory response with vasodilation; which leads to (4) progressive remodeling (dilation) with further worsening LV function. If the LV dysfunction is based on ischemia or infarction, changes in myocardial perfusion occurring at different stages of the process can play pivotal roles. No medical therapy has yet proved effective in improving survival in heart failure. Use of intra-aortic balloon therapy for CS, once the cornerstone of treatment, is on the decline owing to clinical trials showing lack of benefit. Several active blood pumps are now available that provide significantly more hemodynamic support than balloon pumps. Although all devices increase blood pressure and flow, pumps that take blood from different sites of the circulation (venous system, left atrium, LV) have different effects on pulmonary pressures and ventricular loading conditions. Furthermore, the responses to any one of these devices vary.
among patients because of differences in intrinsic RV and LV contractile reserves, pulmonary and systemic vascular properties, background medical therapies, and functionality of the baroreceptors. These factors can in part be quantified through the appropriate use of PAC, which has been inappropriately declined; prior studies showing no benefit of hemodynamic monitoring do not apply to CS, especially when mechanical circulatory support devices are being used. Furthermore, it is important that clinicians appreciate and understand the physiologic meaning of these measurements and take them into account when treating patients who have CS.

REFERENCES