Hemodynamics of Cardiogenic Shock

Ariel Furer, MD[a,*], Jeffrey Wessler, MD[b], Daniel Burkhoff, MD, PhD[b,c]

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.[1] 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).[2] 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

Disclosures: D. Burkhoff is a consultant to Medtronic, Corvia Medical. Cardiovascular Research Foundation is recipient of an unrestricted educational grant from Abiomed.
[a] Internal Medicine T, Tel-Aviv Sourasky Medical Center, 6 Wiezmann street, Tel Aviv 64239, Israel; [b] Division of Cardiology, Columbia University, 161 Fort Washington Avenue, New York, NY 10032-3784, USA; [c] Cardiovascular Research Foundation, 1700 Broadway, New York, NY 10019, USA
* Corresponding author.
E-mail address: furera@gmail.com

Intervent Cardiol Clin 6 (2017) 359–371
http://dx.doi.org/10.1016/j.iccl.2017.03.006

Table 1
Definitions of pre–cardiogenic shock, cardiogenic shock, and refractory cardiogenic shock according to clinical and hemodynamic criteria and response to therapy

	Pre-CS (Nonhypotensive)	CS	Refractory CS
Clinical criteria	Signs of peripheral hypoperfusion: Oliguria (urine output <30 mL/h) Cold extremities Altered mental status Increased serum lactate	Signs of peripheral hypoperfusion	Signs of peripheral hypoperfusion
Hemodynamic criteria	SBP ≥90 mm Hg without circulatory support[3]	SBP <90 for >30 min or the need for pharmacologic or intra-aortic balloon pump support to maintain a systolic blood pressure >90 mm Hg or mean arterial pressure 30 mm Hg lower than baseline. Cardiac index <2.2 L/min/m^2. Elevated filling pressures of the left, right, or both ventricles	Same as CS
Response to treatment			Ongoing evidence of tissue hypoperfusion despite administration of adequate doses of 2 vasoactive medications and treatment of the underlying etiology.[9]

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^{-5}, $P = .07$).[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 long-standing 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 decompensated valvular disease, acute myocarditis, left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy, cardiomyopathy, pericardial tamponade, arrhythmias, mechanical (traumatic) injury to the heart, postcardiotomy syndrome, uncontrolled arrhythmia, and progression of congenital lesions. The prevalence 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 myocarditis (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 evaluation of a patient suspected of having CS, increasing emphasis on hemodynamic evaluation 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 unstable patients owing to rapidly changing hemodynamics and the frequent contribution of multiple comorbid processes.[12] Traditional signs of heart failure, including pulmonary congestion and jugular venous distention, may be misleading in a patient with right ventricular (RV) failure, pulmonary embolism, chronically compensated heart failure, arrhythmias, and mechanical complications—thus reducing the specificity of these signs to diagnose CS. Invasive hemodynamic assessment using pulmonary artery catheterization (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 determinants 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 pressures, adequacy of oxygen delivery, and the degree of pulmonary vascular resistance. These hemodynamic data in turn can guide the therapeutic choices through volume optimization, vasodilators, vasopressors, and inotropes as appropriate and the critical decision regarding whether to provide mechanical circulatory support (MCS). In fact, invasive hemodynamic measurements 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 potential confounders, including the possibility that the neutral results actually reflected a negation of the benefit of aggressive reduction in filling pressures by the harmful effects of therapies 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 diminished.[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 examining physician ability to predict hemodynamic findings without the use of PAC compared with invasive measures that showed only half of the estimations were correct.[22] Additionally, in a reported series of patients treated for

circulatory shock, 63% of cases underwent a change in treatment plan after insertion of PAC.[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.[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.[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.[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.[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.[24] 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.[28] 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.[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.[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.[30] 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.[5] Several groups have reported that nearly half of CS nonsurvivors died with a normal CI[31]; despite this, among CS patients, LVEF was found to be a reliable predictor of mortality.[30] 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.[32]

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

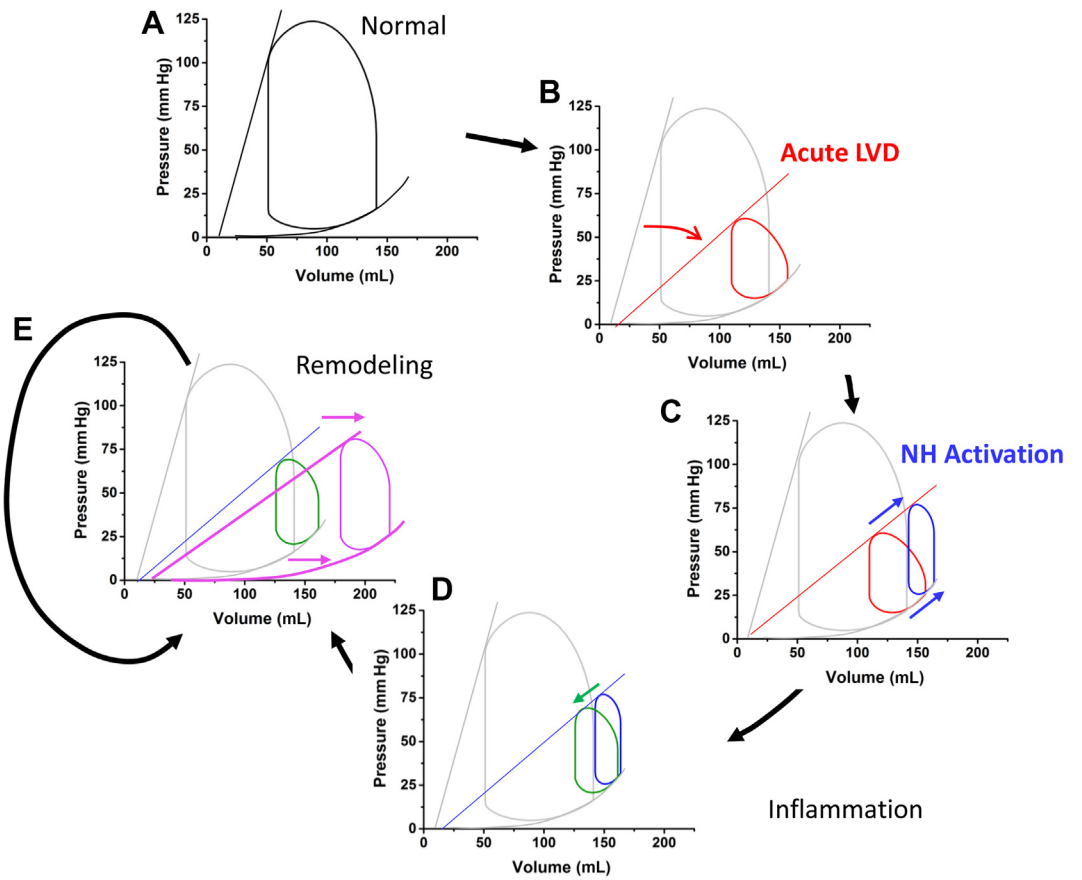

Fig. 1. The pathophysiology of CS illustrated by use of PV loops. (*A*) Normal state. (*B*) PV loop shows changes after acute MI (*red*); (*C*) PV loop shows changes caused by autonomic response to decreased contractility (*blue*); (*D*) PV loop shows changes caused by release of inflammatory mediators (*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 venoconstriction. Venoconstriction plays a critical role in the pathophysiology of CS[33] 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.[1,9] Among the explanations for this observation are (1) the pronounced cytokine-mediated response seen in CS after acute MI,[34,35] (2) sepsis or bacteremia (eg, gut bacterial transmigration),[36] and (3) oxygen free radicals buildup and amplified nitric oxide synthesis as part of ischemia-reperfusion syndrome.[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).

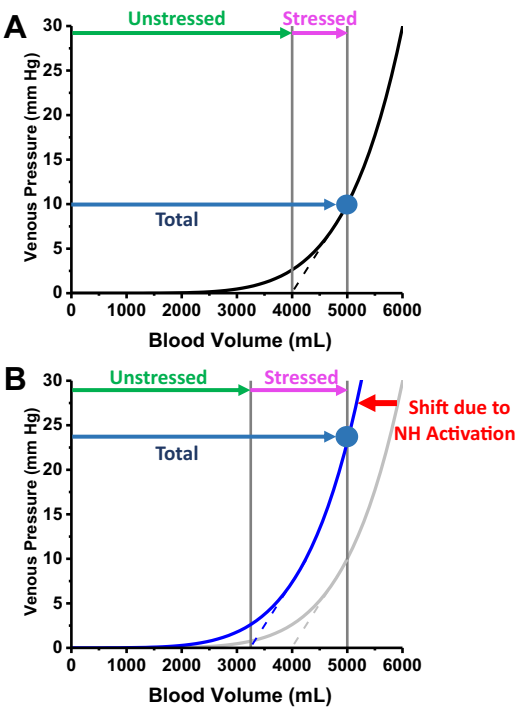

Fig. 2. (*A*) Venous PV relationship (*blue*) shows functional compartmentalization of blood between unstressed and stressed compartment. (*B*) With venoconstriction caused by increased neurohormonal activation, leftward shift of the curve increases venous pressure owing to functional shift of blood 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.[33] NH, neurohormonal.

Remodeling

Persistent neurohormonal activation and elevated filling pressures drive the process of remodeling,[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.[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.[39] This finding is particularly evident in patients with prior multivessel 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.[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.[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

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),[42] yet patients with CS caused by RV 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.[42] 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.[43,44] 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,[45] septal ischemia involvement of LV infarction can have a marked impact on RV function because of RV-LV interactions.[46]

Fortunately, several studies found an impressive recovery of RV function in survivors of CS caused mainly by RV dysfunction.[47,48] 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[47] 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.[9] 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.[49]

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.[50,51] 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%.[51] 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[52]).

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 $\geq$1.9 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.[10]

Finally, cardiac power index may be useful not only as a means of estimating cardiac contractile reserve[14,15] but also as a strong predictor of mortality in AMI CS.[15] Low initial cardiac power index is considered a predictor of unfavorable outcomes in CS patients (0.6 W/m^2 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.[9] 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.[9,53,54] Despite the sharp increase of percutaneous coronary intervention rates in CS patients and guideline recommendations for early revascularization in CS,[53,55] percutaneous coronary intervention rates remain underutilized, with only 50% to 70% of eligible patients receiving intervention.[4,56]

However, as summarized in Fig. 3 reproduced from Thiele and colleagues,[4] commonly used

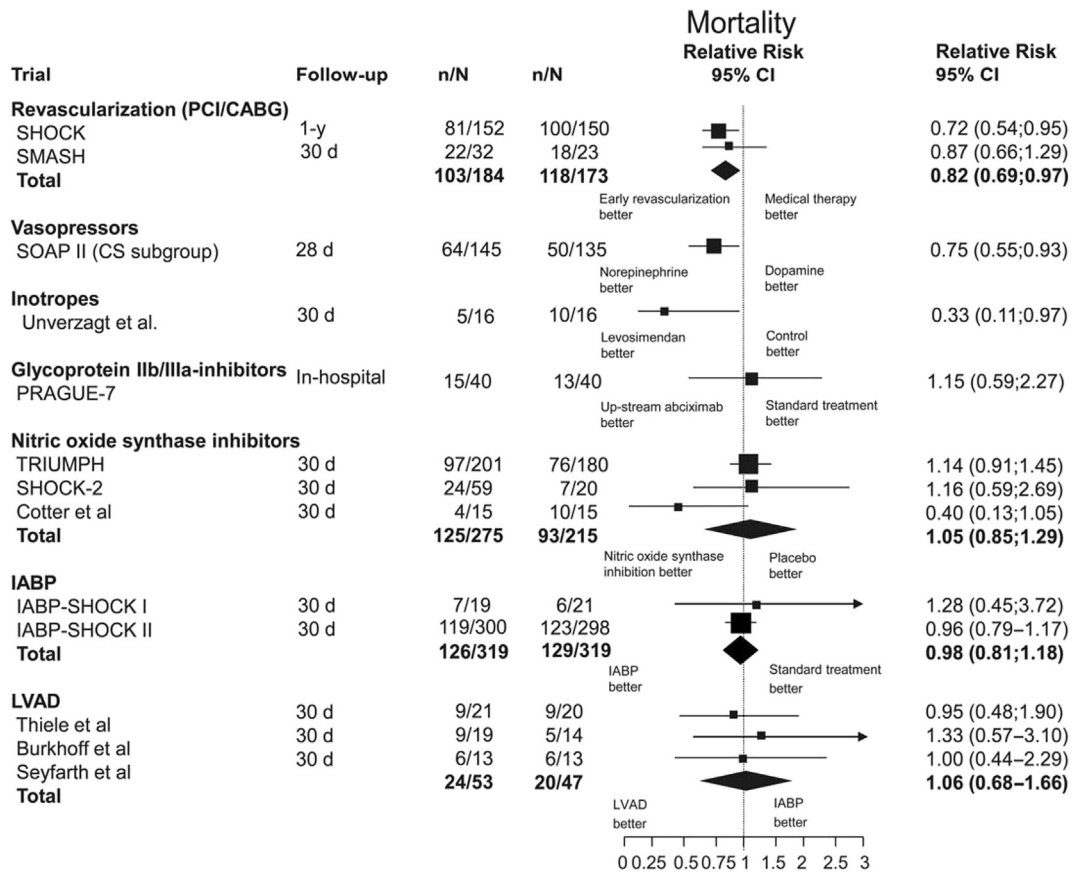

Fig. 3. Summary for the evidence from randomized, controlled trials studying different treatment modalities in cardiogenic shock patients. CABG, coronary artery bypass grafting; CI, confidence interval; IABP, intra-aortic balloon pump; IABP-SHOCK, intra-aortic balloon pump in shock; LVAD, left-ventricular 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, tilarginine 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.[57] 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.[9] 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,[58] intramyocardial delivery of miR-29a,[59] intracoronary supersaturated oxygen,[60] and pressure-controlled intermittent coronary sinus occlusion[61] among many other approaches and (2) allowing better treatment once CS is present—as in the development of acute mechanical circulatory support (AMCS) devices.[62] 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.[63] 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.[8] 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).[64]

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

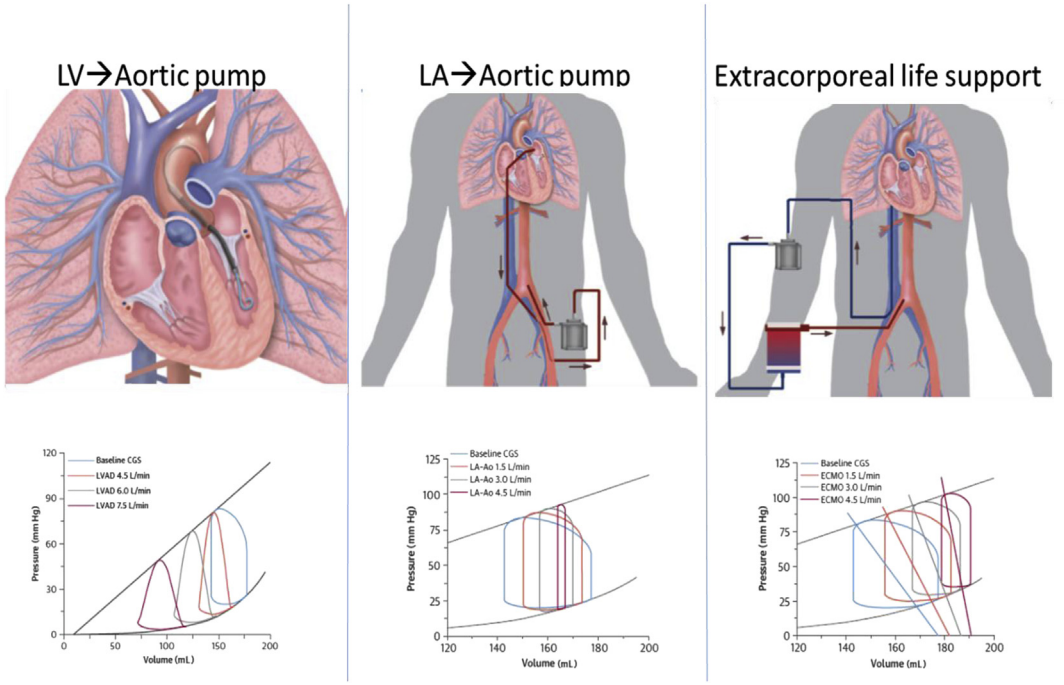

Fig. 4. Three modes of AMCS (*upper panel*) and corresponding PV loops (*lower panel*) in a cardiogenic shock state with progressively increasing rates of device flow. Although each mode can improve blood pressure and total blood flow, each mode has a different effect on LV because of the different sites 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.)

setting.[65] 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

1. Thiele H, Allam B, Chatellier G, et al. Shock in acute myocardial infarction: the cape horn for trials? Eur Heart J 2010;31(15):1828–35.
2. Hasdai D. Cardiogenic shock, in cardiogenic shock. Springer; 2002. p. 3–6.
3. Menon V, Slater JN, White HD, et al. Acute myocardial infarction complicated by systemic hypoperfusion without hypotension: report of the SHOCK trial registry. Am J Med 2000;108(5):374–80.
4. Thiele H, Ohman EM, Desch S, et al. Management of cardiogenic shock. Eur Heart J 2015; 36(20):1223–30.
5. Reynolds HR, Hochman JS. Cardiogenic shock current concepts and improving outcomes. Circulation 2008;117(5):686–97.
6. Goldberg RJ, Spencer FA, Gore JM, et al. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction a population-based perspective. Circulation 2009;119(9):1211–9.
7. De Luca G, Parodi G, Sciagrà R, et al. Preprocedural TIMI flow and infarct size in STEMI undergoing primary angioplasty. J Thromb Thrombolysis 2014;38(1):81–6.
8. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367(14): 1287–96.
9. Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. Nat Rev Cardiol 2016;13(8):481–92.
10. Harjola VP, Lassus J, Sionis A, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail 2015;17(5): 501–9.
11. Tavazzi L, Maggioni AP, Lucci D, et al. Nationwide survey on acute heart failure in cardiology ward services in Italy. Eur Heart J 2006;27(10):1207–15.
12. Connors AF Jr, McCaffree DR, Gray BA. Evaluation of right-heart catheterization in the critically ill patient without acute myocardial infarction. N Engl J Med 1983;308(5):263–7.
13. Gorlin R. Practical cardiac hemodynamics. N Engl J Med 1977;296(4):203–5.
14. Fincke R, Hochman JS, Lowe AM, et al. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. J Am Coll Cardiol 2004; 44(2):340–8.
15. Popovic B, Fay R, Cravoisy-Popovic A, et al. Cardiac power index, mean arterial pressure, and simplified acute physiology score II are strong predictors of survival and response to revascularization in cardiogenic shock. Shock 2014;42(1): 22–6.
16. Wiener R, Welch H. TRends in the use of the pulmonary artery catheter in the United States, 1993-2004. JAMA 2007;298(4):423–9.
17. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA 2005;294(13):1625–33.
18. Cohen MG, Kelly RV, Kong DF, et al. Pulmonary artery catheterization in acute coronary syndromes: insights from the GUSTO IIb and GUSTO III trials. Am J Med 2005;118(5):482–8.
19. Zion MM, Balkin J, Rosenmann D, et al. Use of pulmonary artery catheters in patients with acute myocardial infarction. Analysis of experience in 5,841 patients in the SPRINT registry. SPRINT study group. Chest 1990;98(6):1331–5.
20. Connors AF, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically III patients. JAMA 1996; 276(11):889–97.
21. Murdoch SD, Cohen AT, Bellamy MC. Pulmonary artery catheterization and mortality in critically ill patients. Br J Anaesth 2000;85(4):611–5.
22. Staudinger T, Locker GJ, Laczika K, et al. Diagnostic validity of pulmonary artery catheterization for residents at an intensive care unit. J Trauma 1998;44(5):902–6.
23. Mimoz O, Rauss A, Rekik N, et al. Pulmonary artery catheterization in critically ill patients: a prospective analysis of outcome changes associated with catheter-prompted changes in therapy. Crit Care Med 1994;22(4):573–9.
24. Hadian M, Pinsky MR. Evidence-based review of the use of the pulmonary artery catheter: impact data and complications. Crit Care 2006;10(Suppl 3):S8.
25. Suess EM, Pinsky MR. Hemodynamic monitoring for the evaluation and treatment of shock: what is the current state of the art? Semin Respir Crit Care Med 2015;36(6):890–8.

26. Cooper LB, Mentz RJ, Stevens SR, et al. Hemodynamic predictors of heart failure morbidity and mortality: fluid or flow? J Card Fail 2016;22(3):182–9.
27. Uriel N, Sayer G, Addetia K, et al. Hemodynamic ramp tests in patients with left ventricular assist devices. JACC Heart Fail 2016;4(3):208–17.
28. Gnaegi A, Feihl F, Perret C. Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: time to act? Crit Care Med 1997;25(2):213–20.
29. Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet 2005;366(9484):472–7.
30. Picard MH, Davidoff R, Sleeper LA, et al. Echocardiographic predictors of survival and response to early revascularization in cardiogenic shock. Circulation 2003;107(2):279–84.
31. Lim N, Dubois MJ, De Backer D, et al. Do all nonsurvivors of cardiogenic shock die with a low cardiac index? Chest 2003;124(5):1885–91.
32. Robotham JL, Takata M, Berman M, et al. Ejection fraction revisited. Anesthesiology 1991;74(1):172–83.
33. Burkhoff D, Tyberg JV. Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis. Am J Physiol 1993;265(5):H1819–28.
34. Shpektor A. Cardiogenic shock: the role of inflammation. Acute Card Care 2010;12(4):115–8.
35. Gowda RM, Fox JT, Khan IA. Cardiogenic shock: basics and clinical considerations. Int J Cardiol 2008;123(3):221–8.
36. Kohsaka S, Menon V, Iwata K, et al. Microbiological profile of septic complication in patients with cardiogenic shock following acute myocardial infarction (from the SHOCK study). Am J Cardiol 2007;99(6):802–4.
37. Esposito E, Cuzzocrea S. Role of nitroso radicals as drug targets in circulatory shock. Br J Pharmacol 2009;157(4):494–508.
38. Pfeffer MA, Pfeffer JM, Fishbein MC, et al. Myocardial infarct size and ventricular function in rats. Circ Res 1979;44(4):503–12.
39. Widimsky P, Gregor P, Cervenka V, et al. Severe diffuse hypokinesis of the remote myocardium–the main cause of cardiogenic shock? An echocardiographic study of 75 patients with extremely large myocardial infarctions. Cor Vasa 1988;30(1):27–34.
40. Olivetti G, Quaini F, Sala R, et al. Acute myocardial infarction in humans is associated with activation of programmed myocyte cell death in the surviving portion of the heart. J Mol Cell Cardiol 1996;28(9):2005–16.
41. Stone GW, Selker HP, Thiele H, et al. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. J Am Coll Cardiol 2016;67(14):1674–83.
42. Jacobs AK, Leopold JA, Bates E, et al. Cardiogenic shock caused by right ventricular infarction: a report from the SHOCK registry. J Am Coll Cardiol 2003;41(8):1273–9.
43. Gayat E, Mebazaa A. Normal physiology and pathophysiology of the right ventricle. In: Mebazaa A, et al, editors. Acute heart failure. London: Springer London; 2008. p. 63–9.
44. Lee FA. Hemodynamics of the right ventricle in normal and disease states. Cardiol Clin 1992;10(1):59–67.
45. Goldstein JA, Tweddell JS, Barzilai B, et al. Importance of left ventricular function and systolic ventricular interaction to right ventricular performance during acute right heart ischemia. J Am Coll Cardiol 1992;19(3):704–11.
46. Ratliff NB, Hackel DB. Combined right and left ventricular infarction: pathogenesis and clinicopathologic correlations. Am J Cardiol 1980;45(2):217–21.
47. Anderson MB, Goldstein J, Milano C, et al. Benefits of a novel percutaneous ventricular assist device for right heart failure: the prospective RECOVER RIGHT study of the Impella RP device. J Heart Lung Transplant 2015;34(12):1549–60.
48. Dell'Italia LJ, Lembo NJ, Starling MR, et al. Hemodynamically important right ventricular infarction: follow-up evaluation of right ventricular systolic function at rest and during exercise with radionuclide ventriculography and respiratory gas exchange. Circulation 1987;75(5):996–1003.
49. Menon V, Webb JG, Hillis LD, et al. Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK trial registry. J Am Coll Cardiol 2000;36(3 Suppl A):1110–6.
50. Hasdai D, Califf RM, Thompson TD, et al. Predictors of cardiogenic shock after thrombolytic therapy for acute myocardial infarction. J Am Coll Cardiol 2000;35(1):136–43.
51. Hasdai D, Topol EJ, Califf RM, et al. Cardiogenic shock complicating acute coronary syndromes. Lancet 2000;356(9231):749–56.
52. Katz JN, Stebbins AL, Alexander JH, et al. Predictors of 30-day mortality in patients with refractory cardiogenic shock following acute myocardial infarction despite a patent infarct artery. Am Heart J 2009;158(4):680–7.
53. De Luca L, Olivari Z, Farina A, et al. Temporal trends in the epidemiology, management, and outcome of patients with cardiogenic shock complicating acute coronary syndromes. Eur J Heart Fail 2015;17(11):1124–32.

54. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA 2006;295(21):2511–5.
55. Wayangankar SA, Bangalore S, McCoy LA, et al. Temporal trends and outcomes of patients undergoing percutaneous coronary interventions for cardiogenic shock in the setting of acute myocardial infarction: a report from the CathPCI registry. JACC Cardiovasc Interv 2016;9(4):341–51.
56. Jeger RV, Radovanovic D, Hunziker PR, et al. Ten-year trends in the incidence and treatment of cardiogenic shock. Ann Intern Med 2008;149(9):618–26.
57. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail 2016;18(8):891–975.
58. Pizarro G, Fernández-Friera L, Fuster V, et al. Long-term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction: results from the METOCARD-CNIC trial (effect of metoprolol in cardioprotection during an acute myocardial infarction). J Am Coll Cardiol 2014;63(22):2356–62.
59. Ma Z, et al. Intramyocardial delivery of miR-29a improves cardiac function and prevents pathological remodelling following myocardial infarction. Heart Lung Circ 2016;25:S79.
60. Hanson ID, David SW, Dixon SR, et al. "Optimized" delivery of intracoronary supersaturated oxygen in acute anterior myocardial infarction: a feasibility and safety study. Catheter Cardiovasc Interv 2015;86(Suppl 1):S51–7.
61. Egred M, et al. TCT-164 pressure-controlled intermittent coronary sinus occlusion reduces infarct size and results in functional recovery after STEMI; interim analysis of an ongoing trial. J Am Coll Cardiol 2016;68(18_S):B67.
62. Morine KJ, Kapur NK. Percutaneous mechanical circulatory support for cardiogenic shock. Curr Treat Options Cardiovasc Med 2016;18(1):1–14.
63. Shekar K, Gregory SD, Fraser JF. Mechanical circulatory support in the new era: an overview. Crit Care 2016;20:66.
64. Burkhoff D, Sayer G, Doshi D, et al. Hemodynamics of mechanical circulatory support. J Am Coll Cardiol 2015;66(23):2663–74.
65. Kapur NK, Esposito ML. Door to unload: a new paradigm for the management of cardiogenic shock. Curr Cardiovasc Risk Rep 2016;10(12):41.
66. Goldstein JA, Kern MJ. Percutaneous mechanical support for the failing right heart. Cardiol Clin 2012;30(2):303–10.
67. Cheung AW, White CW, Davis MK, et al. Short-term mechanical circulatory support for recovery from acute right ventricular failure: clinical outcomes. J Heart Lung Transpl 2014;33(8):794–9.
68. Burkhoff D. Device therapy: where next in cardiogenic shock owing to myocardial infarction? Nat Rev Cardiol 2015;12(7):383–4.