Cardiogenic Shock

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KEYWORDS

• Cardiogenic shock • Intra-aortic balloon pump
• Percutaneous ventricular assist device • Inotropes • Revascularization

KEY POINTS

- Cardiogenic shock is the leading cause of death for patients hospitalized with an acute myocardial infarction.
- Early revascularization is the therapy of choice for patients with cardiogenic shock complicating an acute myocardial infarction.
- Intra-aortic balloon pumps have not been shown to improve survival for patients who are suffering from an acute myocardial infarction in the modern era of early revascularization.
- Percutaneous ventricular assist devices are a promising therapy for temporary support of patients in cardiogenic shock, but rigorous clinical data demonstrating improved outcomes are lacking.
- Routine utilization of a pulmonary artery catheter in managing patients with cardiogenic shock is unnecessary, but may be vital to determining a care plan in select patients being considered for mechanical support or transplant.

Shock is characterized by a state of end-organ hypoperfusion resulting in abnormal organ homeostasis, leading to high patient morbidity and mortality. Cardiogenic shock (CS) is a clinical syndrome characterized by systemic hypotension and hypoperfusion secondary to insufficient cardiac output. In states of pure CS, cardiac filling pressures are elevated and cardiac output is low.[1] CS can lead to multisystem organ failure, manifested by oliguria, lactic acidosis, altered mentation, and cool extremities. Most commonly, CS is the direct sequelae of an acute myocardial infarction (MI), and acute ischemic CS carries an in-hospital mortality of greater than 50%.[2,3] However, CS can also arise as an acute presentation of a cardiomyopathy of nonischemic cause or as a severe decompensation of chronic (ischemic or nonischemic) cardiomyopathy. The latter presentations are less common and account for only 1% of acute heart failure syndromes.[4]

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Critical care management is centered on an efficient, rapid, and organized approach to the shock patient using a multidisciplinary care approach between intensivists, heart failure specialists, cardiac surgery, and interventional cardiology. The tenets of therapy include restoring cardiac output and identifying and treating one or multiple potential causative factors: hypoxia, hypervolemia, acidosis, arrhythmias, coronary ischemia, and mechanical complications of an MI. In certain clinical situations (eg, requirement for multiple inotropes or vasopressors, worsening hemodynamics despite inotrope support), it may be prudent to refer the patient to the nearest left ventricular assist device (LVAD)/transplant program for further management.

PHYSICAL FINDINGS

The importance of a focused physical examination in the management of a patient with CS should be emphasized. It is at this critical juncture in the clinical evaluation process that obtaining the correct information can direct the caregiver down the right diagnostic and therapeutic pathway. A thorough assessment allows for evaluation of intravascular volume status and adequacy of end-organ function (**Box 1**).

Jugular Venous Pressure and S_3 Gallop

The internal jugular vein forms a direct fluid column with the right atrium and provides a noninvasive measure of right atrial pressure. The correct method for determining jugular venous pressure (JVP) is depicted in **Fig. 1**. The patient should be placed in bed at a 45° angle, which can be confirmed by use of the ball found commonly on the side of a

Box 1
Components of the heart failure physical examination

- JVP
- Rales
- Displaced and sustained point of maximal impulse
- Gallops—third or fourth heart sounds
- Heart murmurs
- Cool extremities
- Peripheral, scrotal, or presacral edema
- Right ventricular heave/parasternal lift
- Hypotension
- Tachycardia
- Tachypnea
- Abdominal ascites
- Hepatomegaly
- Pulsatile liver
- Pulsus alternans
- Orthopnea
- Dullness to percussion in lung bases
- Restlessness
- Temporal wasting

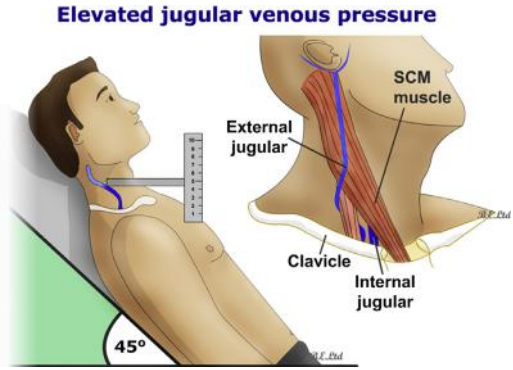

Fig. 1. Assessment of JVP. The appropriate assessment of JVP relies on an estimation of the distance of the meniscus of the jugular venous pulsation above the sternal angle and is correctly performed by having the patient in a semi-recumbent position with the body angled at 45°. The distance of the meniscus of the jugular venous pulsation over the angle of Louis is then added to 5 cm to estimate the JVP or the right atrial pressure. SCM, sternocleidomastoid muscle. (*From* Clinical examination of the cardiovascular system DVD-3, Bloomsbury Educational Ltd, 97 Judd Street, London WC1H 9JB; with permission.)

hospital bed. Careful observation of internal jugular vein with the head and neck as aligned in **Fig. 1** allows one to appreciate the JVP. It is important to avoid having the patient extend their neck because this can cause the internal jugular vein to flatten. Once the meniscus of the JVP has been located, an estimate of the right atrial pressure can be made by adding 5 cm to the distance of the JVP meniscus above the angle of Louis. The constant of 5 cm is added because it represents the distance from the sternum to the right atrium. The normal JVP is 6 to 8 cm of water, and 1 cm of water is equivalent to 0.74 mm Hg. In patients who have a very low or high JVP, it is often necessary to lay the patient flat or elevate the head of the bed at 90°, respectively, to appreciate the meniscus of the JVP.[5,6]

The ventricular gallop, S_3, or third heart sound is a relatively specific finding of heart failure in the adult population. In the setting of heart failure, an S_3 gallop occurs because of early and rapid ventricular filling often in a dilated ventricle. The sound can originate from either the right or the left ventricle and leads to a right-sided or left-sided third, early diastolic heart sound (S_3). The quality and intensity of the S_3 gallop are related to the atrial pressure, ventricular compliance, and diastolic filling rate. An S_3 tends to be louder in states of volume overload and can be heard with significant mitral regurgitation (MR) even in those with normal left ventricular function.[7] In pregnant women and children, an S_3 may also be a benign finding.

The JVP and S_3 gallop are not only useful tools for diagnosing heart failure, but are also predictive of patient outcome. The prognostic importance of these physical examination findings was studied within the large multicenter Studies of Left Ventricular Dysfunction trial, which evaluated the efficacy of enalapril in the treatment of systolic heart failure.[8,9] In a multivariable analysis that included ejection fraction, age, as well as other demographic and clinical variables, the only predictors of death or hospitalization for heart failure were JVP and an S_3 gallop.[9] The presence of elevated JVP in heart failure patients was associated with an increased risk of death (relative risk = 1.52) compared with patients without an elevation of JVP.[9] A similar increased risk of death was seen in patients with an S_3 gallop (relative risk = 1.35) compared with those patients with heart failure and no ventricular gallop.[9]

Determining the Cardiac Output on Examination

JVP, dependent edema, and rales are all physical examination findings associated with fluid overload, but give little information as to the adequacy of end-organ perfusion by the myopathic heart. A variety of physical examination findings can be used to assist in determining whether the cardiac output is normal or low. These findings include, but are not limited to, the presence of cool or mottled extremities with a reduced capillary refill, the presence of a pulsus alternans, a narrow pulse pressure, hypotension, and impaired mentation.[10] Patients can be grouped into 4 profiles based on the presence of elevated filling pressures and the adequacy of cardiac output as outlined in **Fig. 2**.[11] These profiles guide the usage and timing of diuretics, vasodilators, and vasoactive and inotropic medications. These hemodynamic profiles not only guide therapy but also have prognostic implications similar to those obtained by invasive measurements of cardiac output and pulmonary capillary wedge pressure.[12,13]

Physical Examination Pitfalls

A common pitfall in the evaluation of heart failure patients is the overreliance on certain physical examination findings to determine a volume overloaded state. Although wet

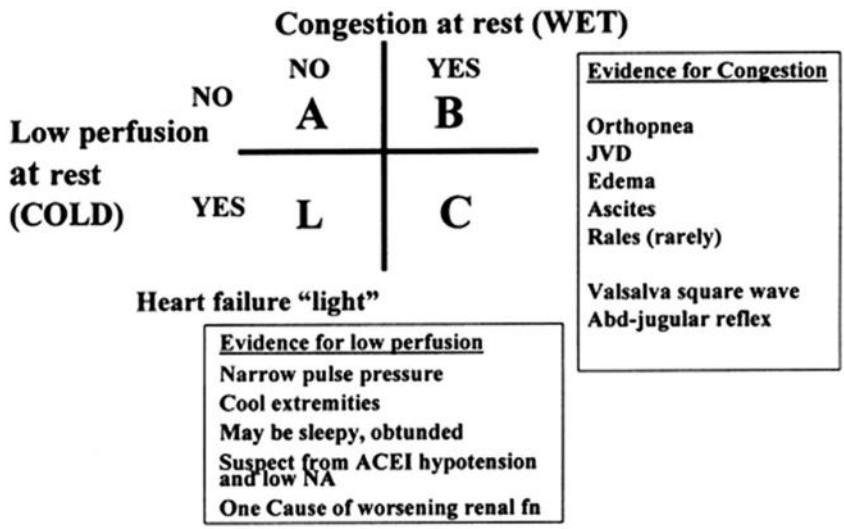

Fig. 2. Physical examination and hemodynamic profiles. Patients with systolic heart failure can be assigned to 1 of 4 profiles, based on a clinical assessment of congestion and perfusion as proposed by Stevenson.[11] Congestion is assessed based on the presence of elevated JVP, dependent edema, rales, orthopnea, ascites, or hepatojugular reflux. Perfusion can be determined based on cool extremities, altered mentation, worsening renal function, hypotension, pulsus alternans, and narrow pulse pressure. The hemodynamic profile then dictates the appropriate course of therapy. Profile A patients are stable and require no escalation of therapy. Profile B ("wet and warm") patients benefit from diuretics to reduce congestion. Profile L ("dry and cold") patients are adequately compensated at rest, but usually have severe functional intolerance. Finally, profile C ("wet and cold") patients are in CS and require vasodilators or inotropic support to augment cardiac output and then diuretics to help reduce symptoms of congestion. Abd, abdominal; ACEI, angiotensin converting enzyme inhibitor; fn, function; JVD, jugular venous distention; NA, sodium. (*From* Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. Eur J Heart Fail 1999;1(3):251–7; with permission.)

crackles (ie, rales) may be appreciated in patients with acute heart failure, they may be absent on examination of CS patients with a past history of chronic heart failure.[14] Patients with chronic heart failure tend to exhibit rales only in very severe states of volume overload because their pulmonary lymphatics accommodate higher pulmonary venous pressures over time. Rales may not be heard in some individuals with chronic heart failure presenting with acute shock until left ventricular filling pressures are very high. Peripheral edema is neither sensitive nor specific for CS. Although lower extremity edema can be a marker of elevated right-sided filling pressures, edema can also occur in the setting of protein calorie malnutrition or venous incompetence.

HEMODYNAMIC ASSESSMENT

The first pulmonary arterial catheterization (PAC) was performed by Lewis Dexter in 1945 and was performed to diagnose congenital heart disease.[15] It was not until 1970 when Swan and and colleagues[16] developed the balloon-tipped catheter that widespread use of the device became popular. Initial excitement for the device has contemporaneously been tempered by a growing body of evidence that its routine use in managing a variety of patient groups may be unwarranted and potentially harmful.[17–20] Over the past decade, the utilization of PACs has fallen dramatically and some would argue that many clinicians now lack adequate training in how to place, interpret, or manage a PAC.[21,22]

The routine use of PACs in patients with an acute exacerbation of heart failure was studied in the multicenter Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.[23] Patients who had their heart failure managed in conjunction with a PAC failed to demonstrate an improvement in hospital length of stay or mortality compared with those managed without a PAC. The PAC group had an increased incidence of adverse events largely driven by catheter-related complications including line infection.[23] It is important to note, however, that these patients were not necessarily in CS: the mean cardiac index was 1.9 L/min/m^2 and the trial explicitly excluded those patients receiving an intravenous inotrope.[23]

Studies specifically looking at PAC use in patients after an MI showed similar results to that of the ESCAPE trial. In an analysis of greater than 26,000 patients presenting with an acute coronary syndrome who were enrolled in to the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO) IIb and III trials, only 735 patients received a PAC.[24] Pulmonary arterial catheters were more commonly used in the post-MI setting when patients had higher resource utilization (eg, coronary artery bypass grafting, percutaneous coronary intervention) and/or a more unstable clinical presentation (eg, need for mechanical ventilation, intra-aortic balloon pumps [IABP]).[24] PAC use was associated with an increased risk of adverse events including an adjusted 6-fold increase in 30-day mortality. However, when looking at the subgroup of patients with CS, the use of a PAC had a neutral effect on mortality. The nonrandomized nature of this study makes the findings about the utility of PAC placement questionable.[24]

The PAC measurements also provide prognostic information in the setting of acute MI. The Forrester criteria assess pulmonary congestion (pulmonary capillary wedge pressure greater than 18 mm Hg) and systemic hypoperfusion (cardiac index less than 2.2 L/min/m^2) by using PAC data to categorize patients in quartiles.[25] Patients who exhibit both pulmonary congestion and systemic hypoperfusion have a 60% in-hospital mortality. It is important to note that the study was performed in the 1970s and management of acute coronary syndromes and CS has changed dramatically

since then. Nevertheless, an appreciation for the severity of the hemodynamic derangement allows for an objective assessment of myocardial dysfunction and may prompt evaluation for advanced therapies including mechanical circulatory support.

Although routine invasive hemodynamic monitoring in patients with an acute heart failure exacerbation seems unwarranted, use in CS may still be clinically indicated. Potential indications for a PAC are listed in **Box 2**; these indications lack quality evidence from rigorously conducted randomized trials but continue to be supported in professional society guidelines, largely because of expert opinion.[26,27] Further details on PACs and hemodynamic monitoring are presented in the article in this issue by Kenaan and colleagues.

ILLNESS SEVERITY CLASSIFICATION SYSTEMS

Killip Class

The most widely recognized illness classification system to characterize patients with heart failure after an MI was developed by Killip and Kimball in 1967.[28] These physicians are credited with not only developing the Killip Classification system for heart failure severity (**Table 1**) but also creating the modern day coronary care unit. In the global registry of acute coronary events risk score, a higher Killip classification at time of hospital presentation was associated with a 2-fold increased risk of death per increase in Killip class.[29,30] Similar prognostication potential is also seen when the Killip classification system is applied to patients with non–ST-elevation acute coronary syndromes.[31]

APACHE II and SOFA Score

Although no well-validated tools have been developed for the explicit purpose of prognosticating outcome in patients presenting with CS, various risk scores derived for predicting outcome in a wide breadth of patients admitted to an intensive care unit (ICU) have been extrapolated to those in CS. The Acute Physiology and Chronic Health

Box 2
Recommendations for the use of pulmonary artery catheter

The routine use of invasive hemodynamic monitoring in patients with decompensated heart failure is not recommended.

Invasive hemodynamic monitoring should be considered in patients

a. When volume status and cardiac filling pressures are unclear

b. When refractory to initial therapy

c. Who have clinically significant hypotension or persistent symptoms

d. With worsening renal function during therapy

e. Being considered for cardiac transplant or mechanical circulatory support

f. To assess the response to vasoactive medications

g. When chronic outpatient infusion is being considered and documentation of an adequate hemodynamic response to the inotropic agent is necessary.

Data from Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2013;62:e147–239; and Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010;16(6):e1–194.

Table 1
Killip classification

Class A	No heart failure. No clinical signs of cardiac decompensation.
Class B	Heart failure. Diagnostic criteria include rales, S_3 gallop, and venous hypertension.
Class C	Severe heart failure. Frank pulmonary edema.
Class D	CS. Signs include hypotension (systolic pressure of 90 mm Hg or less) and evidence of peripheral vasoconstriction, such as oliguria, cyanosis, and diaphoresis. Heart failure, often with pulmonary edema, has also been present in most of these patients.

Data from Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol 1967;20(4):457–64.

Evaluation II (APACHE II) was developed to prognosticate outcomes in patients presenting to the ICU with various unstable medical maladies.[32] The 12-item model calculates a risk score ranging from 0 to 71, taking into account patient age, chronic illnesses/comorbidities, physiologic measurements, end-organ function, the Glasgow coma scale, and postoperative state. Generally lower scores are assigned to patients in the postoperative state and higher overall scores predict a higher in-hospital mortality.[32] For those patients with a score greater than 25, in-hospital mortality exceeds 50%. Although the initial APACHE II validation cohort comprised a limited number of patients with cardiovascular disease, subsequent studies applying the APACHE II score to patients presenting in CS have demonstrated good predictive power.[33–35] In a study of more than 6000 patients presenting with an acute MI in Spain, each unit increase in APACHE II score was associated with a 16% increase in mortality.[34]

The Sequential Organ Failure Assessment (SOFA) score,[36] originally devised for describing complications in those with multisystem dysfunction due to sepsis, has also been used to predict mortality in patients with multisystem organ failure due to cardiac causes. The SOFA score comprises markers of renal function (serum creatinine or urine output), hepatic function (serum bilirubin), hemodynamic stability (mean arterial pressure or use of vasopressors), neurologic function (Glasgow coma scale), hematologic derangement (platelet count), and respiratory stability (the ratio of PaO_2/FiO_2). In a retrospective analysis of 726 acute MI patients, each unit increase in SOFA score was associated with a 1.3-fold increase in mortality.[37] The score offered reasonable risk discrimination with an area under the receiver operating characteristic curve of 0.79.

Although both the APACHE II and the SOFA models were not derived from a CS cohort, the leading cause of death in these patients is multisystem organ failure, which accounts for the prognostication of both models. The models do not predict long-term outcome after hospital discharge or death due to arrhythmias. Large studies comparing the APACHE II, SOFA, and the (updated) APACHE III scoring systems in the patients in CS are lacking.

INTERMACS Profiles

As durable ventricular assist devices become increasingly common in the management of patients with refractory end-stage heart failure, a unique patient registry that tracks clinical outcomes in LVAD recipients has been devised: the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).[38] The registry is supported by the National Institutes of Health, Food and Drug Administration,

Centers for Medicaid and Medicare Services, industry, and the individual institutions that participate. From the group who developed the registry, there has also been a parallel development of a heart failure classification scheme termed INTERMACS profiles. INTERMACS profiles (**Table 2**) are more appropriate than the New York Heart Association (NYHA) classification scheme or the American College of Cardiology Foundation/American Heart Association (ACC/AHA) heart failure stages (A–D) for categorizing disease severity and predicting outcome in patients who have end-stage heart failure (ie, NYHA class IIIB–IV symptoms and stage D status).[39,40] The profiles implicate a certain clinical course that provides prognostic information to the health team that can assist in clinical decision-making.[41] Patients in profile 1 are termed "Crash and Burn" and are in a state of severe end-organ malperfusion caused by CS. Patients in profile 2 (also known as "sliding on inotropes") have evidence of cardiac insufficiency (eg, worsening renal function) despite inotrope dependence, and patients in profile 3 are clinically stable, but are dependent on inotrope therapy. Although profile 3 patients are the most "stable" of the described scenarios, inotrope dependence is associated with a greater than 50% mortality at 1 year.[42] Even those who receive intravenous inotropes for heart failure support who are not deemed inotrope dependent at hospital discharge have higher morbidity and mortality than those with heart failure who have never received inotropes.[43]

MECHANICAL COMPLICATIONS

Patients with any type of mechanical complication post-MI carry a higher mortality when compared with patients with CS due to left ventricular dysfunction alone.[44] Previously, it was thought that these complications occurred at a predictable time course after an MI and was largely driven by the extent of tissue necrosis and timing of myocardial fibrosis.[45] As revascularization strategies have improved for MI, the modern day incidence of mechanical complications has dropped to less than 1% and most events occur within the first 24 hours of presentation.[46] Detection of a mechanical complication necessitates careful clinical attention to patient's signs and symptoms coupled with prompt echocardiographic evaluation to confirm the diagnosis.

Right Ventricular Infarction

One of the most widely recognized, but difficult to diagnose, complications of an inferior MI is a right ventricular infarction (RVI). The marginal branches that supply the right

Table 2
INTERMACS profiles

INTERMACS Profile	Profile Description	Clinical Example
1	Critical CS	Crash and burn
2	Progressive decline	Sliding on inotropes
3	Stable, but inotrope dependent	Dependent stability
4	Resting symptoms	Dyspnea at rest
5	Exertion intolerant	Dyspnea with activities of daily living
6	Exertion limited	Dyspnea with independent activities of daily living
7	NYHA class IIIB	Limited to mild physical activity

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.[40]

ventricle with blood typically originate from the right coronary artery, the culprit vessel in most inferior MIs. RVI complicating an inferior MI occurs at a rate of approximately 30% to 50% and accurate diagnosis is often difficult.[47] A right-sided V_4 electrocardiogram lead has a sensitivity and specificity of 88% and 78%, respectively, for the diagnosis.[47] Overall RVI is responsible for the development of CS in only 5% of CS cases, but carries a high mortality.[48] Patients with RVI also have a 3-fold higher risk of ventricular arrhythmias and atrioventricular node block compared with inferior MI patients without right ventricular involvement.[49]

The mainstay of therapy in RVI has been to maintain right ventricular preload by avoidance of nitrates and diuretics. Other strategies for management include adequate saline hydration such that the central venous pressure (ie, right atrial pressure) is above 10 mm Hg. In those patients with significant hypotension and bradycardia, insertion of a temporary pacemaker and/or initiation of inotrope support may be indicated to maintain a higher heart rate. This strategy of promoting relative tachycardia seems counterintuitive in an acute MI but is often necessary to maintain adequate left ventricular filling. Of note, the right ventricle is extremely resilient and often shows dramatic recovery on both clinical and echocardiographic follow-up, indicating the underlying pathophysiology of right ventricular dysfunction may represent stunning more so than myocardial necrosis.[50]

Acute MR

Acute MR after MI is associated with a poor survival.[51] Risk factors for the development of MR after MI include older age, female sex, and inferior or posterior infarction.[52] In a study of 773 patients presenting with an acute MI, mild MR occurred in 38% of subjects and an additional 12% had moderate or severe MR.[51] Event-free survival at 5 years was 84%, 74%, and 35% for those with no, mild, and moderate or severe MR, respectively. The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial studied 1190 patients presenting in CS due to an acute MI and found that severe MR complicated 8% of patient courses.[52] Despite a mean left ventricular ejection fraction of 38%, in-hospital mortality was 55% in those with severe MR.

Mild or moderate MR during acute ischemia is often transient and resolves after restoration of blood flow, unlike acute papillary muscle rupture, which is life-threatening. Acute papillary muscle rupture occurs in about 7% of CS patients and affords about 5% of the mortality in patients presenting with an acute MI.[2,53] The occurrence of papillary muscle rupture has to do with the location of coronary occlusion and the time to reperfusion. There are 2 papillary muscles that attach to the mitral valve leaflets via chordae tendineae: the anterolateral and posteromedial papillary muscles. The anterolateral papillary muscle receives dual blood supply from the left anterior descending artery and marginal branches from the left circumflex artery, whereas the posteromedial papillary muscle has a singular blood supply from the posterior descending artery alone. Because of the blood supply pattern, the posteromedial papillary muscle is much more likely to rupture and this complication can be seen in the setting of an inferior infarction.[54,55] Rupture of the muscle can be either partial or complete with the clinical severity corresponding directly to the degree of muscle rupture (**Fig. 3**).[56] Older literature cited an onset of rupture of 3 to 7 days post-MI, but in the contemporary era of rapid reperfusion, the time clock for rupture has moved earlier (median time of 13 hours in the SHOCK trial)[52] and is likely caused by reperfusion injury (inflammation) in the territory of the injured papillary muscle.

Clinically, the presentation of acute MR secondary to papillary muscle rupture is often sudden with patients developing flash pulmonary edema (**Fig. 4**) and rapid

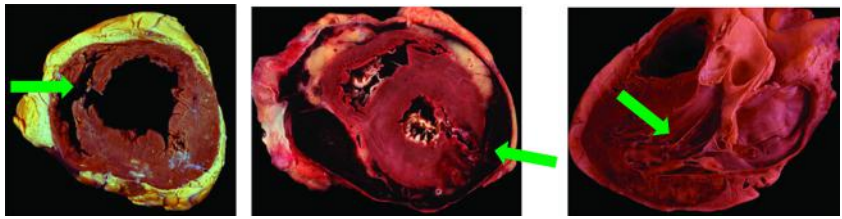

Fig. 3. Mechanical complications of an MI. Mechanical complications of a MI are depicted, from left to right, as: ventricular septal defect, free wall rupture, and papillary muscle rupture. (*From* Antman EM, Anbe DT, Kushner FG, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. Circulation 2004;110:e82–292; with permission.)

hemodynamic instability. Because of rapid equalization of pressures between the left atrium and ventricle, a murmur may be absent. Therapy is focused on prompt clinical recognition, urgent echocardiographic visualization, afterload reduction with vasoactive medications, and/or an IABP followed by emergent surgical correction.[57–59]

Ventricular Septal Defects

Unlike papillary muscle rupture, ventricular septal defects typically occur in the setting of an anterior MI.[60] The incidence is quite uncommon, occurring in only 0.2% of patients in the current reperfusion era.[61] The mortality with medical management of acute septal defect is greater than 50%, and survival at 30 days is 71% to 100% in those with rapidly recognized and surgically corrected defects.[61,62] As percutaneous treatment of structural heart disease continues to develop, use of a septal occlusion device has shown some promise as a potential therapy for MI-associated ventricular

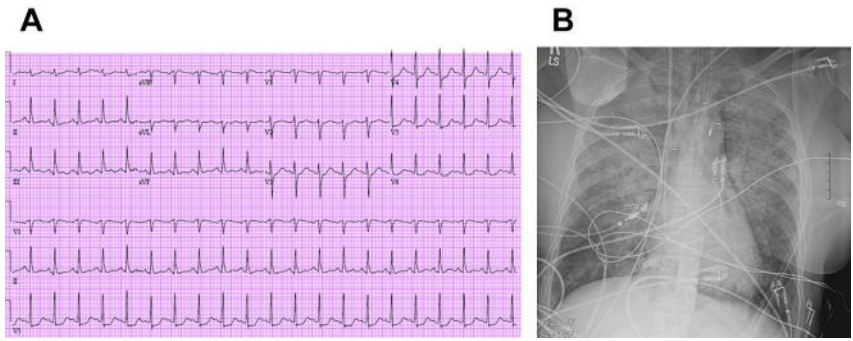

Fig. 4. Flash pulmonary edema. The electrocardiogram and chest radiograph are from a 60-year-old woman who presented to the emergency department with stuttering chest pain for 2 days. On presentation, her electrocardiogram showed inferior ST-segment elevation (*A*). She was promptly taken to the cardiac catheterization laboratory, where she was found to have total occlusion of her right coronary artery (*B*). The patient underwent percutaneous coronary intervention and stent placement. Four days later in the ICU, she was noted to develop acute-onset hypoxia and found to be in flash pulmonary edema. The patient was diagnosed with posteromedial papillary muscle partial rupture and underwent mitral valve replacement with preservation of the mitral valve apparatus as well as single-vessel coronary artery bypass surgery. She survived to discharge and was doing well on follow-up 1-year after surgery.

septal defects.[63,64] Use of a septal occlusion device may be particularly attractive in those patients who are deemed nonoperative candidates due to other medical comorbidities. Until a head-to-head study or large retrospective analysis comparing septal occlusion to surgery is completed, surgery continues to be the "gold standard" for treatment of ventricular septal defects in the setting of an MI (see **Fig. 3**).

Free Wall Rupture

Ventricular rupture of the free wall presents dramatically with electromechanical dissociation and pericardial tamponade (see **Fig. 3**). Free wall rupture occurs in less than 3% of patients with an acute MI, but accounts for more than 10% of the mortality; it is a common finding at autopsy in both out-of-hospital and in-hospital acute MI deaths.[65] Acute free wall rupture only occurs in patients with a transmural MI with a median time to onset of 5 days post-MI. The complication is more likely to occur in patients who are older, who are female gender, who have had anterior ST-elevation myocardial infarctions (STEMI), and for those in whom there is a delay in coronary revascularization.[66] Management is focused on hemodynamic support with fluids and vasoactive medications, bedside pericardiocentesis, followed by prompt surgical correction.

REVASCULARIZATION

The beneficial effects of revascularization of MI patients presenting in CS were established with the landmark SHOCK trial.[67] In patients presenting with CS as a complication of their MI, early revascularization with primary angioplasty and/or coronary artery bypass grafting was associated with a nonsignificant reduction in the primary endpoint of mortality at 30 days when compared with medical therapy alone. There was, however, a significant reduction in the prespecified secondary endpoints of 6-month and 1-year mortality, with an absolute reduction of mortality by 13%.[67,68] In the parallel SHOCK registry, the benefits of early revascularization were similarly noted.[2] At the time of the SHOCK trial in the late 1990s, early revascularization time was defined as occurring within 6 hours of presentation and only 36% of the revascularization patients received coronary stenting. In the current "door-to-balloon" era of revascularization, where most MI patients receive prompt revascularization with primary percutaneous coronary intervention, stent placement, and aggressive adjunctive medical therapy (ie, dual antiplatelet therapy, statins, anticoagulants, β-blockers, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs), and aldosterone blockade), the rates of CS have dropped to approximately 5% for patients presenting with an STEMI.[69] Furthermore, general trends have shown a decreased incidence in the overall rate of STEMI over time, dropping from 47% in 1999 to 23% by 2008, which has also contributed to the reduced rate of CS over time.[70] The mortality from CS has also dropped from 60% in 1995 to 48% in 2004.[71]

One controversial finding in the original SHOCK trial was the patient group aged 75 years or older had no additional mortality benefit with revascularization when compared with their younger counterparts.[68] However, conclusions from this subgroup analysis should be interpreted with caution because only one-sixth of the overall randomized trial population was aged 75 or older. Results of subsequent clinical registries have shown that the benefit of revascularization extends to those over the age of 75 and even the oldest old, aged 85 years or older.[2,72] Reflecting this clinical data, the most recent ACC/AHA guidelines no longer use age to differentiate which patients will benefit from revascularization.[73] If primary angioplasty is not available, thrombolytic therapy should be initiated, although the results are generally less favorable.[74]

MEDICAL MANAGEMENT

Medical management of patients in CS should focus on improving cardiac output and addressing complications of CS (eg, electrolyte disturbances, hypoxia) that may amplify the effects of shock. Options for medical management include intravenous inotrope and vasopressor support, and patients in severe CS often need both to maintain organ perfusion. Patients with low-grade CS/insufficiency who are not requiring vasopressor support may (paradoxically) gain benefit from the cautious addition of vasodilators.

Inotrope Support

The routine use of inotrope support in heart failure for short-term or long-term support is clearly linked to an increased mortality.[43,75] The routine use of these agents in management of most heart failure syndromes is inappropriate and should be discouraged,[43] but they have an important role in maintaining systemic perfusion and restoring end-organ function for patients in CS.[26] Both dobutamine and milrinone increase the inotropy of the failing heart to improve cardiac output. Dobutamine stimulates both β_1 receptors and β_2 receptors, triggering the G-protein adenylate cyclase cascade that leads to increased cyclic AMP production. Although dobutamine is mainly a β_1 agonist, stimulation of peripheral β_2 receptors can lead to a drop in blood pressure noted on medication initiation. Typical doses of dobutamine range from 2.5 to 20 μg/kg/min. In rare cases, patients may develop an allergic reaction to dobutamine, which is manifested as acute, unexplained, renal failure and eosinophilia in both urine and blood smears and (often) evidence of eosinophilic infiltration on myocardial biopsy. Discontinuation of the agent is required and a reintroduction of the medication in the future should be done with caution as recurrence is known to occur.

Milrinone is a selective phosphodiesterase-3 inhibitor that increases intramyocyte cyclic AMP levels leading to increased intracellular calcium for myofilament binding. The net result is a vasodilatory effect in the pulmonary and systemic circulations and increased inotropy within the heart without significant chronotropic alterations.[76] Typical milrinone doses are 0.125 to 0.75 μg/kg/min. Because of a long half-life (2.5 hours), the agent takes about 7 hours before peak effects can be seen. The long time to drug onset may be offset with an intravenous bolus load (50 μg/kg/min), but this practice is strongly discouraged (especially in unstable patients) due to the increased risk for acute hypotension. Active and inactive metabolites of milrinone are renally cleared and dose adjustments should be made in patients with low glomerular filtration rates.

Both dobutamine and milrinone are associated with an increased risk of atrial and ventricular arrhythmias and systemic hypotension. Dobutamine has a shorter half-life, which is associated with an earlier onset of action and elimination from the body should ectopy or hypotension develop. Because of milrinone's long half-live, it is the preferred agent for outpatient parenteral therapy and is a more potent pulmonary arterial vasodilator.[77] Clinical outcomes are similar and the choice of agent is generally determined by clinician preference, institutional availability, and potential need to transition to outpatient parenteral therapy.[78]

One other intravenous inotropic agent is Levosimendan. This drug binds to troponin C and sensitizes the myofilament to calcium.[79] When compared head-to-head with dobutamine, there was no beneficial effect on clinical outcomes at 180 days and this drug remains unapproved for clinical use within the United States.[80]

Vasodilators

Although the use of a vasodilator in patients with critical CS is contraindicated, they can be initiated with caution in patients with low-grade shock. Intravenous vasodilators include nitroglycerin, nitroprusside, and nesiritide. Nitroglycerin is a strong venodilator that is effective in reducing preload and in vasodilating the coronary vasculature.[81] Unfortunately, tachyphylaxis requiring dose escalation is common, limiting its clinical application to mainly those patients with refractory angina. Nitroprusside vasodilates the arterial and venous vasculature by means of the guanyl cyclase pathway. This agent is commonly used in acute heart failure syndromes in patients without evidence of severe shock to reduce systemic and pulmonary afterload. In selected patient with lower grades of CS stabilized with inotropes, the addition of nitroprusside may lead to a reduction in left and right ventricular afterloads, leading to improved left-sided and right-sided stroke volumes. Paradoxically, because of the benefits in cardiac output, blood pressures can even increase with nitroprusside therapy. In head-to-head comparisons with inotropic agents, nitroprusside has been shown to reduce the systemic and pulmonary vascular resistance, pulmonary capillary wedge pressure and improve cardiac output as effectively as an inotrope.[82] The very short half-life of nitroprusside compared with other intravenous vasodilators makes it particularly attractive for ICU management of those with cardiac insufficiency. Nitroprusside should be started at low doses (0.5 μg/kg/min) with an arterial line in place. The dose may be titrated by 0.5 μg/kg/min increments while maintaining a goal blood pressure. It is important to monitor patients for signs and symptoms of cyanide toxicity. Patients with cyanide toxicity may present with confusion, nausea, vomiting, or hyperreflexia and laboratory test results may demonstrate new or worsening lactic acidosis. Monitoring of serum thiocyanate levels is useful if provided by an in-hospital laboratory in a timely fashion. Toxicity is more common in patients with renal dysfunction and with prolonged administration.

The last class of intravenous vasodilators used for patients in CS includes nesiritide. Nesiritide is a recombinant B-type natriuretic peptide that is an arterial and venous vasodilator and has natriuretic peptide properties. Initial studies of this drug showed not only a favorable hemodynamic profile but also improved short-term mortality.[83] Later pooled analyses showed worsening renal function and higher short-term mortality in patients receiving nesiritide, curbing a high initial enthusiasm for the medication.[84,85] Nevertheless, the drug remains a useful adjunctive agent for managing patients with CS.

Vasopressors

For those patients with profound hypotension, use of vasopressors is often required to maintain adequate blood pressure and organ homeostasis. Dopamine has classically been used in the management of heart failure patients who are suffering from acute hypotension because this medication has been shown to vasodilate the renal vasculature.[86] Despite these assumed beneficial effects in heart failure patients, dopamine appears to offer a less favorable short-term mortality when compared with norepinephrine.[87] In 280 patients with CS managed with vasopressor support, dopamine was associated with increased tachyarrhythmias and mortality compared with norepinephrine.[87] Given the high mortality for any patient receiving vasopressor therapy, the focus of treatment should not be on the specific agent, but rather on the restoration of normal cardiac output and resumption of normal organ homeostasis. In appropriate patients, use of temporary mechanical support should supersede addition or further titration of vasopressors.

MECHANICAL CIRCULATORY SUPPORT

Temporary circulatory support is a promising option for management of patients in CS.

Intra-Aortic Balloon Pump

In the landmark SHOCK trial, more than 86% of patients with CS received IABP support.[67] In the subsequent SHOCK registry, the use of an IABP with or without thrombolytics was associated with a significant reduction in in-hospital mortality from 72% to 50%.[88] Despite the widespread use of IABP counterpulsation to manage patients with CS, the data supporting favorable outcomes are quite limited, particularly in the setting of early revascularization. A recent meta-analysis that evaluated both randomized clinical trials and observational cohort studies of STEMI patients with CS showed an increased mortality for those patients receiving an IABP at the time of primary percutaneous coronary intervention.[89] In CS patients treated with fibrinolytics, mortality was reduced with IABP support.[89]

Two recent randomized clinical trials have been undertaken to evaluate the efficacy of IABPs for patients in CS: the IABP-SHOCK I and II trials. The initial IABP-SHOCK trial was a small, single-center study that randomized 45 patients with MI and CS.[90] The primary endpoint was a reduction in the APACHE II score at 4 days. There was a reduction in APACHE II scores for both patient groups, suggesting no added benefit of IABP therapy.[90] To confirm these results, the IABP-SHOCK II trial was conducted in 600 patients with CS complicating an acute MI.[91] Across all analyzed outcomes—including adverse events—there was no difference found between groups.[91] In the most recent revision of the ACC/AHA STEMI guidelines, the use of an IABP for patients with CS has been downgraded from a class I to a class IIa recommendation.[73,92]

Percutaneous Ventricular Assist Devices

As mechanical circulatory support continues to grow with improvements in LVAD technology, a parallel growth is occurring within percutaneous ventricular assist devices. As the technology continues to evolve, a durable entirely percutaneous implantable ventricular assist device is not unfathomable. Some of the more commonly used percutaneous devices include the TandemHeart (Cardiac Assist Inc, Pittsburgh, PA, USA), Impella 2.5, Impella CP (Abiomed Inc, Danvers, MA, USA), and peripheral extracorporeal membrane oxygenation (ECMO) (**Fig. 5**). The Impella 2.5 and CP are placed across the aortic valve using a transcatheter approach. Both devices have an axial-flow rotor that withdraws blood from the left ventricle via a pigtail and ejects blood into the ascending aorta directly above the coronary ostia. The Impella 2.5 provides up to 2.5 L of flow, whereas the CP can provide 3.5 L of flow. Hemolysis and pigtail migration are not infrequent complications. The TandemHeart device withdraws oxygenated blood from an inflow cannula that is placed via the femoral vein in the left atrium through a transseptal puncture. Oxygenated blood returns to a pump, which sits outside the patient and is then returned via a cannula placed within the femoral artery. The TandemHeart device is capable of providing 4 to 5 L of flow depending on the size of the return cannula used. Complications with this device include catheter dislodgment, hemolysis, bleeding, and limb ischemia, with limb ischemia being alleviated with the use of antegrade perfusion catheter.

Well-powered, randomized studies of percutaneous support devices in CS are lacking. Two small randomized studies have been conducted comparing the use of the

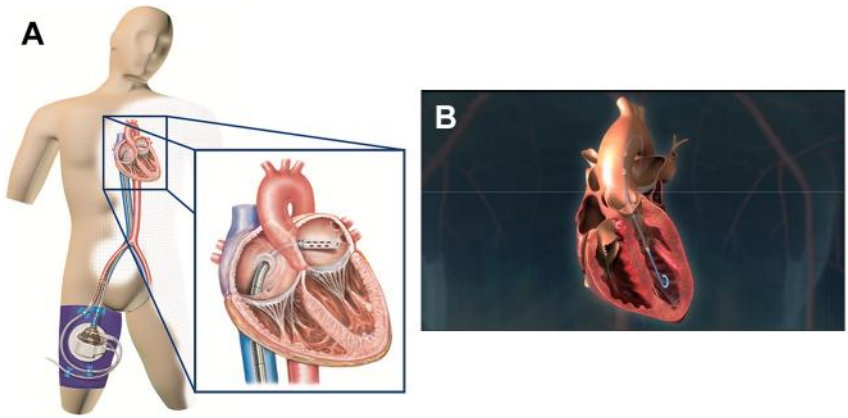

Fig. 5. Percutaneous ventricular assist devices. Demonstration of 2 percutaneous ventricular assist devices. (*A*) The TandemHeart device, where oxygenated blood is removed from the left atrium via a 21-F inflow cannula, which originates in the femoral vein and is placed in the left atrium via a transeptal puncture using intracardiac or transesophageal echocardiographic guidance. The oxygenated blood then flows through the pump and is returned to the body via a 15-F or 17-F cannula placed in the femoral artery. (*B*) The Impella devices are placed in the femoral artery using either a 13-F (Impella 2.5) or a 14-F (Impella CP) sheath. The device has a pigtail that sits across the aortic valve where blood is removed, rotated through the axial-flow rotor, which sits across the aortic valve. Blood is then ejected from the pump above the ostia of the coronary arteries. (*Courtesy of* CardiacAssist, Inc, Pittsburg, PA; with permission.)

TandemHeart versus IABP in CS patients.[93,94] Both studies showed an improvement in hemodynamic parameters, such as cardiac index or pulmonary capillary wedge pressure, but showed no significant difference in mortality.[93,94] Each study only included approximately 40 patients and were underpowered to assess mortality. Another randomized study compared the Impella 2.5 device with an IABP in 25 CS patients and found similar improvement in hemodynamics, but again no improvement in clinical outcomes.[95] A recent meta-analysis of all 3 trials showed no improvement in short-term mortality when these devices are used in patients with CS.[96] Importantly, these studies have failed to look at the efficacy of the percutaneous ventricular assist device when used as a bridge-to-bridge strategy for patients who go on to receive a durable LVAD. There is some data that suggest these devices may be effective in improving outcomes after a durable LVAD is implanted (eg, right ventricular failure, renal failure, and operative mortality).[97]

The artificial heart-lung machine was developed in 1937 by John Heysham Gibbon Jr, MD to allow performance of open heart surgery.[98,99] The initial experience was complicated by hemolysis, thrombocytopenia, and hemorrhage due to direct contact of the blood and gases used for oxygenation. The technology was improved through the use of a membrane to separate the gas from blood,[100] and after years of work, the use of extracorporeal membrane oxygenation to support adults and children with respiratory failure successfully became reported.[101,102] Because of decades of experience and a relatively inexpensive cost compared with newer percutaneous devices, ECMO continues to be the device of choice for many institutions in patients with critical CS. It has been used successfully as a bridge-to-bridge device to mitigate the risks of putting in a durable LVAD.[103,104] There are, however, some potential advantages of a percutaneous ventricular assist device over ECMO: (1) the ability

to decompress the cardiac chambers; (2) a reduction in wall stress and oxygen consumption should myocardial recovery be an intent; (3) normalization of hemodynamics (central venous and pulmonary capillary wedge pressures); and (4) physiologically mimicking a durable ventricular assist device by allowing one a "guess-estimate" of the expected response to a more durable LVAD. Because of the perceived beneficial effects of ventricular decompression, some centers have begun to use the Impella 2.5 device with ECMO and others decompress the LV using the TandemHeart.[105] As reviewed later in this issue, mortality following initiation of ECMO in patients with cardiac arrest and CS remains high. Survival with the use of any percutaneous support is best when instituted before a patient is "crashing and burning."

Newer generations of percutaneous ventricular assist devices promise to increase the cardiac output without the requirement for a larger French-size access sheath or the need for a surgical cut down. Some upcoming devices in order of potential clinical availability include the following: the Reitan Catheter Pump (Kiwimed, London, UK), iVAC 3L PVAD (PulseCath BV, Amsterdam, the Netherlands), and the Percutaneous Heart Pump (Thoratec Corp, Pleasanton, CA, USA).

PERSPECTIVE FOR THE FUTURE

The improvements in clinical outcomes following the onset of CS have largely been driven by early revascularization. Adjunctive therapies such as inotropes, IABPs, and PACs have not been shown to improve outcomes systematically. Clinically, we exist at a plateau, where despite continued improvements in adjunctive pharmacology and revascularization techniques, CS mortality remains high. With newer percutaneous support devices, the ability to rest or recover the heart until the stunned myocardium recruits or until a durable LVAD can be placed is a hope. The field will only move forward, however, with increased randomized clinical trials such as the SHOCK trial—which is now more than a decade old—seemingly the only influential trial of CS patients.

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