Cardiogenic Shock

Current Concepts and Improving Outcomes

Harmony R. Reynolds, MD; Judith S. Hochman, MD

Cardiogenic shock (CS) occurs in ≈5% to 8% of patients hospitalized with ST-elevation myocardial infarction (STEMI). Recent research has suggested that the peripheral vasculature and neurohormonal and cytokine systems play a role in the pathogenesis and persistence of CS. Early revascularization for CS improves survival substantially. New mechanical approaches to treatment are available, and clinical trials are feasible even in this high-risk population. Most importantly, hospital survivors have an excellent chance for long-term survival with good quality of life. This review will outline the causes, pathophysiology, and treatment of CS with a focus on CS complicating myocardial infarction (MI.) The case will be made for viewing CS as a serious disorder with a high early death rate, but one that is treatable and that, if approached aggressively, can result in full recovery.

Diagnosis and Causes

CS is a state of end-organ hypoperfusion due to cardiac failure. The definition of CS includes hemodynamic parameters: persistent hypotension (systolic blood pressure <80 to 90 mm Hg or mean arterial pressure 30 mm Hg lower than baseline) with severe reduction in cardiac index (<1.8 L · $min^{-1} \cdot m^{-2}$ without support or <2.0 to 2.2 L · $min^{-1} \cdot m^{-2}$ with support) and adequate or elevated filling pressure (eg, left ventricular [LV] end-diastolic pressure >18 mm Hg or right ventricular [RV] end-diastolic pressure >10 to 15 mm Hg). The diagnosis is usually made with the help of pulmonary artery (PA) catheterization; however, Doppler echocardiography may also be used to confirm elevation of LV filling pressures.[1] Hypoperfusion may be manifest clinically by cool extremities, decreased urine output, and/or alteration in mental status. Hemodynamic abnormalities form a spectrum that ranges from mild hypoperfusion to profound shock, and the short-term outcome is directly related to the severity of hemodynamic derangement.

MI with LV failure remains the most common cause of CS. It is critical to exclude complicating factors that may cause shock in MI patients. Chief among these are the mechanical complications: ventricular septal rupture, contained free wall rupture, and papillary muscle rupture. Mechanical complications must be strongly suspected in patients with CS complicating nonanterior MI, particularly a first MI. Echocardiography is the technique of choice to rule out these entities and should be performed early unless the diagnosis is extensive anterior MI and the patient is undergoing prompt percutaneous coronary intervention (PCI). In addition, the detection of valvular disease before angiography may alter the revascularization approach.

Hemorrhage, infection, and/or bowel ischemia may contribute to shock in the setting of MI. As with mechanical complications, a high index of suspicion is required to make these diagnoses in MI patients, and survival may depend on timely recognition and treatment.

Any cause of acute, severe LV or RV dysfunction may lead to CS. Acute myopericarditis, tako-tsubo cardiomyopathy, and hypertrophic cardiomyopathy may all present with ST elevation, release of cardiac markers, and shock in the absence of significant coronary artery disease. Stress-induced cardiomyopathy, also known as apical ballooning or tako-tsubo cardiomyopathy, is a syndrome of acute LV dysfunction after emotional or respiratory distress that leads to CS in 4.2% of cases.[2] Acute valvular regurgitation, typically caused by endocarditis or chordal rupture due to trauma or degenerative disease, may also cause CS. Aortic dissection may lead to CS via acute, severe aortic insufficiency or MI. Acute stress in the setting of aortic or mitral stenosis can also cause shock. Cardiac tamponade or massive pulmonary embolism can present as cardiogenic shock without associated pulmonary congestion.

Incidence

After decades of remarkable stability in the incidence of CS, it appears that the incidence is on the decline in parallel with increasing rates of use of primary PCI for acute MI. CS continues to complicate approximately 5% to 8% of STEMI[3,4] and 2.5% of non-STEMI cases.[5] This translates to 40 000 to 50 000 cases per year in the United States.[6] The routine use of troponin to define non-STEMI will result in a drop in this percentage as more MIs are detected but will not alter the total number of cases of CS.

Identification of Patients at Risk

The only way to prevent CS appears to be very early reperfusion therapy for MI. A randomized trial of early, in-ambulance thrombolysis versus primary PCI found no CS among patients assigned to prehospital thrombolysis.[7] Among

From The Leon H. Charney Division of Cardiology, Cardiovascular Clinical Research Center, New York University School of Medicine, New York, NY.
Correspondence to Judith S. Hochman, MD, New York University School of Medicine, 530 First Ave, SKI-9R, New York, NY 10016. E-mail Judith.Hochman@nyumc.org

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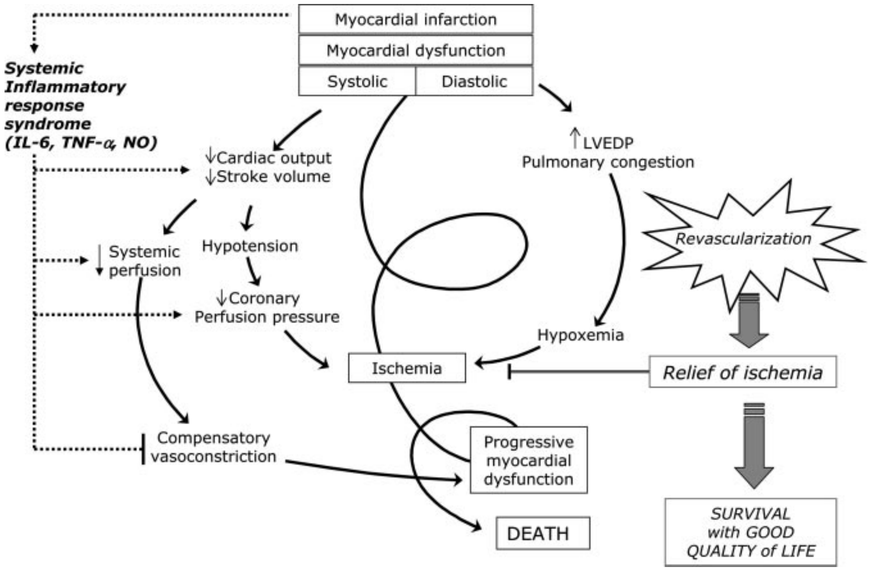

Figure 1. Current concept of CS pathophysiology. The classic description of CS pathogenesis is shown in black. Myocardial injury causes systolic and diastolic dysfunction. A decrease in CO leads to a decrease in systemic and coronary perfusion. This exacerbates ischemia and causes cell death in the infarct border zone and the remote zone of myocardium. Inadequate systemic perfusion triggers reflex vasoconstriction, which is usually insufficient. Systemic inflammation may play a role in limiting the peripheral vascular compensatory response and may contribute to myocardial dysfunction. Whether inflammation plays a causal role or is only an epiphenomenon remains unclear. Revascularization leads to relief of ischemia. It has not been possible to demonstrate an increase in CO or LVEF as the mechanism of benefit of revascularization; however, revascularization does significantly increase the likelihood of survival with good quality of life. IL-6 indicates interleukin-6; TNF-α, tumor necrosis factor-α; and LVEDP, LV end-diastolic pressure. Adapted from Hochman[42] and Hollenberg et al[43] with permission of the publishers. Copyright © 2003, the American Heart Association, and copyright © 1999, the American College of Physicians.

PCI-assigned patients, just 0.5% developed CS in the group randomized <2 hours from symptom onset. A major focus of public health campaigns is the very early recognition and reperfusion of MI, which should reduce CS incidence.

Risk factors for development of CS in the context of MI include older age, anterior MI, hypertension, diabetes mellitus, multivessel coronary artery disease, prior MI or angina, prior diagnosis of heart failure, STEMI, and left bundle-branch block.[8] There may be clues to impending shock: Heart rate is higher and blood pressure lower on hospital presentation among patients who develop CS after admission.

Pathophysiology

CS is the result of temporary or permanent derangements in the entire circulatory system. LV pump failure is the primary insult in most forms of CS, but other parts of the circulatory system contribute to shock with inadequate compensation or additional defects. Many of these abnormalities are partially or completely reversible, which may explain the good functional outcome in most survivors.

Left Ventricle

The degree of myocardial dysfunction that initiates CS is often, but not always, severe. LV dysfunction in shock reflects new irreversible injury, reversible ischemia, and damage from prior infarction. The unique position of the heart as an organ that benefits from low blood pressure via afterload reduction and also suffers from low blood pressure via compromise of coronary flow creates a situation in which changes in hemodynamics may be simultaneously beneficial and detrimental. As depicted in Figure 1, a decrease in coronary perfusion lowers cardiac output (CO), which further decreases perfusion of the heart and other vital organs. Coronary flow may be additionally compromised by atherosclerosis of vessels other than the infarct artery. Metabolic derangements occur in the remote myocardium and in the infarct region.[9] Hypoperfusion causes release of catecholamines, which increase contractility and peripheral blood flow, but catecholamines also increase myocardial oxygen demand and have proarrhythmic and myocardiotoxic effects.

Inotropic agents and vasoconstrictors temporarily improve CO and peripheral perfusion but do not interrupt this vicious circle. Rapid intra-aortic balloon pump (IABP) support may temporarily relieve ischemia and support the circulation, but IABP is not definitive therapy. Relief of coronary occlusion, best achieved through PCI or surgery, interrupts the vicious circle and saves lives.

In light of the complex pathophysiology of CS, it is not surprising that in many cases, severe impairment of contractility does not lead to shock, and conversely, LV ejection fraction (LVEF) may be only moderately depressed in CS (Figure 2).[10] In fact, the mean LVEF in the SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK) trial was ≈30%,[11] and the distribution of LVEF in SHOCK overlaps with that in many post-MI trials in patients with reduced LVEF with or without heart failure (Figure 2),[11–22] who were generally ambulatory outpatients. Although LVEF in SHOCK was usually measured while patients were on inotropic and/or balloon support, similar values in shock and in the subacute/chronic phases of MI indicate that the magnitude of myocardial insult that causes CS need not be profound. LVEF is similar in the acute phase of CS and 2 weeks later,[23] when functional status is quite different, as discussed below. Furthermore, some patients present with CS despite preservation of LVEF in the absence of severe mitral regurgitation.[24] Among patients in shock, however, LVEF remains a prognostic indicator.[25] Approximately half of all CS patients have small or normal LV size,[23,25] which represents failure of the adaptive mechanism of acute dilation to maintain stroke volume in the early phase of MI. Progressive LV dilation (remodeling) in the chronic phase can be maladaptive. Serial echocardiography has dem-

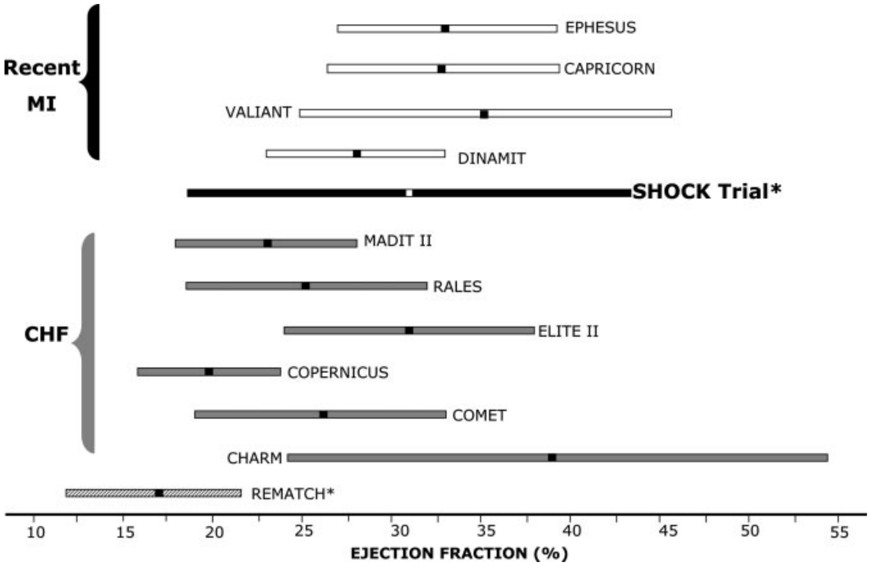

Figure 2. Range of LVEF in studies of heart failure and in the SHOCK trial. Range of LVEF (mean±SD) is presented for a variety of trials of recent MI with asymptomatic or mildly symptomatic LV dysfunction or chronic HF. The range of LVEF in the SHOCK trial (mean±SD) overlaps with the range of LVEF in these trials, although LVEF in SHOCK was obtained on support measures. Note that REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure) studied LVAD use as destination therapy. *Measured on support. CHF indicates congestive heart failure; EPHESUS, Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study; CAPRICORN, CArvedilol Post infaRct SurvIval COntRol in LV dysfunctioN; VALIANT, VALsartan In Acute myocardial iNfarcTion; DINAMIT, Defibrillator IN Acute Myocardial Infarc-Tion; MADIT II, Multicenter Automatic Defibrillator Implantation Trial II; RALES, Randomized ALdactone Evaluation Study; ELITE II, Evaluation of Losartan In The Elderly II; COPERNICUS, CarvedilOl ProspEctive RaNdomIzed CUmulative Survival study; COMET, Carvedilol Or Metoprolol European Trial; and CHARM, Candesartan in Heart failure: Assessment of moRtality and Morbidity. Adapted from Ramanathan et al, [10] with permission of the author.

onstrated a small increase in LV end-diastolic volume in 2-week survivors of CS (15-mL change in median LV end-diastolic volume).[23] Contractile function can be assessed with echocardiography or LV angiography. In addition, the indwelling PA catheter allows ongoing evaluation of CO in response to changes in therapy and volume status. Diastolic function is more difficult to assess. It is likely that abnormalities of ventricular relaxation and compliance contribute to CS in some, if not all, cases.

Right Ventricle

RV dysfunction may cause or contribute to CS. Predominant RV shock represents only 5% of cases of CS complicating MI.[26] RV failure may limit LV filling via a decrease in CO, ventricular interdependence, or both. Treatment of patients with RV dysfunction and shock has traditionally focused on ensuring adequate right-sided filling pressures to maintain CO and adequate LV preload; however, patients with CS due to RV dysfunction have very high RV end-diastolic pressure, often >20 mm Hg.[26] This elevation of RV end-diastolic pressure may result in shifting of the interventricular septum toward the LV cavity, which raises left atrial pressure but impairs LV filling due to the mechanical effect of the septum bowing into the LV. This alteration in geometry also impairs LV systolic function.[27] Therefore, the common practice of aggressive fluid resuscitation for RV dysfunction in shock may be misguided. Inotropic therapy is indicated for RV failure when CS persists after RV end-diastolic pressure has been optimized. RV end-diastolic pressure of 10 to 15 mm Hg has been associated with higher output than lower or higher pressures,[28] but marked variability exists in optimal values. Inhaled nitric oxide (NO) may be useful to lower pulmonary vascular resistance and promote forward flow. Both pericardiectomy and creation of atrial septal defects have been used in extreme cases.

Shock due to isolated RV dysfunction carries nearly as high a mortality risk as LV shock.[26] The benefit of revascularization was similar in the SHOCK registry for patients with primarily RV versus primarily LV dysfunction.

Peripheral Vasculature, Neurohormones, and Inflammation

Hypoperfusion of the extremities and vital organs is a hallmark of CS. The decrease in CO caused by MI and sustained by ongoing ischemia triggers release of catecholamines, which constrict peripheral arterioles to maintain perfusion of vital organs. Vasopressin and angiotensin II levels increase in the setting of MI and shock, which leads to improvement in coronary and peripheral perfusion at the cost of increased afterload, which may further impair myocardial function. Activation of the neurohormonal cascade promotes salt and water retention; this may improve perfusion but exacerbates pulmonary edema. The reflex mechanism of increased systemic vascular resistance (SVR) is not fully effective, as demonstrated by variable SVR, with median SVR during CS in the normal range despite vasopressor therapy in the SHOCK Trial.[29] In some patients, SVR may be low, similar to septic shock. In fact, sepsis was suspected in 18% of the SHOCK trial cohort, 74% of whom developed positive bacterial cultures.[29] SVR was lower in these patients, and low SVR preceded the clinical diagnosis of infection and culture positivity by days.

These findings are consistent with the observation that MI can cause the systemic inflammatory response syndrome (SIRS) and suggest that inappropriate vasodilation as part of SIRS results in impaired perfusion of the intestinal tract, which enables transmigration of bacteria and sepsis. SIRS is more common with increasing duration of shock,[30] even though levels of interleukin-6 and tumor necrosis factor-α have been found to be elevated on admission among MI patients who were initially in Killip class I and later developed CS.[31] Cytokine levels rise more dramatically over the 24 to 72 hours after MI. Tumor necrosis factor-α and interleukin-6 have myocardial depressant action. Tumor ne-

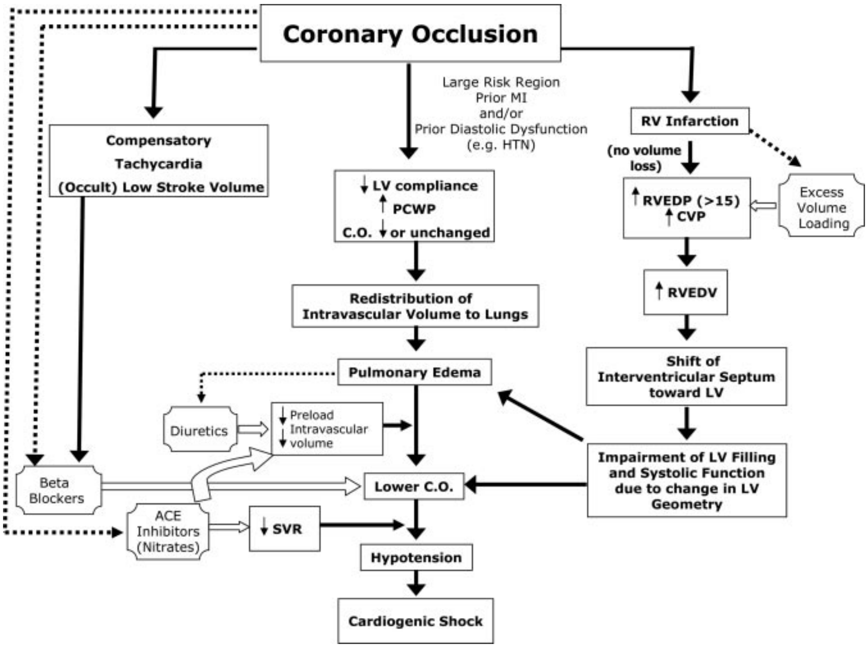

Figure 3. Iatrogenic shock. The pathophysiology of iatrogenic shock that results from different scenarios of MI and pulmonary edema treatment is depicted. Acute pulmonary edema is a state of redistribution of intravascular volume into extracellular space in the lungs. When hemodynamic stability is tenuous, the additional decrease in plasma volume caused by diuretics in patients without prior heart failure may induce shock. Tachycardia is often compensatory for lower stroke volume but is not appreciated as such. Treatment with β-blockade lowers heart rate and stroke volume, leading to frank shock. Decompensation may also occur when patients who are reliant on compensatory vasoconstriction are treated with angiotensin-converting enzyme inhibitors, particularly intravenously and early. Nitrates would be expected to have a similar effect but did not in the only systematic study, which used oral, low-dose treatment. Volume expansion may be deleterious when used to excess or when RV filling pressure is already elevated, because the RV may become volume overloaded with shift of the septum causing impairment in LV filling and contraction. CVP indicates central venous pressure; HTN, hypertension; PCWP, pulmonary capillary wedge pressure; RVEDP, RV end-diastolic pressure; and RVEDV, RV end-diastolic volume.

crosis factor-α also induces coronary endothelial dysfunction, which may further diminish coronary flow.[32] Other circulating factors (complement, procalcitonin, neopterin, C-reactive protein, and others) have been reported to contribute to SIRS in CS. Despite a promising randomized phase 2 study, a trial of complement (C5) inhibition in patients with MI found that pexelizumab did not reduce the development of shock or mortality.[33,34]

Excess NO may also contribute to SIRS. MI is associated with increased expression of inducible NO synthase, which leads to excess NO, which causes vasodilation, myocardial depression, and interference with catecholamine action. Although isoform-nonselective NO synthase inhibitors appeared to improve hemodynamics and outcome in small studies of CS patients, N^{G}-monomethyl-L-arginine at the same dose and duration did not reduce mortality in a large multicenter trial.[35] N^{G}-monomethyl-L-arginine did, however, result in an early blood pressure rise in patients with persistent shock despite vasopressors and opening of the infarct artery, which suggests that excess NO contributes to hypotension.[36] Additional studies will be needed to test the hypothesis that prevention/treatment of SIRS or excess inducible NO synthase will improve outcomes.

CS May Be an Iatrogenic Illness

Approximately three fourths of patients with CS complicating MI develop shock after hospital presentation.[4,37] In some, medication use contributes to the development of shock. Several different classes of medications used to treat MI have been associated with shock, including β-blockers, angiotensin-converting enzyme inhibitors, and morphine. Although early use of each of these medications is associated with only a small excess risk of CS, the large number of patients treated with these therapies translates into a substantial potential number of events.[38–41] The timing of CS (early after medication initiation) in the placebo-controlled, randomized trials of β-blockade and angiotensin-converting enzyme inhibition combined with their mechanisms of action indicate that they may contribute to CS development in those at high risk.

Diuretics may also cause or contribute to shock in patients with MI (Figure 3).[42,43] As depicted in Figure 3, MI may lead to pulmonary edema even without a decrease in CO, because the earliest effect of ischemia is often a decrease in LV compliance. Redistribution of intravascular volume into the lungs leads to a net acute decrease in circulating plasma volume in those without prior heart failure. When high-dose diuretics are administered, plasma volume declines further. A trial of a low diuretic dose coupled with low-dose nitrates and positional measures to decrease preload (eg, seated position with legs down) should be attempted in patients with MI and pulmonary edema to avoid precipitating shock. Excess volume loading in patients with RV infarction may also cause or contribute to shock.

Treatment

General Support Measures

Antithrombotic therapy with aspirin and heparin should be given as routinely recommended for MI. Clopidogrel may be deferred until after emergency angiography, because on the basis of angiographic findings, coronary artery bypass grafting (CABG) may be performed immediately. Clopidogrel is indicated in all patients who undergo PCI, and on the basis of extrapolation of data from MI patients who were not in shock, it should also be useful in patients with shock as well. Negative inotropes and vasodilators (including nitroglycerin) should be avoided. Arterial oxygenation and near-normal pH should be maintained to minimize ischemia. Intensive insulin therapy improves survival in hyperglycemic critically ill patients and is recommended for use in complicated MI.[44] There should be a low threshold to institute mechanical ventilation via mask or endotracheal tube. Positive end-expiratory pressure decreases preload and afterload. Mechanical ventilation also reduces work of breathing.

Hemodynamic Management

PA (Swan-Ganz) catheterization is frequently performed to confirm the diagnosis of CS, to ensure that filling pressures are adequate, and to guide changes in therapy. The best use of this technique is to establish the relationship of filling pressures to CO in the individual patient and supplement clinical assessment of responses with these data. Hemodynamic data, particularly cardiac power and stroke work index, have powerful short-term prognostic value.[45] There has been a decline in PA catheter use relating to controversy sparked by a prospective observational study that suggested that PA catheters were associated with poor outcome.[46] No such association has been shown in CS.[47]

Individualized PA catheter use is recommended for severely hypotensive MI patients[44]; however, many centers now choose to manage CS without PA catheterization. Clinical assessment with echocardiography is a reasonable alternative: Both PA systolic pressure and wedge pressure can be accurately estimated with Doppler echocardiography, and in particular, the finding of a short mitral deceleration time ($\leq$140 ms) is highly predictive of pulmonary capillary wedge pressure $\geq$20 mm Hg in CS.[24] The clinical examination and chest radiograph are not reliable predictors of pulmonary capillary wedge pressure; neither detects elevation in 30% of CS patients.

Pharmacological Treatment

Pharmacological support includes inotropic and vasopressor agents, which should be used in the lowest possible doses. Higher vasopressor doses are associated with poorer survival[48]; this represents both more severe underlying hemodynamic derangement and direct toxic effects.

Inotropic agents have a central role in treatment because the initiating event involves contractile failure. Unfortunately, inotropes increase myocardial ATP consumption such that short-term hemodynamic improvement occurs at the cost of increased oxygen demand when the heart is already failing and supply is already limited. Still, use of inotropic and vasopressor agents is always required to maintain coronary and systemic perfusion until (and often after) an IABP is placed or until shock resolves. Data on comparison of vasopressors are scant. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend norepinephrine for more severe hypotension because of its high potency.[44] Although both dopamine and norepinephrine have inotropic properties, dobutamine is often needed in addition. Pharmacological treatments that warrant further investigation include vasopressin; levosimendan, a calcium-sensitizing agent that has so far shown little additional value in randomized heart failure trials[49,50]; and/or activated protein C, which has been tried in conjunction with mechanical support in myocarditis patients.[51]

Mechanical Support: IABP

Intra-aortic balloon counterpulsation has long been the mainstay of mechanical therapy for CS. Use of an IABP improves coronary and peripheral perfusion via diastolic balloon inflation and augments LV performance via systolic balloon deflation with an acute decrease in afterload. Accurate timing of inflation and deflation provides optimal support. Not every patient has a hemodynamic response to IABP; response predicts better outcome.[52] IABP support should be instituted as quickly as possible, even before any transfer for revascularization if a skilled operator is available and insertion can be performed quickly.

In the large National Registry of Myocardial Infarction, IABP use was independently associated with survival at centers with higher rates of IABP use, whether PCI, fibrinolytic therapy, or no reperfusion had been used[53]; however, no completed trials demonstrate benefit. Complications associated with IABP are less common in the modern era; in the largest series, the overall and major complication rates were 7.2% and 2.8%, respectively.[54] Risk factors for complications include female sex, small body size, and peripheral vascular disease.

Reperfusion

The survival benefit of early revascularization in CS, reported in several observational studies, was shown convincingly in the randomized SHOCK trial, which found a 13% absolute increase in 1-year survival in patients assigned to early revascularization.[11,55] This corresponds to a number needed to treat of <8 patients to save 1 life. The benefit was similar in the incomplete, randomized Swiss Multicenter Study of Angioplasty for Shock.[56] Numerous registry studies have confirmed the survival advantage of early revascularization, whether percutaneous or surgical, in the young and the elderly. Thrombolytic therapy is less effective but is indicated when PCI is impossible or if a delay has occurred in transport for PCI and when MI and CS onset were within 3 hours.

Timing of PCI

As in MI without shock, earlier revascularization is better in CS. Presentation 0 to 6 hours after symptom onset was associated with the lowest mortality among CS patients undergoing primary PCI in the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte (ALKK) registry, in which door-to-angiography times were <90 minutes in approximately three fourths of patients.[57] In the SHOCK trial, there appeared to be increasing long-term mortality as time to revascularization increased from 0 to 8 hours.[55] However, there is a survival benefit as long as 48 hours after MI and 18 hours after shock onset.

Stenting and Glycoprotein IIb/IIIa Inhibition

Stenting and glycoprotein IIb/IIIa inhibitors were independently associated with improved outcomes in patients undergoing PCI for CS in multiple registries, including the large ACC-National Cardiovascular Data Registry.[58] A trend toward benefit of abciximab was noted in a small subset of STEMI patients with CS undergoing PCI in a randomized trial. [58a]

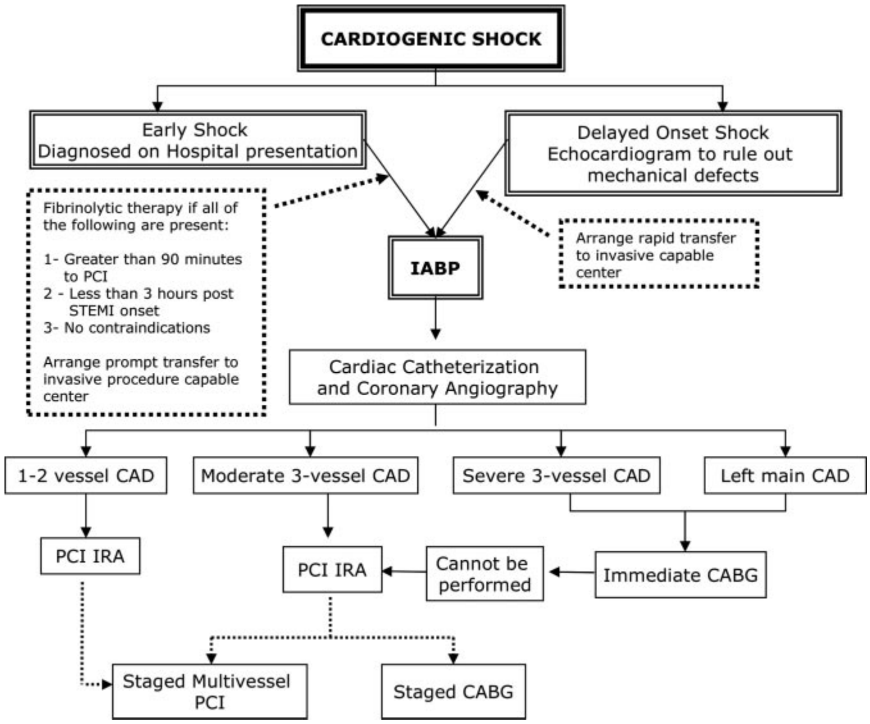

Figure 4. Algorithm for revascularization strategy in cardiogenic shock, from ACC/AHA guidelines.[42,44] Whether shock onset occurs early or late after MI, rapid IABP placement and angiography are recommended. Immediate CABG is the preferred method of revascularization when severe triple-vessel or left main disease is present and should be performed as needed when VSR or severe mitral regurgitation exists. PCI of the infarct-related artery is recommended in the case of single- or double-vessel disease or moderate triple-vessel disease and when CABG is not possible for patients with more extensive disease. CAD indicates coronary artery disease; IRA, infarct-related artery.

Revascularization Approach: Surgery or PCI

Revascularization in the SHOCK trial could be percutaneous or surgical. Thirty-seven percent of patients assigned to the early revascularization strategy underwent CABG at a median of 2.7 hours after randomization.[59] Despite a higher prevalence of triple-vessel or left main disease and diabetes mellitus in patients who underwent CABG compared with PCI, survival and quality of life were similar.[59,60] The rate of emergency CABG in CS is much lower in the community (<10%).[4]

Survival in patients with CS who have CABG may improve further with advancing surgical techniques. In a series of CS patients undergoing surgery, a trend toward better survival with beating heart techniques was present despite the use of slightly lower numbers of grafts.[61] A left internal mammary artery graft was used in >98% of patients with CS in this study as opposed to 15.2% in SHOCK. This latter point could be of particular importance when one considers the potential for long-term survival in CS patients.

Multivessel Disease

The optimal revascularization strategy (ie, percutaneous or surgical, single or multivessel PCI) for patients with multivessel coronary artery disease and CS is not clear. This is of particular importance because multivessel disease is common; 87% of patients in SHOCK had multivessel disease.[62] In some patients, coronary anatomy may be most amenable to CABG. It is not clear whether multivessel PCI is useful in CS. In SHOCK, the rate of multivessel PCI increased over the study period, which perhaps suggests that operators gained experience with PCI in CS patients; however, this small subset had a worse adjusted outcome than those with single-vessel PCI.[63] Short-term PCI of non–infarct-related artery vessels during MI is associated with more complications than delayed non–infarct-related artery treatment.[64] In clinical practice, as in the SHOCK trial,[59] multivessel PCI is performed in approximately one fourth of patients with CS undergoing PCI. This translates into multivessel PCI in just over one third of those with multivessel disease.

Figure 4 depicts the ACC/AHA guidelines for revascularization in shock, which recommend surgery for extensive disease. Staged multivessel PCI may be performed if surgery is not an option, and a single-stage procedure may be considered if the patient remains in shock after PCI of the infarct-related artery and if the other vessel has a lesion that is flow limiting at rest and supplies a large risk region.

Risk Stratification and Targeting the Population for Revascularization

Mortality due to CS is not as high as many clinicians may believe and is ≈50% in the modern era, far lower than historic figures of 80% to 90%. Mortality can range from 10% to 80% depending on demographic, clinical, and hemodynamic factors. These factors include age, clinical signs of peripheral hypoperfusion, anoxic brain damage, LVEF, and stroke work. Female sex does not appear to be an independent predictor of poor outcome. Hemodynamic data are predictive of short-term but not long-term mortality. Factors associated with long-term survival in the SHOCK trial are shown in the Table. Revascularization provides benefit at every level of risk.[65] Among CS patients undergoing PCI, age, time from symptom onset to PCI, and post-PCI TIMI (Thrombolysis In Myocardial Infarction) flow grade are independent predictors of mortality.[55,58] Mortality due to CS is on the decline in the United States and Europe in parallel with increasing use of revascularization.[3,4,57]

The initial misperception that elderly patients do not benefit from PCI arose from the interaction between treat-

Table. SHOCK Trial Long-Term Survival Rates by Subgroup

Subgroup	No.	3-Year Survival, %	6-Year Survival, %	P*
Age <75 y	246	38.2	27.6	0.063
Age ≥75 y	56	20.6	20.6	...
Males	205	33.9	24.0	0.931
Females	97	36.9	30.9	...
Shock on admission	41	24.8	12.4	0.016
No shock on admission	230	36.7	28.5	...
Prior MI	98	22.9	15.3	0.005
No prior MI	204	40.2	31.0	...
History of hypertension	137	30.5	18.2	0.027
No history of hypertension	159	39.6	34.0	...
Anterior MI	177	33.6	25.0	0.209
Nonanterior MI	119	36.8	29.8	...
Systemic hypoperfusion rapidly reversed with IABP	90	43.3	32.9	<0.0001
Systemic hypoperfusion not rapidly reversed	131	20.6	16.5	...
CI $<2.0\ L \cdot min^{-1} \cdot min^{-2}$	177	33.4	26.1	0.103
CI $\geq 2.0\ L \cdot min^{-1} \cdot min^{-2}$	83	44.3	37.3	...
PCWP <25 mm Hg	143	43.8	33.4	0.010
PCWP ≥25 mm Hg	126	28.3	22.0	...
LVEF <25%	58	29.9	19.2	0.002
LVEF ≥25%	114	50.8	40.9	...
Single-vessel disease	31	64.5	49.2	0.044
Multivessel disease	208	37.6	28.2	...
Baseline creatinine <1.9 mg/dL†	205	37.9	29.5	0.0002
Baseline creatinine ≥1.9 mg/dL	53	13.8	13.8	...
Thrombolytic therapy at index MI	170	39.3	31.4	0.016
No thrombolytic therapy at index MI	132	28.8	18.6	...
Left main stenosis ≥50%‡	50	31.6	28.9	0.066
Left main stenosis <50%	188	44.6	32.2	...

Table provided by Dr Lynn Sleeper; data analyzed for Hochman et al.[55] Hemodynamic values from time of shock diagnosis while on support measures. No significant interaction was present between any subgroup factor and treatment assignment. Multivariate modeling revealed that older age (P=0.007), shock on admission (P=0.012), creatinine >1.9 mg/dL (P<0.0001), a history of hypertension (P=0.032), and noninferior MI location (P=0.022) were independent risk factors for lower survival rates in a clinical model (N=230). The model that also incorporated hemodynamic measurements and LVEF (N=148) demonstrated that only older age (P=0.035), lower LVEF (P<0.0001), and creatinine >1.9 mg/dL (P=0.012) were independently associated with death. CI indicates cardiac index; PCWP, pulmonary capillary wedge pressure.

*Log-rank P value comparing survival curves between subgroups.

†Quartile 4 vs quartiles 1 through 3 for creatinine.

‡Coronary anatomy was available for 239 of 302 patients. The single vessel disease group includes 5 patients with nonsignificant coronary artery disease.

ment effect and age in the SHOCK trial.[11] The apparent lack of benefit for the elderly in the SHOCK trial was likely due to imbalances in baseline ejection fraction between groups. Several studies, including the SHOCK registry, have shown a consistent benefit of revascularization in elderly patients selected for it (20% to 33%), which suggests that clinicians are capable of identifying those older patients who are appropriate for revascularization.[66]

ACC/AHA guidelines recommend early revascularization in CS for those <75 years of age (class I) and for suitable candidates ≥75 years of age (class IIa).[44] Rapid transfer is also recommended for most patients who present to hospitals without revascularization capability (Figure 4). Unfortunately, real-world revascularization rates range from 27% to 54%.[4] Revascularization will likely be more widely used if clinicians recognize that benefit exists despite high risk and if they need not fear adverse consequences of state and local public mortality reporting.[67] New York State will analyze PCI and CABG mortality rates for CS separately and will exclude them from public reporting for a 2-year period.

Healthcare policy planners may consider patients with multiple risk indicators to be at such high risk that in a resource-limited system, it may not be feasible to perform PCI or CABG when the associated mortality rate is >80%. However, models demonstrate that benefit is derived across the risk spectrum. A group exists for whom additional treatment is futile, particularly when irreversible multiple end-organ failure or anoxic brain damage has occurred. Clearly, a revascularization approach must be individualized. We propose that the most important consideration, especially for the elderly, is functional status before the index event.

Total Circulatory Support: LV Assist Devices and Extracorporeal Life Support

Temporary mechanical circulatory support with LV assist devices (LVADs) is theoretically appealing to interrupt the vicious spiral of ischemia, hypotension, and myocardial dysfunction, allowing for recovery of stunned and hibernating myocardium and reversal of neurohormonal derangements. Device-related complications and irreversible organ failure remain major limitations.

LVAD support involves circulation of oxygenated blood through a device that drains blood from the left side of the heart and returns blood to the systemic arteries with pulsatile or continuous flow. Surgically implanted LVADs remove blood through a cannula placed at the LV apex and return blood to the ascending aorta. Percutaneous LVADs are also available. The TandemHeart (Cardiac Assist, Inc, Pittsburgh, Pa) removes blood from the left atrium using a cannula placed through the femoral vein and into the left atrium via transseptal puncture. Blood is then returned to a systemic artery, usually the femoral, with retrograde perfusion of the abdominal and thoracic aorta. Another percutaneous device, the Impella (Abiomed, Inc, Danvers, Mass), is placed across the aortic valve and is under investigation.[68] Extracorporeal life support (ECLS) involves extracorporeal circulation of blood through a membrane oxygenator, which relieves both the right and left heart and the lungs of part of their workload. Anticoagulation is required for extracorporeal life support and for percutaneous LVADs but may be optional with surgically placed LVADs.

Extracorporeal life support and LVAD have been used sequentially in CS patients, usually as a bridge to heart transplantation.[69] In the largest reported LVAD series to date, 74% of 49 patients survived to transplantation, and 87% of transplanted patients survived to hospital discharge after receiving a variety of surgical LVADs.[70] The risk of bleeding is no higher after MI than in chronic heart failure despite placement of a cannula in the LV apex, which may be necrotic.[70]

Although early LVAD and extracorporeal life support use followed by transplantation has been proposed as an alternative approach to urgent revascularization, direct comparison has not been systematic, and observational studies have had conflicting results. The role of combined treatment is not clear. A nonrandomized comparison of "aggressive" and "conservative" approaches found that early use of circulatory support and heart transplantation was associated with better survival than selection for revascularization,[71] but a study of surgical treatment with LVAD with or without CABG found that mortality was higher in patients who had CABG with LVAD placement early after MI.[72]

Two randomized trials of the TandemHeart versus IABP in CS complicating MI have been conducted.[73,74] Hemodynamic improvement was better in LVAD groups, but a higher rate of multiorgan system dysfunction was observed in the LVAD group with a clinical profile that suggested SIRS, and the mortality rates were the same.

Perhaps most promising given the limited supply of donor organs is the use of LVADs as destination therapy for viable patients who may or may not be transplant candidates.[75,76] Randomized trials are needed for a more complete assessment of the role of different circulatory support strategies in CS.

Treatment of CS Due to Mechanical Complications

Mechanical complications of MI, including rupture of the ventricular septum, free wall, or papillary muscles, cause 12% of CS cases; of these, ventricular septal rupture (VSR) has the highest mortality, 87%.[77] Women and the elderly are at increased risk,[78] and, at least among elderly patients, risk is higher with thrombolysis than with primary PCI.[79] In general, thrombolysis shifts the time course of rupture, with an increase in early and a decrease in later rupture such that the overall rate is reduced.[80] Rupture should be strongly suspected in patients with small infarct size and shock. Echocardiography is instrumental in the diagnosis.

Acute mitral regurgitation may cause or exacerbate CS. Mitral regurgitation may occur due to papillary muscle/chordal rupture or may be due to acute LV dilation with tethering of the mitral apparatus and failure of coaptation. Papillary muscle rupture is more common with inferior infarction.

Timely repair of myocardial rupture associated with CS is critical for survival. It was previously thought that optimal timing involves a balance of operating before the onset of multiorgan system failure with delaying surgery to allow scarring of involved myocardium for better stability of repair. Repair of VSR and free wall rupture present technical difficulties to the surgeon because of the need to suture in an area of necrotic myocardium. Repair of papillary muscle rupture does not involve necrotic myocardium in suture lines, and mortality associated with this repair is lower. The unpredictability of rapid deterioration and death with VSR and papillary muscle rupture makes early surgery necessary even though there may be apparent hemodynamic stabilization with IABP.[81] A subgroup of patients with VSR exists for whom surgery is futile because mortality approaches 100%; this includes the very elderly and patients with poor RV function. RV function is a more important determinant of outcome in VSR than LV function.[81]

Investigation is ongoing to find new techniques to reduce this very high operative risk. Newer off-pump techniques include external septal plication for VSR[82] and repair of free wall rupture with surgical glue and a Gore-Tex patch.[83] Percutaneous VSR repair has been reported for simple and complex defects[84] and after failure of surgical repair.[85] Percutaneous repair is accomplished via venous access with septal occluders that consist of 2 disks connected by a waist. Devices are available in a wide range of sizes. One limitation of this approach is that ventricular septal defect sizing may be technically difficult, and healing of the infarcted myocardium may increase the size of the ventricular septal defect, leading to device malapposition or even embolization.[86] The use of devices with diameter larger than the ventricular septal defect has been associated with relatively good outcome.[87]

Management of Special Conditions

The treatment of certain conditions that lead to CS is marked by important differences from management of CS due to LV failure. The recognition of LV outflow obstruction is critical in patients with hypotension, because diuretics and inotropic agents exacerbate obstruction. Treatment of CS with hypertrophic obstructive cardiomyopathy includes volume resuscitation and β-blockade. Pure α-agonists may also be used to increase afterload, increasing cavity size and decreasing obstruction. Outflow obstruction may also be seen in some cases of tako-tsubo cardiomyopathy when extensive akinesis/dyskinesis of apical zones occurs with hyperkinesis of remaining myocardium. Therapy is guided by echocardiography and clinical response. IABP may provide circulatory support. β-Blockade is often not indicated in this circumstance because it exacerbates LV dysfunction. α-Agonists may be helpful for vasopressor effect until myocardial recovery, which typically occurs if the patient can be supported. Inotropes improve function in the stunned myocardium and may therefore be useful when outflow obstruction is not visualized. Low doses should be initiated, with careful monitoring of the response.

Long-Term Survival and Quality of Life

Long-term survival data from the SHOCK trial were reported recently. Remarkably, the 3- and 6-year survival rates in the early revascularization group were 41.4% and 32.8% with persistence of treatment benefit[55] (Figure 5). These rates are similar to or better than 30-day survival rates reported in

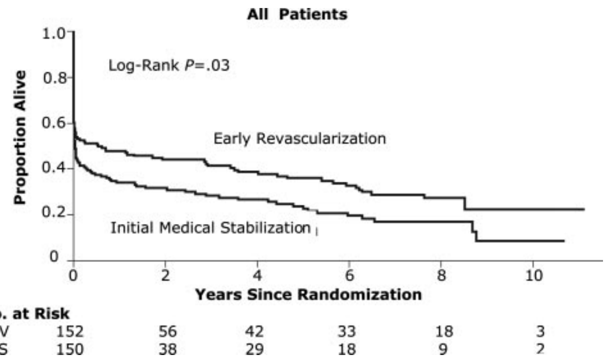

Figure 5. Long-term follow-up of the SHOCK trial cohort.[55] Early revascularization (ERV) is associated with sustained benefit. The annualized mortality rate was lower among 1-year survivors who had been randomized to revascularization than among those assigned to medical stabilization (IMS), which indicates a continued protective effect of early revascularization. Reprinted from Hochman et al,[55] with permission from the publisher. Copyright © 2006, American Medical Association. All rights reserved.

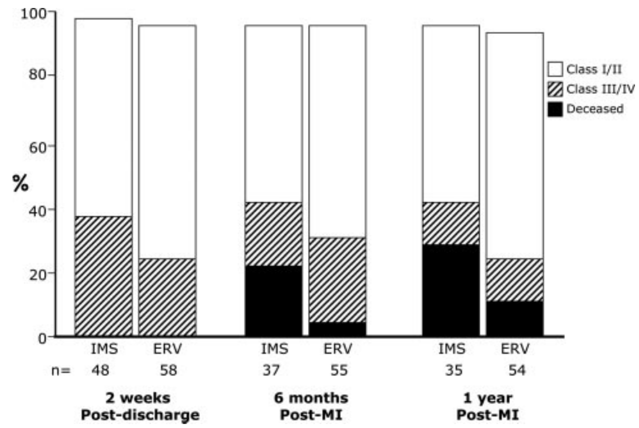

Figure 6. Functional status in the SHOCK trial.[60] The majority of patients who survived 2 weeks after discharge had good functional status (and quality of life) at that time point. Functional status continued to be good up to 1 year after the event. ERV indicates early revascularization; IMS, initial medical stabilization. Reprinted from Sleeper et al,[60] copyright © 2005, with permission from The American College of Cardiology Foundation.

studies in which patients did not routinely receive invasive therapy[88] and similar to 5-year survival rates for many forms of cancer. These findings are consistent with the 55% 11-year survival rate observed in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial among 30-day CS survivors. Furthermore, in GUSTO-I, annual mortality rates after 1 year (2% to 4%) were similar for those with and without shock.[89]

At least as important as long-term survival is quality of life in survivors. Again, this is far better than many clinicians would suspect. Already at 2 weeks after discharge, 75.9% of patients assigned to revascularization and 62.5% of patients assigned to medical stabilization in the SHOCK trial were in New York Heart Association functional class I to II (Figure 6).[60] Among patients who were in functional class III to IV at 2 weeks, 55% of survivors improved to class I to II by 1 year. Similarly, in a series of CS patients treated with early revascularization, 80% of survivors were completely asymptomatic at a median of 18 months, and all were in functional class I to II.[90] Bicycle exercise testing in a subgroup showed age-appropriate exercise capacity in all. In a series of CS patients treated with circulatory support, nearly all performed activities of daily living >1 year after the event, and some had even returned to full-time employment.[91]

Conclusions

CS is a treatable illness with a reasonable chance for full recovery. The CS literature has traditionally focused on the very high mortality associated with this diagnosis. It is important to recognize that although patients with CS are at very high risk for early death, great potential exists for salvage. Recent evidence challenges the notion that patients with CS are a "lost cause." In fact, an early invasive approach can increase short- and long-term survival and can result in excellent quality of life. Revascularization is associated with some benefit at every level of risk. Taken together, these survival and quality-of-life data should prompt consideration of aggressive early care for even highly unstable patients and additional clinical trials of new pharmacological and mechanical therapies. Clinicians and researchers must focus on the potential for full recovery if we are truly to make an impact on the burden of this disease. Prevention with very early reperfusion therapy remains the major goal.

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