

Cardiogenic Shock

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Purpose: To review the cause, epidemiology, pathophysiology, and treatment of cardiogenic shock.

Data Sources: A MEDLINE search of the English-language reports published between 1976 and 1998 and a manual search of bibliographies of relevant papers.

Study Selection: Experimental, clinical, and basic research studies related to cardiogenic shock.

Data Extraction: Data in selected articles were reviewed, and relevant clinical information was extracted.

Data Synthesis: Cardiogenic shock is a state of inadequate tissue perfusion due to cardiac dysfunction, most commonly caused by acute myocardial infarction. Mortality rates for patients with cardiogenic shock remain frustratingly high, ranging from 50% to 80%. The pathophysiology of cardiogenic shock involves a downward spiral: Ischemia causes myocardial dysfunction, which, in turn, worsens ischemia. Areas of nonfunctional but viable (stunned or hibernating) myocardium can also contribute to the development of cardiogenic shock. The key to achieving a good outcome is an organized approach that includes rapid diagnosis and prompt initiation of therapy to maintain blood pressure and cardiac output. Expedient coronary revascularization is crucial. When available, emergency cardiac catheterization and angioplasty seem to improve survival. More recent developments, such as placement of coronary stents and use of glycoprotein IIb/IIIa antagonists, are promising but have not yet been well studied in patients with cardiogenic shock. In hospitals without direct angioplasty capability, stabilization with intra-aortic balloon counterpulsation and thrombolysis followed by transfer to a tertiary care facility may be the best option.

Conclusions: Improved understanding of the pathophysiology of shock and myocardial infarction has led to improved treatment. If cardiogenic shock is managed with rapid evaluation and prompt initiation of supportive measures and definitive therapy, outcomes can be improved.

Cardiogenic shock is a state of inadequate tissue perfusion due to cardiac dysfunction, usually acute myocardial infarction (1). Shock, in turn, is the most common cause of death in hospitalized patients with acute myocardial infarction; reported mortality rates range from 50% to 80% (1). Rapid evaluation and prompt initiation of supportive measures and definitive therapy in patients with cardiogenic shock may improve early and long-term outcomes.

Methods

We reviewed the cause, epidemiology, pathophysiology, and treatment of cardiogenic shock. Using the keywords *shock*, *cardiogenic shock*, *myocardial infarction*, *thrombolytic therapy*, *angioplasty*, and *complications*, we performed a MEDLINE search of English-language reports published between 1976 and 1998 and manually searched bibliographies of relevant papers. We included experimental, clinical, and basic research studies related to cardiogenic shock.

Definition

The clinical definition of *cardiogenic shock* is decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume. Hemodynamic criteria are sustained hypotension (systolic blood pressure < 90 mm Hg for at least 30 minutes) and a reduced cardiac index (<2.2 L/min per m²) in the presence of elevated pulmonary capillary occlusion pressure (>15 mm Hg) (2).

Circulatory shock is diagnosed at the bedside by observing hypotension and clinical signs indicating poor tissue perfusion, including oliguria; clouded sensorium; and cool, mottled extremities. Cardiogenic shock is diagnosed after documentation of myocardial dysfunction and exclusion or correction of such factors as hypovolemia, hypoxia, and acidosis.

Incidence

Recent estimates of the incidence of cardiogenic shock have ranged from 5% to 10% of patients with myocardial infarction. The precise incidence is difficult to measure because patients who die before

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reaching the hospital are not given the diagnosis (3–7). In contrast, early and aggressive monitoring can increase the apparent incidence of cardiogenic shock. The Worcester Heart Attack Study (3), a community-wide analysis, found an incidence of cardiogenic shock of 7.5%; this incidence remained stable from 1975 to 1988. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO-1) trial (8), the incidence of cardiogenic shock was 7.2%, a rate similar to that found in other multicenter thrombolytic trials (4–6).

Cause and Epidemiology

The most common cause of cardiogenic shock is extensive acute myocardial infarction, although a smaller infarction in a patient with previously compromised left ventricular function may also precipitate shock. Shock that has a delayed onset may result from infarction extension, reocclusion of a previously patent infarcted artery, or decompensation of myocardial function in the noninfarction zone because of metabolic abnormalities. It is important to recognize that large areas of nonfunctional but viable myocardium can also cause or contribute to the development of cardiogenic shock in patients after myocardial infarction.

Cardiogenic shock can also be caused by mechanical complications—such as acute mitral regurgitation, rupture of the interventricular septum, or rupture of the free wall—or by large right ventricular infarctions. Other causes of cardiogenic shock include myocarditis, end-stage cardiomyopathy, myocardial contusion, septic shock with severe myocardial depression, myocardial dysfunction after

prolonged cardiopulmonary bypass, valvular heart disease, and hypertrophic obstructive cardiomyopathy (**Table 1**). In a recent report of the SHOCK (*SHould we emergently revascularize Occluded Coronaries for shock*) trial registry of 1160 patients with cardiogenic shock (1, 9), 74.5% of patients had predominant left ventricular failure, 8.3% had acute mitral regurgitation, 4.6% had ventricular septal rupture, 3.4% had isolated right ventricular shock, 1.7% had tamponade or cardiac rupture, and 8% had shock that was a result of other causes.

Patients may have cardiogenic shock at initial presentation, but shock often evolves over several hours (10, 11). In the SHOCK trial registry (1, 9), 75% of patients developed cardiogenic shock within 24 hours after presentation; the median delay was 7 hours from onset of infarction. Results from the GUSTO trial (8) are similar: Among patients with shock, 11% were in shock on arrival and 89% developed shock after admission.

Among patients with myocardial infarction, shock is more likely to develop in those who are elderly, are diabetic, and have anterior infarction (10, 12–14). Patients with cardiogenic shock are also more likely to have histories of previous infarction, peripheral vascular disease, and cerebrovascular disease (13, 14). Decreased ejection fractions and larger infarctions (as evidenced by higher cardiac enzyme levels) are also predictors of the development of cardiogenic shock (13, 14).

Cardiogenic shock is most often associated with anterior myocardial infarction. In the SHOCK trial registry (1, 9), 55% of infarctions were anterior, 46% were inferior, 21% were posterior, and 50% were in multiple locations. These findings were consistent with those in other series (15). Angiographic evidence most often demonstrates multivessel coronary disease (left main occlusion in 29% of patients, three-vessel disease in 58% of patients, two-vessel disease in 20% of patients, and one-vessel disease in 22% of patients) (9). This is important because compensatory hyperkinesis normally develops in myocardial segments that are not involved in an acute myocardial infarction; this response helps maintain cardiac output. Failure to develop such a response because of previous infarction or high-grade coronary stenoses is an important risk factor for cardiogenic shock and death (11, 16).

Pathophysiology

Systemic Effects

Cardiac dysfunction in patients with cardiogenic shock is usually initiated by myocardial infarction or ischemia. The myocardial dysfunction resulting from ischemia worsens that ischemia, creating a down-

Table 1. Causes of Cardiogenic Shock

Acute myocardial infarction
Pump failure
Large infarction
Smaller infarction with preexisting left ventricular dysfunction
Infarction extension
Reinfarction
Infarction expansion
Mechanical complications
Acute mitral regurgitation caused by papillary muscle rupture
Ventricular septal defect
Free-wall rupture
Pericardial tamponade
Right ventricular infarction
Other conditions
End-stage cardiomyopathy
Myocarditis
Myocardial contusion
Prolonged cardiopulmonary bypass
Septic shock with severe myocardial depression
Left ventricular outflow tract obstruction
Aortic stenosis
Hypertrophic obstructive cardiomyopathy
Obstruction to left ventricular filling
Mitral stenosis
Left atrial myxoma
Acute mitral regurgitation (chordal rupture)
Acute aortic insufficiency

ward spiral (**Figure 1**). When a critical mass of left ventricular myocardium is ischemic or necrotic and fails to pump, stroke volume and cardiac output decrease. Myocardial perfusion, which depends on the pressure gradient between the coronary arterial system and the left ventricle and on the duration of diastole, is compromised by hypotension and tachycardia. This, in turn, exacerbates ischemia. The increased ventricular diastolic pressures caused by pump failure further reduce coronary perfusion pressure, and the additional wall stress elevates myocardial oxygen requirements, further worsening ischemia. Decreased cardiac output also compromises systemic perfusion, which can lead to lactic acidosis and further compromise of systolic performance.

When myocardial function is depressed, several compensatory mechanisms are activated, including sympathetic stimulation to increase heart rate and contractility and renal fluid retention to increase preload. These compensatory mechanisms may become maladaptive and can actually worsen the situation when cardiogenic shock develops. Increased heart rate and contractility increase myocardial oxygen demand and exacerbate ischemia. Fluid retention and impaired diastolic filling caused by tachycardia and ischemia may result in pulmonary congestion and hypoxia. Vasoconstriction to maintain blood pressure increases myocardial afterload, further impairing cardiac performance and increasing myocardial oxygen demand. This increased demand, in the face of inadequate perfusion, worsens ischemia and begins a vicious cycle that will end in death if uninterrupted (**Figure 1**).

One important consequence of this downward spiral, in which ischemia worsens myocardial performance, is that early intervention to relieve ischemia reduces the incidence of cardiogenic shock. The fact that most cases of cardiogenic shock occur after hospital admission emphasizes the importance of initiating therapy for myocardial infarction—including aspirin, nitrates, and β -blockers, as outlined in the American College of Cardiology/American Heart Association guidelines (17)—as soon as possible after presentation. Prompt initiation of reperfusion therapy with direct angioplasty or thrombolytic agents is crucial once cardiogenic shock has ensued.

Myocardial Pathology

Cardiogenic shock is characterized by both systolic and diastolic myocardial dysfunction (11, 18). Progressive myocardial necrosis has been consistently observed in clinical and pathologic studies of patients with cardiogenic shock (11, 19). Patients who develop shock after admission often have evidence of infarct extension, which can result from reocclusion of a transiently patent infarct artery, propagation of intracoronary thrombus, or a combi-

nation of decreased coronary perfusion pressure and increased myocardial oxygen demand (13, 14). Myocytes at the border zone of an infarction are more susceptible to additional ischemic episodes; therefore, these adjacent segments are at particular risk (20). Mechanical infarct expansion, which is seen most dramatically after extensive anterior myocardial infarction, can also contribute to late development of cardiogenic shock (13, 21).

Ischemia that is remote from the infarct zone may be particularly important in producing systolic dysfunction in patients with cardiogenic shock (16, 22). Patients with cardiogenic shock usually have multivessel coronary artery disease (1, 9, 11), with limited vasodilator reserve, impaired autoregulation, and consequent pressure-dependent coronary flow in several perfusion territories (23). Hypotension and metabolic derangements may therefore impair the contractility of noninfarcted myocardium in patients with shock (24). This can limit hyperkinesis of uninvolved segments, which is a compensatory mechanism usually seen early after myocardial infarction (16, 22).

Myocardial diastolic function is also impaired in patients with cardiogenic shock. Myocardial ischemia causes decreased compliance, increasing the left ventricular filling pressure at a given end-diastolic volume (25). Compensatory increases in left ventricular volumes to maintain stroke volume further increase filling pressures. Elevation of left ventricular

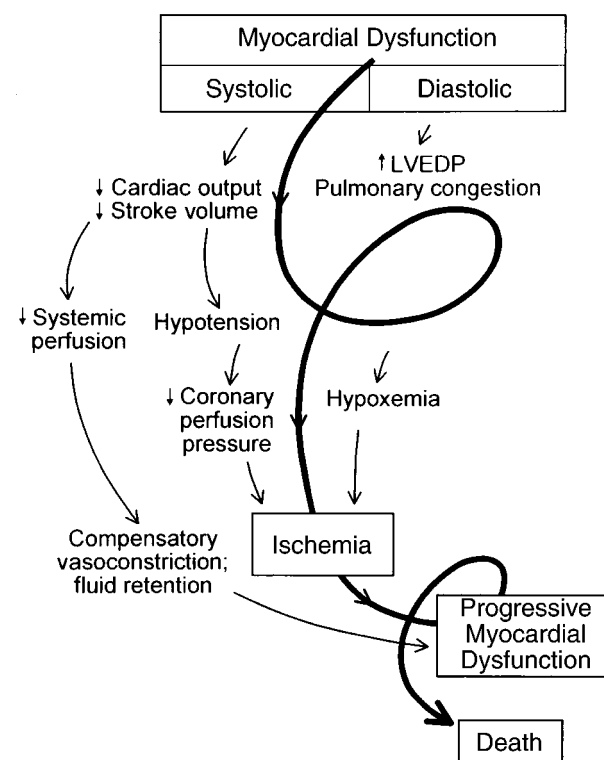


Figure 1. The downward spiral in cardiogenic shock. LVEDP = left ventricular end-diastolic pressure.

pressures can lead to pulmonary edema and hypoxemia (Figure 1).

In addition to abnormalities in myocardial performance, valvular abnormalities can contribute to increased pulmonary congestion. Papillary muscle dysfunction caused by ischemia is common and can lead to substantial increases in left atrial pressure; the degree of mitral regurgitation may be lessened by afterload reduction. Complete rupture of the papillary muscle presents dramatically, with pulmonary edema and cardiogenic shock.

Cellular Pathology

Tissue hypoperfusion and consequent cellular hypoxia lead to anaerobic glycolysis, with depletion of adenosine triphosphate and intracellular energy reserves. Anaerobic glycolysis also causes accumulation of lactic acid and resultant intracellular acidosis. Failure of energy-dependent ion transport pumps decreases transmembrane potential, causing intracellular accumulation of sodium and calcium and myocyte swelling (26). Cellular ischemia and intracellular calcium accumulation can activate intracellular proteases (26). If the ischemia is severe and prolonged, myocardial cellular injury can become irreversible, with the classic pattern of myonecrosis: mitochondrial swelling; accumulation of denatured proteins and chromatin in the cytoplasm; lysosomal breakdown; and fracture of the mitochondria, nuclear envelope, and plasma membrane (26).

Accumulating evidence indicates that apoptosis (programmed cell death) may also contribute to myocyte loss in myocardial infarction (20, 27). Although myonecrosis clearly outweighs apoptosis in the core of an infarcted area, evidence of apoptosis has been consistently found in the border zone of infarctions after ischemia and reperfusion and sporadically in areas remote from the area of ischemia (20, 27). Activation of inflammatory cascades, oxidative stress, and stretching of myocytes have been proposed as mechanisms that activate the apoptotic pathways (27). Although the magnitude of apoptotic cell loss in myo-

cardial infarction remains uncertain, inhibitors of apoptosis have been found to attenuate myocardial injury in animal models of postischemic reperfusion; these inhibitors may also have therapeutic potential for myocyte salvage after large infarctions (27).

Reversible Myocardial Dysfunction

A key to understanding the pathophysiology and treatment of cardiogenic shock is to realize that large areas of nonfunctional but viable myocardium can also cause or contribute to the development of cardiogenic shock in patients after myocardial infarction (Figure 2). This reversible dysfunction can be described in two main categories: stunning and hibernation.

Myocardial stunning represents postischemic dysfunction that persists despite restoration of normal blood flow; eventually, however, myocardial performance recovers completely (28, 29). Originally defined in animal models of ischemia and reperfusion (30), stunning has been seen in the clinical arena (28, 29, 31). The pathogenesis of stunning has not been conclusively established but seems to involve a combination of oxidative stress (32), perturbation of calcium homeostasis, and decreased myofilament responsiveness to calcium (33), all in the setting of antecedent ischemia (29). In addition to these direct effects, recent data have suggested that circulating myocardial depressant substances may contribute to contractile dysfunction in myocardial stunning (34). The intensity of stunning is determined primarily by the severity of the antecedent ischemic insult (29).

Hibernating myocardium is in a state of persistently impaired function at rest because of severely reduced coronary blood flow; inherent in the definition of hibernating myocardium is the notion that function can be normalized by improving blood flow (35, 36). Hibernation can be seen as an adaptive response to reduce contractile function of hypoperfused myocardium and restore equilibrium between flow and function, thereby minimizing the potential for ischemia or necrosis (37). Revascularization of hibernating myocardium can lead to improved myocardial function (38), and improved function seems to improve prognosis (39).

Although hibernation is conceptually and pathophysiologically different from myocardial stunning, the two conditions are difficult to distinguish in the clinical setting and may in fact coexist (28, 29). Repetitive episodes of myocardial stunning can coexist with or mimic myocardial hibernation (29, 36). Consideration of myocardial stunning and myocardial hibernation is vital in patients with cardiogenic shock because of the therapeutic implications of these conditions. Hibernating myocardium improves with revascularization, and stunned myocardium retains inotropic reserve and can respond to inotropic

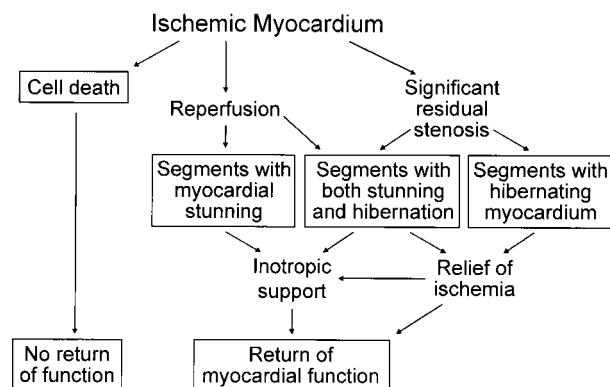


Figure 2. Potential consequences of myocardial ischemia.

stimulation (29). In addition, the fact that the severity of the antecedent ischemic insult determines the intensity of stunning (29) provides one rationale for reestablishment of patency of occluded coronary arteries in patients with cardiogenic shock. Finally, the notion that some myocardial tissue may recover function emphasizes the importance of measures to support hemodynamic and minimize myocardial necrosis in patients with shock.

Clinical Assessment and Initial Management

Evaluation

Cardiogenic shock is an emergency. The clinician must initiate therapy before shock irreversibly damages vital organs; at the same time, he or she must perform the clinical assessment required to understand the cause of shock and target therapy to that cause. A practical approach is to make a rapid initial evaluation on the basis of a limited history, physical examination, and specific diagnostic procedures (Figure 3). Cardiogenic shock is diagnosed after documentation of myocardial dysfunction and exclusion of alternative causes of hypotension, such as hypovolemia, hemorrhage, sepsis, pulmonary embolism, tamponade, aortic dissection, and preexisting valvular disease.

Patients with shock are usually ashen or cyanotic and can have cool skin and mottled extremities. Cerebral hypoperfusion may cloud the sensorium. Pulses are rapid and faint and may be irregular if arrhythmia is present. Jugular venous distention and pulmonary rales are usually present, although their absence does not exclude the diagnosis. A precordial heave resulting from left ventricular dyskinesia may be palpable. The heart sounds may be distant, and third or fourth heart sounds, or both, are usually present. A systolic murmur of mitral regurgitation or ventricular septal defect may be heard, but these complications may also occur without an audible murmur.

Electrocardiography should be performed immediately; other initial diagnostic tests usually include chest radiography and measurement of arterial blood gas, electrolytes, complete blood count, and cardiac enzymes.

Echocardiography is an excellent initial tool for confirming the diagnosis of cardiogenic shock and ruling out other causes of shock; therefore, early echocardiography should be routine. Echocardiography provides information on overall and regional systolic function and can lead to a rapid diagnosis of mechanical causes of shock, such as papillary muscle rupture and acute mitral regurgitation, acute ventricular septal defect, and free-wall rupture and tamponade (40). Unsuspected severe mitral regurgitation is not uncommon. In some cases, echocardiography

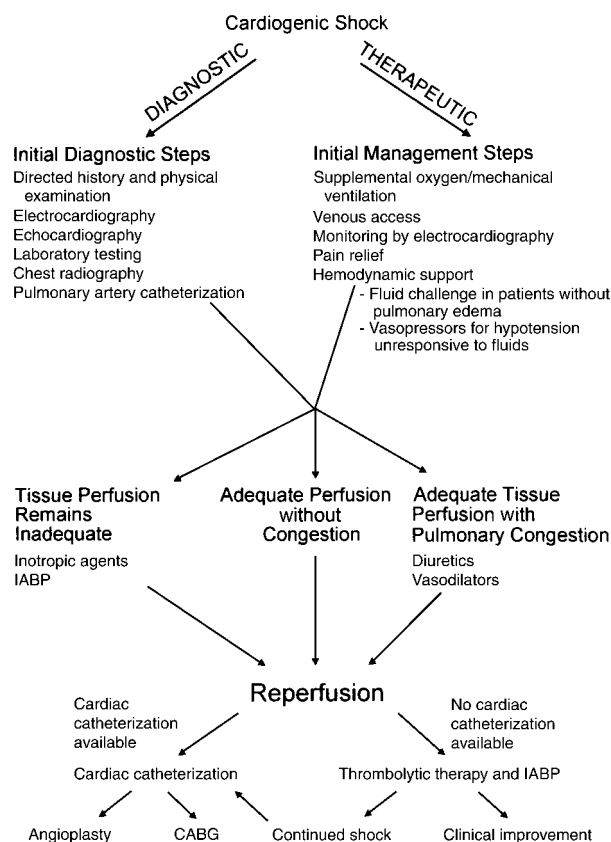


Figure 3. An approach to the diagnosis and treatment of cardiogenic shock caused by myocardial infarction. CABG = coronary artery bypass grafting; IABP = intra-aortic balloon pumping.

may show findings that are compatible with right ventricular infarction.

Invasive hemodynamic monitoring can be useful to exclude volume depletion, right ventricular infarction, and mechanical complications (11, 26). The hemodynamic profile of cardiogenic shock includes a pulmonary capillary occlusion pressure greater than 15 mm Hg and a cardiac index less than 2.2 L/min per m² (2). It should be recognized that optimal filling pressures may be greater than 15 mm Hg in individual patients because of left ventricular diastolic dysfunction. Right-heart catheterization may show a “step-up” in oxygen saturation that is diagnostic of ventricular septal rupture or a large “V” wave that suggests severe mitral regurgitation. The hemodynamic profile of right ventricular infarction includes high right-side filling pressures in the presence of normal or low occlusion pressures (41).

Initial Management

The initial approach to the patient in cardiogenic shock should include fluid resuscitation unless pulmonary edema is present. Central venous and arterial access, bladder catheterization, and pulse oximetry are routine. Oxygenation and airway protection are critical; intubation and mechanical ventilation are often required, if only to reduce the work of

breathing and facilitate sedation and stabilization before cardiac catheterization. Electrolyte abnormalities should be corrected. Hypokalemia and hypomagnesemia are predisposing factors to ventricular arrhythmia, and acidosis can decrease contractile function. Relief of pain and anxiety with morphine sulfate (or fentanyl if systolic pressure is compromised) can reduce excessive sympathetic activity and decrease oxygen demand, preload, and afterload. Arrhythmia and heart block may substantially affect cardiac output and should be corrected promptly with antiarrhythmic drugs, cardioversion, or pacing. Cardiology consultation has been shown to be associated with improved outcomes in patients with myocardial infarction and is strongly indicated in the setting of cardiogenic shock (42). In addition, medications proven to improve outcome after myocardial infarction, such as nitrates, β -blockers, and angiotensin-converting enzyme inhibitors (43), may exacerbate hypotension in a patient with cardiogenic shock; therefore, therapy with these medications should be discontinued until the patient stabilizes.

In patients with inadequate tissue perfusion and adequate intravascular volume, cardiovascular support with inotropic agents should be initiated. Dobutamine, a selective β_1 -adrenergic receptor agonist, can improve myocardial contractility and increase cardiac output without markedly changing heart rate or systemic vascular resistance; it is the initial agent of choice in patients with systolic pressures greater than 80 mm Hg (44–46). Dobutamine may exacerbate hypotension in some patients and can precipitate tachyarrhythmia. Dopamine acts directly on myocardial β_1 -adrenergic receptors and acts indirectly by releasing norepinephrine. It has both inotropic and vasopressor effects, and its use is preferable in the presence of systolic pressures less than 80 mm Hg (23, 47, 48). Tachycardia and increased peripheral resistance with dopamine administration may exacerbate myocardial ischemia. In some situations, a combination of dopamine and dobutamine can be more effective than either agent alone (49). When hypotension remains refractory, norepinephrine—a natural catecholamine with potent α - and β_1 -adrenergic effects—may be necessary to maintain organ perfusion pressure (50, 51).

Catecholamine infusions must be carefully titrated in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Invasive hemodynamic monitoring can be extremely useful in allowing optimization of therapy in these unstable patients because clinical estimates of filling pressure can be unreliable (52); in addition, changes in myocardial performance, compliance, and therapeutic interventions can change cardiac output and filling pressures precipitously. Optimization of filling pres-

ures and serial measurements of cardiac output (and other measures, such as mixed venous oxygen saturation) allow titration of the dosage of inotropic agents and vasopressors to the minimum dosage required to achieve the chosen therapeutic goals. This minimizes the increases in myocardial oxygen demand and arrhythmogenic potential (53).

The phosphodiesterase inhibitors amrinone and milrinone have positive inotropic and vasodilatory actions (54–56). They have long half-lives and may cause hypotension and thrombocytopenia (57); therefore, they are reserved for use only when other agents have proven ineffective (11). Because they do not stimulate adrenergic receptors directly, they may be effective when added to catecholamines (58) or when β -adrenergic receptors have been downregulated (59). Compared with catecholamines, phosphodiesterase inhibitors have minimal chronotropic and arrhythmogenic effects (60).

Diuretics should be used to treat pulmonary congestion and enhance oxygenation. Vasodilators should be used with extreme caution in the acute setting because of the risk for precipitating further hypotension and decreasing coronary blood flow. After blood pressure has been stabilized, however, vasodilator therapy can decrease both preload and afterload. Sodium nitroprusside is a balanced arterial and venous vasodilator that decreases filling pressures and can increase stroke volume in patients with heart failure by reducing afterload (61). Nitroglycerin is an effective venodilator that reduces the pulmonary capillary occlusion pressure and can decrease ischemia by reducing left ventricular filling pressure and redistributing coronary blood flow to the ischemic zone (62). Both agents may cause acute and rapid decreases in blood pressure, and dosages must be titrated carefully; invasive hemodynamic monitoring can be useful in optimizing filling pressures when these agents are used.

Thrombolytic Therapy

Although it has been convincingly demonstrated that thrombolytic therapy reduces mortality rates in patients with acute myocardial infarction (4, 63–65), the benefits of this therapy in patients with cardiogenic shock are less certain. It is clear that thrombolytic therapy can reduce the likelihood of subsequent development of shock after initial presentation (7, 8, 63, 64). This is important because most patients develop cardiogenic shock more than 6 hours after hospital presentation (1, 8, 9).

Nonetheless, no trials have demonstrated that thrombolytic therapy reduces mortality rates in patients with established cardiogenic shock. The numbers of patients are small because most thrombolytic trials have excluded patients with cardiogenic

shock at presentation (66). In the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial (4, 66), 30-day mortality rates were 69.9% in 146 patients with cardiogenic shock who received streptokinase and 70.1% in 134 patients receiving placebo. The International Study Group reported a mortality rate of 65% in 93 patients with shock who received streptokinase and a mortality rate of 78% in 80 patients treated with recombinant tissue plasminogen activator (5). In the GUSTO trial (7), 315 patients had shock on arrival; the mortality rate was 56% in patients treated with streptokinase and 59% in patients treated with recombinant tissue plasminogen activator (8, 67).

The failure of thrombolytic therapy to improve survival in patients with cardiogenic shock may seem paradoxical in light of evidence that the absolute reduction in mortality rates resulting from use of thrombolytic agents is greatest in persons who are at highest risk at presentation. The meta-analysis performed by the Fibrinolytic Therapy Trialists Collaborative Group (68) demonstrated a reduction in mortality rate from 36.1% to 29.7% when thrombolytic therapy was used in patients with initial systolic blood pressures less than 100 mm Hg. In patients with initial heart rates greater than 100 beats/min, the mortality rate decreased from 23.8% to 18.9%. However, most patients in these subgroups did not meet the criteria for cardiogenic shock.

Consideration of the efficacy of thrombolytic therapy once cardiogenic shock has been established makes the disappointing results in this subgroup of patients easier to understand. The degree of reperfusion correlates with outcome (69, 70), and reperfusion is less likely for patients in cardiogenic shock (15, 70, 71). When reperfusion is successful, mortality rates have been shown to be substantially reduced (70). The lower rates of reperfusion in patients with shock may explain some of the disappointing results in this subgroup in the thrombolytic trials.

The reasons for decreased thrombolytic efficacy in patients with cardiogenic shock are not fully understood but probably include hemodynamic, mechanical, and metabolic factors. Decreased arterial pressure limits the penetration of thrombolytic agents into a thrombus (72). Passive collapse of the infarct artery in the setting of hypotension can also contribute to decreased thrombolytic efficacy, as can acidosis, which inhibits the conversion of plasminogen to plasmin (72). Two small studies (73, 74) support the notion that vasopressor therapy to increase aortic pressure improves thrombolytic efficacy.

Intra-Aortic Balloon Pumping

Intra-aortic balloon pumping (IABP) reduces systolic afterload and augments diastolic perfusion pres-

sure, increasing cardiac output and improving coronary blood flow (75). These beneficial effects, in contrast to those of inotropic or vasopressor agents, occur without an increase in oxygen demand. Intra-aortic balloon pumping is efficacious for initial stabilization of patients with cardiogenic shock (76). Small randomized trials in the prethrombolytic era, however, did not show that IABP alone increases survival (77, 78). Intra-aortic balloon pumping alone does not substantially improve blood flow distal to a critical coronary stenosis (79).

Intra-aortic balloon pumping is probably not best used as an independent method to treat cardiogenic shock. It may, however, be an essential support mechanism to allow definitive therapeutic measures to be undertaken. In the GUSTO trial, patients who presented with shock and had early IABP placement showed a trend toward lower mortality rates, even after exclusion of patients who had revascularization (7, 80). A similar trend was seen in the SHOCK trial registry (1), although it did not persist after adjustment for age and catheterization. Several observational studies have also suggested that IABP can improve outcome in patients with shock, although revascularization procedures are a confounding factor in these studies (81–84). Intra-aortic balloon pumping has been shown to decrease reocclusion and cardiac events after emergency angioplasty for acute myocardial infarction (85, 86).

In hospitals without direct angioplasty capability, stabilization with IABP and thrombolysis followed by transfer to a tertiary care facility may be the best management option. Intra-aortic balloon pumping may be a useful adjunct to thrombolysis in this setting by increasing drug delivery to the thrombus, improving coronary flow to other regions, preventing hypotensive events, or supporting ventricular function until areas of stunned myocardium can recover (87). Two retrospective studies (83, 84) have shown that patients with cardiogenic shock who were treated in a community hospital with IABP placement followed by thrombolysis had improved in-hospital survival and improved outcomes after subsequent transfer for revascularization, although selection bias is clearly a confounding factor. The role of IABP as an adjunct to thrombolytic agents in the community hospital is being addressed in the ongoing randomized, multicenter Thrombolysis And Counterpulsation To Improve Cardiogenic Shock Survival (TACTICS) trial.

Revascularization

Pathophysiologic considerations and extensive retrospective data favor aggressive mechanical revascularization for patients with cardiogenic shock caused

Table 2. Studies of Coronary Angioplasty for Cardiogenic Shock*

Study (Reference)	Year	Patients <i>n</i>	Overall Survival	Reperfusion Rate	Survival after Successful PTCA	Survival after Unsuccessful PTCA
			← % →			
O'Neill et al. (93)	1985	27	70	89	75	33
Shani et al. (94)	1986	9	67	67	83	0
Heuser et al. (95)	1986	10	70	60	83	25
Disler et al. (96)	1987	7	43	71	60	0
Landin et al. (97)	1988	34	59	79	70	14
Laramée et al. (98)	1988	39	59	86	NR	NR
Lee et al. (99)	1988	24	50	54	77	18
Verna et al. (100)	1989	7	86	100	86	–
Kaplan et al. (101)	1990	88	58	61	65	29
Meyer et al. (102)	1990	25	53	88	59	0
Brodie et al. (103)	1991	22	50	68	NR	NR
Lee et al. (104)	1991	69	55	71	69	20
Bengtson et al. (15)	1992	44	57	84	62	29
Gacioch et al. (105)	1992	48	55	73	61	7
Hibbard et al. (106)	1992	45	56	62	71	29
Moosvi et al. (107)	1992	38	NR	78	56	8
Yamamoto et al. (108)	1992	26	38	76	56	10
Seydoux et al. (109)	1992	21	57	85	67	0
Laney et al. (110)	1993	52	81	94	86	0
Morrison et al. (111)	1995	17	47	71	67	0
Elthchaninoff et al. (112)	1995	33	64	75	76	25
Berger et al. (71)	1997	175	75	75	65	19†
Antoniucci et al. (114)	1998	66	74	94	79	0

* NR = not reported; PTCA = percutaneous transluminal coronary angioplasty.

† Includes patients who had PTCA only; excludes patients who had PTCA followed by coronary artery bypass grafting.

by myocardial infarction. Recently, a landmark study (the SHOCK trial [88]) presented data from a randomized, controlled trial.

Direct Coronary Angioplasty

Reestablishment of brisk (TIMI [Thrombolysis in Myocardial Infarction] grade 3) flow in the infarct-related artery is an important determinant of left ventricular function and survival after myocardial infarction (69). Direct percutaneous transluminal coronary angioplasty (PTCA) can achieve TIMI grade 3 flow in 80% to 90% of patients with myocardial infarction (89–91), compared with rates of 50% to 60% 90 minutes after thrombolytic therapy (69, 92). In the Primary Angioplasty in Myocardial Infarction (PAMI) trial (89), which compared direct angioplasty with thrombolytic therapy, a mortality benefit for PTCA (in-hospital mortality rate, 2.0% compared with 10.4%; $P = 0.01$) was seen in high-risk patients (age >70 years, large anterior myocardial infarction, heart rate >100 beats/min). Therefore, patients with cardiogenic shock are candidates for direct angioplasty. In addition to improving wall motion in the infarct territory, increased perfusion of the infarct zone has been associated with augmented contraction of remote myocardium, possibly caused by recruitment of collateral blood flow (16).

Several retrospective trials (15, 71, 93–114) have examined the effect of angioplasty on mortality rates in patients with cardiogenic shock (Table 2). Researchers have consistently found that patients with successful reperfusion have much better outcomes

than those without successful reperfusion. In a subgroup analysis of the 2972 patients with cardiogenic shock, the GUSTO-1 trial (8) showed that the 30-day mortality rate was significantly lower in patients who had angioplasty (43% compared with 61% for patients with shock on arrival; 32% compared with 61% for patients who developed shock). In this trial, patients treated with an aggressive strategy (coronary angiography performed within 24 hours of shock onset with revascularization by PTCA or bypass surgery) had a significantly lower mortality rate (38% compared with 62%) (71). This benefit was present even after adjustment for baseline characteristics (71) and persisted for up to 1 year (115).

The role of newer developments in PTCA for acute myocardial infarction in patients with cardiogenic shock remains to be defined. Recent reports have suggested that placement of coronary stents may improve outcome, after either failed or suboptimal PTCA (116) or as a primary approach (117, 118). The PAMI stent pilot trial (119) and the Intracoronary Stenting and Antithrombotic Regimens (ISAR) trial (120) have recently shown that primary stenting is feasible in patients with acute myocardial infarction; TIMI grade 3 flow is restored in more than 90% of patients, and short-term outcome is good. Data in patients with cardiogenic shock are more sparse. A recent study of direct PTCA in patients with shock (114) reported a success rate of 94%, with placement of stents in 47% of patients; the in-hospital mortality rate was 26%. Another study

of stenting for failed angioplasty in patients with cardiogenic shock reported a mortality rate of 27% (121).

The role of adjunctive antiplatelet therapy is also evolving. Platelet glycoprotein IIb/IIIa antagonists have been shown to improve short-term clinical outcomes after angioplasty, especially in patients at high risk for complications (122, 123). Published experience with IIb/IIIa receptor inhibition in patients with cardiogenic shock is thus far limited to case reports (124), but extrapolation from other settings suggests that they may play an important adjunctive role in patients with shock who undergo angioplasty (125).

Coronary Artery Bypass Surgery

Many trials have reported favorable outcomes for patients with cardiogenic shock who have coronary artery bypass surgery (81, 121, 126, 127). Left main and three-vessel coronary disease are common in patients with cardiogenic shock (1, 9, 69), and the potential contribution of ischemia in the noninfarct zone to myocardial dysfunction in patients with shock would support complete revascularization. Nonetheless, the logistic and time considerations involved in mobilizing an operating team, the high surgical morbidity and mortality rates, and the generally favorable results of percutaneous interventions discourage routine bypass surgery for these patients. In DeWood and colleagues' series (81), IABP support was used successfully as a bridge to coronary artery bypass surgery. The roles of other supportive measures, such as emergency cardiopulmonary bypass surgery (128), remain to be defined.

These studies of revascularization in patients with cardiogenic shock were retrospective and uncontrolled. Selection bias is clearly present because patients selected for revascularization tend to be younger, less critically ill, and more likely to receive IABP support; they also tend to have less comorbidity (1, 8, 71). In addition, patients whose conditions deteriorate before planned revascularization is performed are counted in the nonrevascularized group. In the SHOCK trial registry (1), not only was the mortality rate in patients selected for cardiac catheterization lower than in those not selected (51% compared with 85%), but the mortality rate was also lower in catheterized patients who did not undergo revascularization (58%). A small randomized study, the Swiss Multicenter Evaluation of Early Angioplasty for SHock (SMASH) trial (129), showed no significant difference in mortality rate between patients who were randomly assigned to undergo angioplasty and those who were randomly assigned to receive medical treatment (69% compared with 78%), although the trial was stopped early because of difficulties in patient recruitment (129).

The recently presented multicenter SHOCK trial (88) is a landmark study because it contains the

only data from a randomized, controlled study addressing revascularization in patients with cardiogenic shock. The SHOCK trial randomly assigned patients with cardiogenic shock to receive optimal medical management—including IABP and thrombolytic therapy—or cardiac catheterization with revascularization using PTCA or coronary artery bypass grafting. The results of the trial were recently presented at the annual meeting of the American College of Cardiology (88).

The trial was powered to detect a 20% absolute decrease in 30-day all-cause mortality rates; 302 patients were enrolled. The mortality rate at 30 days was 46.7% in patients treated with early intervention and 56% in patients treated with initial medical stabilization; however, this difference did not reach statistical significance (absolute risk reduction, $-9.3%$ [95% CI, -20.5 to $1.9%$]; $P = 0.11$). At 6 months, the absolute risk reduction was 12% (54% compared with 66%). Preliminary analysis suggested that this difference was statistically significant. Subgroup analysis showed a substantial improvement in mortality rates in patients younger than 75 years of age at 30 days (41% compared with 57%) and 6 months (48% compared with 69%).

It is important to note that the controls (patients who received medical management) had a lower mortality rate than that reported in previous studies; this may reflect the aggressive use of thrombolytic therapy (64%) and IABP (86%) in these controls (88). These data provide indirect evidence that thrombolysis plus IABP may produce the best outcomes when cardiac catheterization is not immediately available.

In our judgment, the SHOCK trial was underpowered to detect the primary end point (30-day mortality). This may have been due to a lower mortality rate among controls than might have been expected (88). The improved survival with revascularization at 6 months and in patients younger than 75 years of age strongly supports the superiority of a strategy of early revascularization in most patients with cardiogenic shock (Figure 3).

Specific Conditions

Right Ventricular Infarction

Right ventricular infarction occurs in up to 30% of patients with inferior infarction and is clinically significant in 10% (130). Patients present with hypotension, elevated neck veins, and clear lung fields. Diagnosis is made by identifying ST-segment elevation in right precordial leads or characteristic hemodynamic findings on right-heart catheterization (elevated right atrial and right ventricular end-diastolic pressures with normal to low pulmonary artery occlu-

sion pressure and low cardiac output). Echocardiography can show depressed right ventricular contractility (41). Patients with cardiogenic shock on the basis of right ventricular infarction have a better prognosis than those with left-sided pump failure (130). This may be due in part to the fact that right ventricular function tends to return to normal over time with supportive therapy (131), although such therapy may need to be prolonged.

Supportive therapy for patients with right ventricular infarction begins with maintenance of right ventricular preload with fluid administration. In some cases, however, fluid resuscitation may increase pulmonary capillary occlusion pressure but may not increase cardiac output, and overdilation of the right ventricle can compromise left ventricular filling and cardiac output (131). Inotropic therapy with dobutamine may be more effective in increasing cardiac output in some patients, and monitoring with serial echocardiography may also be useful to detect right ventricular overdistention (131). Maintenance of atrioventricular synchrony is also important in these patients to optimize right ventricular filling (41). For patients with continued hemodynamic instability, intra-aortic balloon pumping may be useful, particularly because elevated right ventricular pressures and volumes increase wall stress and oxygen consumption and decrease right coronary perfusion pressure, exacerbating right ventricular ischemia.

Reperfusion of the occluded coronary artery is also crucial. A recent study using direct angioplasty (132) showed that restoration of normal flow resulted in dramatic recovery of right ventricular function and a mortality rate of only 2%, whereas unsuccessful reperfusion was associated with persistent hemodynamic compromise and a mortality rate of 58%.

Acute Mitral Regurgitation

Ischemic mitral regurgitation is usually associated with inferior myocardial infarction and ischemia or infarction of the posterior papillary muscle, which has a single blood supply (usually from the posterior descending branch of a dominant right coronary artery) (133). Papillary muscle rupture usually occurs 2 to 7 days after acute myocardial infarction; it presents dramatically with pulmonary edema, hypotension, and cardiogenic shock. When a papillary muscle ruptures, the murmur of acute mitral regurgitation may be limited to early systole because of rapid equalization of pressures in the left atrium and left ventricle. More important, the murmur may be soft or inaudible, especially when cardiac output is low (134).

Echocardiography is extremely useful in the differential diagnosis, which includes free-wall rupture, ventricular septal rupture, and infarction extension pump failure. Hemodynamic monitoring with pulmonary artery catheterization may also be helpful.

Management includes afterload reduction with nitroprusside and intra-aortic balloon pumping as temporizing measures. Inotropic or vasopressor therapy may also be needed to support cardiac output and blood pressure. Definitive therapy, however, is surgical valve repair or replacement, which should be undertaken as soon as possible because clinical deterioration can be sudden (134, 135).

Ventricular Septal Rupture

Patients who have ventricular septal rupture have severe heart failure or cardiogenic shock, with a pansystolic murmur and a parasternal thrill. The classic finding is a left-to-right intracardiac shunt (a “step-up” in oxygen saturation from right atrium to right ventricle). On pulmonary artery occlusion pressure tracing, ventricular septal rupture can be difficult to distinguish from mitral regurgitation because both can produce dramatic “V” waves. The diagnosis is most easily made with echocardiography.

Rapid stabilization—using intra-aortic balloon pumping and pharmacologic measures—followed by surgical repair is the only viable option for long-term survival. The timing of surgery is controversial, but most experts now suggest that operative repair should be done early, within 48 hours of the rupture (135–137).

Free-Wall Rupture

Ventricular free-wall rupture usually occurs during the first week after myocardial infarction; the classic patient is elderly, female, and hypertensive. The early use of thrombolytic therapy reduces the incidence of cardiac rupture, but late use may increase the risk. Free-wall rupture presents as a catastrophic event with a pulseless rhythm. Salvage is possible with prompt recognition, pericardiocentesis to relieve acute tamponade, and thoracotomy with repair (138).

Reversible Myocardial Dysfunction

In addition to hibernating and stunned myocardium, potentially reversible causes of myocardial dysfunction include sepsis-associated myocardial depression, myocardial dysfunction after cardiopulmonary bypass, and inflammatory myocarditis (139). In sepsis and, to some extent, in myocarditis, myocardial dysfunction seems to result from the effects of inflammatory cytokines, such as tumor necrosis factor and interleukin-1 (140–142). Myocardial dysfunction can be self-limited or fulminant, with severe congestive heart failure and cardiogenic shock (139). In the latter situation, cardiovascular support with a combination of inotropic agents (such as dopamine, dobutamine, or milrinone) and IABP may be required for hours or days to allow sufficient time for recovery. If these measures fail, mechanical circula-

tory support with left ventricular assist devices can be considered (143). These devices can be used as a bridge to cardiac transplantation in eligible patients or as a bridge to myocardial recovery; functional improvement with such support can be dramatic (143).

Conclusions

Mortality rates in patients with cardiogenic shock remain frustratingly high (50% to 80%). The pathophysiology of shock involves a downward spiral: Ischemia causes myocardial dysfunction, which in turn worsens ischemia. Areas of nonfunctional but viable myocardium can also cause or contribute to the development of cardiogenic shock. The key to a good outcome is an organized approach with rapid diagnosis and prompt initiation of therapy to maintain blood pressure and cardiac output. Expedient coronary revascularization is crucial. When available, emergency cardiac catheterization and revascularization with angioplasty or coronary surgery seem to improve survival and represent standard therapy at this time. In hospitals without direct angioplasty capability, stabilization with IABP and thrombolysis followed by transfer to a tertiary care facility may be the best option. The SHOCK multicenter randomized trial (88) provides important data that help clarify the appropriate role and timing of revascularization in patients with cardiogenic shock.

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