Chapter 1

Diagnosis, epidemiology, and risk factors

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Definitions and diagnosis

Definitions

Cardiogenic shock is a state of decreased cardiac output and systemic perfusion in the presence of adequate intravascular volume, resulting in tissue hypoxia [1]. As early as 1912, Herrick described the clinical features of cardiogenic shock in patients with severe coronary artery disease: a weak, rapid pulse; feeble cardiac tones; pulmonary rales; dyspnea; and cyanosis [2]. The term cardiogenic shock is believed to have been originated in 1942 by Stead [3]. He described a series of two patients who had what he called “shock of cardiac origin.” Later, the expression was rephrased as “cardiogenic shock.”

The severity of shock can range from mild to severe, and practical definitions use somewhat arbitrary criteria. An essential feature of cardiogenic shock is systemic hypoperfusion, typically with hypotension; however, there is great variability in the severity of hypotension that defines shock, with the most common cut-off points for systolic blood pressure being <90 mm Hg or <80 mm Hg [4,5]. Patients with shock typically have signs of systemic hypoperfusion, including altered mental state, cool skin, and/or oliguria. Rales, indicating pulmonary edema, may or may not be present. Neither auscultation nor chest radiograph detects pulmonary edema in 30% of patients with cardiogenic shock [6]. The method used to measure blood pressure may also be important. Brachial cuff pressure measurements are often inaccurate in states of shock. Arterial blood pressure is more accurately monitored using intra-arterial cannulas; thus, this method is commonly advocated to ensure precise measurement.
2 Cardiogenic Shock

There is a subset of severe left ventricular (LV) failure patients who have “nonhypotensive cardiogenic shock” [7]. By definition, these patients have the clinical signs of peripheral hypoperfusion described above (with preserved systolic blood pressure measurements $>90$ mm Hg without vasopressor support). This occurs most often among patients with large anterior wall myocardial infarction (MI) and is associated with substantial in-hospital mortality, albeit lower than that of patients with classic cardiogenic shock. Thus, a diagnosis of cardiogenic shock may be made in patients with systemic hypoperfusion and blood pressure measurements of $>90$ mm Hg in several circumstances: (1) if medications and/or support devices are required to maintain normal hemodynamic parameters; (2) in the presence of systemic hypoperfusion with low cardiac output, with blood pressure maintained by marked vasoconstriction; and (3) if mean systemic pressure is $\geq 30$ mm Hg lower than baseline in cases of preexisting hypertension.

In 1967, Killip and Kimball [8] proposed a crude clinical classification of hemodynamic status based on 250 patients with acute myocardial infarction (MI). This classification has withstood the test of time and is still in widespread use (Table 1.1). As the shock state persists, hypoperfusion of both the myocardium and peripheral tissues will induce anaerobic metabolism in these tissues and may result in lactic acidosis. Hyperlactatemia is considered a hallmark of hypoperfusion [9,10] and may supplement the clinical examination and blood pressure measurement when findings are inconclusive regarding shock status. The accumulation of lactic acid may cause mitochondrial swelling and degeneration, inducing glycogen depletion, which in turn may impair myocardial function and inhibit glycolysis, leading to irreversible ischemic damage. Serum lactate level is an important prognostic factor in cardiogenic shock [11]; in one multivariate analysis, a lactate level $>6.5$ mmol/L in cardiogenic shock patients was a very strong independent predictor of in-hospital mortality [odds ratio (OR) 295, $P < 0.01$] even after adjustment for age, sex, hypertension, and diabetes history [10].

| Table 1.1 Clinical classification of hemodynamic status of acute MI patients. |
|-----------------------------|--------------------------------------------------------------------------|
| Class | Definition                                      |
| I    | No clinical signs of heart failure              |
| II   | Basilar rales and/or $S_3$ gallop, and/or elevated jugular venous pressure |
| III  | Frank pulmonary edema                          |
| IV   | Cardiogenic shock                              |
Hemodynamics for diagnosis of cardiogenic shock

Along with metabolic parameters, hemodynamic data are very useful for diagnosis and prognostic assessment in cardiogenic shock patients. One of the earliest attempts to use hemodynamic evaluation to determine prognosis and to guide therapy found that all cardiogenic shock patients with LV filling pressure of $>15$ mm Hg and cardiac index $<2.3$ L/min died despite medical therapy [9]. The measurements with greatest prognostic value in addition to demographic and clinical variables appear to be cardiac output [12] and those measurements that incorporate cardiac output with systolic blood pressure, including stroke work [13] or cardiac power [14].

There is some variability in the definition of cardiogenic shock as used in clinical trials [7,12,14–17]. Most studies define shock as a state with systolic blood pressure of $<90$ mm Hg for at least 1 hour that is (1) not responsive to fluid administration alone; (2) secondary to cardiac dysfunction; and (3) associated with signs of hypoperfusion or a cardiac index of $<2.2$ L/min/m$^2$ and pulmonary artery wedge pressure (PAWP) $>18$ mm Hg. Hypotension that improves (increase in systolic blood pressure to $>90$ mm Hg) within 1 hour following administration of inotropic/vasopressor agents is often included in studies of cardiogenic shock, as is death within 1 hour of onset of hypotension when other criteria for cardiogenic shock are met. Some studies have specified invasive hemodynamic diagnostic criteria for cardiogenic shock, such as severely decreased cardiac output measurements derived from right heart catheterization. In most of these studies, cardiac index measurements of $\leq 2.2$ L/min/m$^2$ were regarded as supporting the diagnosis of cardiogenic shock in the presence of other signs. Other investigators [15], however, regarded measurements of $\leq 1.8$ L/min/m$^2$ as indicative of cardiogenic shock. An important consideration is whether the values were recorded on inotropic/vasopressor or circulatory device support; a 2.2–2.5 L/min/m$^2$ cut point is reasonable for those on support and 1.8–2.2 L/min/m$^2$ for those whose measurements are made off support [16].

The widespread availability of noninvasive means of assessing cardiac function, such as echocardiography, has reduced the use of right heart catheterization. Echocardiography with Doppler imaging has become a readily available modality for bedside hemodynamic assessment and for the evaluation of cardiac function, valvular status, and mechanical complications of acute coronary syndrome (ACS) [18]. Its use has steadily increased over the years, and currently it is performed frequently among ACS patients in many institutions.

In an analysis from Euro Heart Survey ACS, 68% of patients with cardiogenic shock underwent an echocardiographic evaluation [18]. Right heart catheterization was performed in just 111 of 549 patients with cardiogenic shock (20.2%) [18]. Noninvasively derived hemodynamic parameters, such as left atrial pressure approximated by transmitral flow patterns and cardiac output computed by echocardiography (derived stroke volume multiplied by heart rate), can...
advance the timely management of cardiogenic shock patients, obviating the need for right heart catheterization. The restrictive pattern of transmitral flow, defined as E wave deceleration time $<140$ ms, has positive predictive value of 80% for PAWP $\geq 20$ mm Hg [19]. However, deceleration time $>140$ ms did not exclude an elevated PAWP. Transesophageal examination may be used in difficult cases to obtain hemodynamic information and to exclude mechanical causes of LV failure.

There are possible pitfalls in interpreting hemodynamic data. For example, cardiac output measurements may be above normal in patients for whom the underlying cause of cardiogenic shock is ventricular septal defect, and PAWP may be unexpectedly high in patients with right ventricular (RV) infarction because of leftward shift of the intraventricular septum (reversed Bernheim effect) or concomitant LV systolic dysfunction. Additionally, by the time right heart catheterization is performed, the patient with shock typically is already receiving supportive pharmacological treatment that can alter hemodynamic measurements. For example, treatment with a positive inotropic agent may improve a patient’s subsequent cardiac output measurements, and treatment with diuretics may decrease subsequent PAWP measurements.

The caveats listed above illustrate the difficulty of diagnosing cardiogenic shock by means of numerical and laboratory values in isolation. Accordingly, shock is primarily diagnosed based on clinical findings supported by measured hemodynamic values (Table 1.2). Clinical evidence of a reduction in cardiac output with systemic hypoperfusion despite adequate filling pressures must be present for a diagnosis of cardiogenic shock. When right heart catheterization is performed, hemodynamics values should confirm low output and high filling pressures. If right heart catheterization is not planned, the combination of clinical examination, chest radiography, and echocardiography must clearly demonstrate systemic hypoperfusion, low cardiac output, and elevation of left atrial/pulmonary artery pressure and/or right atrial pressure. If the diagnosis is in any way unclear, right heart catheterization should be performed.

**Epidemiology**

**Etiologies**

Cardiogenic shock can occur as a result of a wide variety of cardiac disorders, including ACS, valvular disease, myocardial and/or pericardial disease, congenital lesions (in both children and adults), or mechanical injuries to the heart (Table 1.3; Chapter 8). Due to the great prevalence of coronary artery disease, cardiogenic shock as a complication of ACS is the predominant etiology.

Determining the etiology of cardiogenic shock in the individual patient may be challenging. The history and clinical examination may provide information on the etiology of cardiogenic shock in an individual patient, but there is quite a bit of overlap between syndromes; for example, chest pain is a cardinal feature of acute MI, myocarditis, and pericardial tamponade, and there may be overlap
Table 1.2  Characteristic hemodynamic patterns usually observed in MI with and without hemodynamic instability and non-cardiogenic shock states

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>RVS</th>
<th>RVD</th>
<th>PAS</th>
<th>PAD</th>
<th>PAW</th>
<th>CI</th>
<th>SVR</th>
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<tr>
<td>Normal values</td>
<td>&lt;6</td>
<td>&lt;25</td>
<td>0–12</td>
<td>&lt;25</td>
<td>0–12</td>
<td>&lt;6–12</td>
<td>≥2.5</td>
<td>(800–1600)</td>
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<td>MI without pulmonary edema&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Cardiogenic shock</td>
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<td>LV failure</td>
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<td>RV failure&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Cardiac tamponade</td>
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<td>Acute mitral regurgitation</td>
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<td>Ventricular septal rupture</td>
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<td>↑ PBF</td>
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<tr>
<td>Hypovolemic shock</td>
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<td>Septic shock</td>
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There is significant patient-to-patient variation. Pressures in RA, right atrium; RVS/D, right ventricular systolic/diastolic; PAS/D, pulmonary artery systolic/diastolic; PAW, pulmonary artery wedge are in mm Hg. CI, cardiac index (L/min/m<sup>2</sup>); SVR, systemic vascular resistance (dyne/sec/cm<sup>5</sup>); MI, myocardial infarction; P/SBF, pulmonary/systemic blood flow.

<sup>1</sup>“Isolated” or predominant RV failure. PAW, RVS and PA pressures may rise in RV failure after volume loading due to RV dilation, right-to-left shift of the interventricular septum, resulting in impaired LV filling. When biventricular failure is present, the patterns are similar to those shown for LV failure.

<sup>2</sup>Forrester and colleagues classified nonreperfused MI patients into four hemodynamic subsets (<i>N Engl J Med</i> 1976;295:1356–62). PAWP and CI in clinically stable subset 1 patients are shown. Values in parentheses represent range.

# Cardiogenic Shock

<table>
<thead>
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<th>Table 1.3</th>
<th>Differential diagnosis of suspected cardiogenic shock in the setting of acute MI</th>
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| **A. Myocardial Dysfunction** | Predominant left ventricle  
Predominant right ventricle  
Both ventricles |
| **B. Mechanical Complications** | Ventricular septal rupture  
Papillary muscle rupture  
Free wall rupture and cardiac tamponade |
| **C. Procedural Complications** | Unsuspected coronary perforation  
Unsuspected coronary dissection  
Blood loss: access site, retroperitoneal |
| **D. Significant Valvular Disease** | Aortic stenosis  
Mitral regurgitation  
Mitral stenosis  
Aortic regurgitation |
| **E. Hypovolemia** | Dehydration  
Excessive diuresis  
Hemorrhage |
| **F. Mimicking Conditions** | Acute aortic syndrome: aortic dissection or perforation  
Acute pulmonary embolism  
Pneumothorax  
Adverse drug reaction: anaphylaxis  
Septic shock with myocardial depression |
| **G. Dynamic outflow obstruction** | Hypertrophic cardiomyopathy  
Takotsubo cardiomyopathy |
| **H. Iatrogenic** | Medications affecting hemodynamics (excess negative inotropy, vasodilation, diuresis)  
Procedural complication  
Hemorrhage |
in the description of pain among these syndromes. The timing of symptoms may provide a clue to the occurrence of mechanical complications if, for example, chest pain recurs days after an initial episode and that recurrence is associated with shock. The absence of this pattern is not of diagnostic value, however, and mechanical complications may occur early in the course of MI.

The physical examination may provide diagnostic clues as well, particularly in the form of a new murmur as a herald of ventricular septal or papillary muscle rupture or acute mitral or aortic valve disease. Unfortunately, worsening of valvular heart disease may be accompanied by softening of an existing murmur, and, of course, murmurs are not a reliable indicator of valvular disease or rupture. However, the presence of a murmur in a patient with cardiogenic shock should prompt rapid echocardiographic evaluation.

**Electrocardiography**

The electrocardiogram (ECG) may be helpful in the diagnosis of a particular etiology of shock. When ST-segment elevation acute MI (STEMI) causes LV failure, the degree and severity of the ECG abnormality should be concordant with the severity of the clinical condition. Modest ECG abnormalities should prompt consideration of other etiologies (Table 1.3). When marked ST elevations are present in several precordial leads, anterior MI is the most likely diagnosis and LV pump failure is the most likely cause of shock. A first inferior STEMI is less likely to cause shock; if inferior STEMI were the cause of shock, marked ST elevation with reciprocal ST depression, denoting extensive injury, would be expected on the ECG. RV infarction may complicate inferior MI as well; RV leads should be placed in cases of inferior MI with hypotension to search for right-sided ST elevation. Another possible finding of RV infarction is precordial ST elevation, which is largest in degree in V1-V2 and becomes smaller as one moves across the precordium. The absence of reciprocal changes or signs of RV infarction in the case of inferior MI with shock should prompt a search for complicating factors, such as myocardial or papillary muscle rupture. It should also be noted that ST elevation is not definitive evidence of STEMI; regional ST elevation may also be seen in acute myocarditis. Diffuse and marked ST depressions, most notable in V4-V6, indicate diffuse ischemia due to left main or severe triple vessel disease. Left bundle branch block may be seen as a reflection of a large STEMI, non-STEMI (NSTEMI) with prior infarcts, or underlying conditions associated with LV hypertrophy (e.g., aortic stenosis). Finally, a normal ECG in the presence of profound shock, particularly in the setting of arrhythmias, should lead to consideration of myocarditis.

**ACS as a cause of shock**

Cardiogenic shock complicating ACS is not confined to the typical setting of large ST-segment elevation anterior wall infarction. Although shock occurs more frequently in the setting of ST-segment elevation (4.2–7.2% in fibrinolytic trials, 8.5–14.2% in the registries), it also occurs, albeit less commonly (2.1–2.6%),
Cardiogenic Shock

in ACS patients without ST-segment elevation, even without positive cardiac biomarkers [20–23]. Shock typically results from severe LV dysfunction but may also occur when LV function is well preserved. In the international SHould we emergently revascularize Occluded Coronaries for cardiogenic shock? (SHOCK) trial registry of 1190 patients with cardiogenic shock, the predominant cause of shock was LV failure (78.5%), whereas isolated RV shock occurred in only 2.8% of patients. Mechanical complications of acute MI were observed among the remaining patients: severe mitral regurgitation (MR; 6.9%), ventricular septal rupture (3.9%), and tamponade (1.4%) [24].

Data on the incidence of shock are derived from large population-based analyses as well as from subset analyses of randomized clinical trials examining effects of different treatment modalities in the various forms of ACS. Due to differences in the definition of cardiogenic shock and criteria for including patients, the reported incidence of cardiogenic shock complicating ACS varies among studies. For example, an incidence of cardiogenic shock during hospitalization of 2.6% was reported among 3465 patients with acute MI in the prethrombolysis era, a low figure that reflects exclusion of patients with signs of heart failure upon presentation [25]. In comparison, cardiogenic shock was present in 6.7% of 6676 consecutive acute MI patients managed noninvasively in the Trandolapril Cardiac Evaluation (TRACE) registry, which included STEMI and NSTEMI cases [26].

ST–segment-elevation ACS and cardiogenic shock

Classically, cardiogenic shock has been considered a direct consequence of STEMI, most commonly caused by LV dysfunction resulting from continued ischemia and cell death. In three large international fibrinolytic therapy trials for STEMI, the incidence of shock ranged from 4.2% to 7.2% (Fig. 1.1) [12,27,28]. However, the reported incidence of cardiogenic shock among STEMI patients receiving fibrinolytic therapy may be biased, because patients with shock are often not enrolled in multicenter, randomized trials. Zeymer and colleagues reported a 14.2% incidence of cardiogenic shock in 9422 patients in an 80-hospital primary percutaneous coronary intervention (PCI) German registry [29].

Until recently, the incidence of cardiogenic shock among STEMI patients appeared to be quite stable, despite increasing use of early reperfusion therapy including primary PCI. Goldberg and colleagues [5] evaluated trends in the incidence of cardiogenic shock complicating STEMI in a single community from 1975 to 1997. The overall annual incidence for this period was 7.1% and ranged from 4.5% to 8.6%. In a large observational study [30] from the National Registry of Myocardial Infarction (NRMI-2, -3, -4), which analyzed data from 1.97 million acute STEMI patients hospitalized in the United States between 1994 and 2004, the incidence of cardiogenic shock was 8.6% overall and was quite stable over the study period. In the Euro Heart Survey of Acute Coronary Syndromes,
Fig. 1.1 Incidence of cardiogenic shock in ST-segment elevation MI trials and registries [20,22,28,30,68]. The incidence of shock among patients in GUSTO IIb and III is lower, likely reflecting use of fibrinolytic therapy in all patients in the setting of these clinical trials as opposed to the registry patients. Differing incidences of shock in the registries may be related to different patient populations and/or slight differences in definitions of shock. In addition, the incidence of shock was found to be lower over time in the GRACE registry, which enrolled patients through 2006. Lighter boxes denote clinical trials; darker boxes denote registries. EHS ACS, Euro Heart Survey Acute Coronary Syndromes; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; NRMI, National Registry of Myocardial Infarction.

the incidence of shock was 8.5% in the STEMI group [31], and a recent report from the Global Registry of Acute Coronary Events (GRACE), which recruits patients with ACS in almost 100 hospitals in 14 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, the United Kingdom, and the United States), suggests a reduction in the incidence of cardiogenic shock after STEMI [20]. In this registry, the incidence of cardiogenic shock in the STEMI group was 7.1% in 1999, subsequently decreasing significantly to 4.7% in 2005 ($P = 0.02$) [20].

Non–ST-elevation ACS and cardiogenic shock
In the setting of non–ST-elevation ACS (NSTEMI), data regarding the incidence of cardiogenic shock are relatively limited. This has important
Incidence of cardiogenic shock in non-ST segment elevation ACS – trials and registries

GUSTO IIb (1994–5)
PURSUIT (1995–7)
EHS ACS-I (2000–1)
CRUSADE (2001–3)
GRACE (1999–2006)

Fig. 1.2 Incidence of cardiogenic shock in non–ST-segment elevation acute coronary syndrome trials and registries [20–23,28]. The incidence of shock is uniformly lower among patients with NSTE ACS as compared with STEMI (compare with Fig. 1), most notably in the GUSTO IIb trial and the Euro Heart Survey and GRACE registry, which are also included in Fig. 1.1. These studies include patients with unstable angina, in which cardiogenic shock is known to occur. Lighter boxes denote clinical trials; darker boxes denote registries. CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines; EHS ACS, Euro Heart Survey Acute Coronary Syndromes; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy.

Implications, as the incidence of NSTE ACS appears to be increasing significantly as more sensitive cardiac markers are used [20]. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO IIb) trial [28], one of the largest clinical trials hitherto conducted, cardiogenic shock was predefined as a subset for analysis. Among 7986 patients with NSTE ACS, cardiogenic shock occurred in 2.6% of cases (Fig. 1.2). This was about half the incidence observed in the subgroup with ST-elevation acute coronary syndromes (STEACS) in the same trial [OR 0.50, 95% confidence interval (CI) 0.413, 0.612; P < 0.001]. The subset of patients with cardiogenic shock was also analyzed in the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial of patients with NSTE ACS [21]. Of 9449 patients, 237 (2.5%) developed shock after enrollment. In another large survey (the Euro Heart
Survey of Acute Coronary Syndromes), the incidence of cardiogenic shock among patients admitted with NSTE ACS was 2.4% (of whom three quarters developed it during hospitalization) [22,31]. As more cases that were previously categorized as unstable angina are confirmed as NSTEMI with use of sensitive troponin assays, the incidence, but not the total number of patients, should continue to decline. In the GRACE registry, the incidence of shock among patients with NSTE ACS decreased significantly over a 6-year period, from 2.1% to 1.8% (\( P = 0.01 \)) [20]. However, the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) quality improvement initiative evaluated care patterns and outcomes for 17,926 high-risk NSTE ACS patients (as determined by positive cardiac markers and/or ischemic electrocardiographic changes) at 248 United States hospitals with catheterization and revascularization facilities between March 2000 and September 2002, and found an incidence of cardiogenic shock that was remarkably consistent with all prior reports (2.6%) [23].

RV infarction and cardiogenic shock

RV infarction is a distinct entity within the spectrum of cardiogenic shock. Most patients with RV infarction were not included in randomized trials; thus, detailed data regarding the frequency of shock among these patients are lacking. In the SHOCK registry, the proportion of patients with shock complicating MI who had shock due to “isolated” RV failure was 2.8% [24]. In contrast, RV infarction was a relatively common cause of shock among patients with STEMI, accounting for about 16% of cases in a single-center registry of STEMI [32]. Similarly, at Rabin Medical Center, RV infarction accounted for 19.6% of all cases of shock complicating STEMI [33].

Time to development of cardiogenic shock in ACS

There is an apparent discrepancy, probably due to selection bias, between reports from randomized trials and population-based analyses regarding the timing of shock development. In randomized trials, approximately 90% of patients with shock developed it after study enrollment; only approximately 10% had shock upon arrival at the hospital. However, in a population-based study of unselected acute MI patients, 56% of shock patients had shock upon arrival [34]. In the SHOCK registry and trial, 26% of nontransferred patients were diagnosed with shock upon hospital arrival [35].

In the prethrombolysis era, Leor and colleagues [25] reported that shock developed at a median of 2 days after admission (range 3 hours to 16 days) in patients admitted without heart failure. Hands and colleagues [36] reported that cardiogenic shock developed after hospitalization in 60 (7.1%) of 845 patients presenting with acute MI. Half of patients who did not have shock upon admission developed shock within the first 24 hours.
In large fibrinolytic trials, the median time to the occurrence of shock among patients with persistent ST-segment elevation who developed shock in hospital was 10 or 11 hours [27,28,37], with most experiencing shock within the first 48 hours after enrollment. Shock occurred later, after symptom onset, in patients without ST-segment elevation compared with those with ST-segment elevation and is often associated with reinfarction in these cases. In GUSTO IIb, NSTE ACS patients developed shock a median of 76.2 hours after enrollment, in contrast to STEMI patients for whom the median time to onset was 9.6 hours [28]. In the SHOCK registry [38], time from acute MI onset to shock onset was also different: 8.9 hours for NSTE ACS patients versus 5.9 hours for STEMI patients. In the PURSUIT database of NSTE ACS, shock most commonly developed >48 hours after enrollment (median 94.0 hours) [21].

These data indicate that the window of opportunity for attempting to avert development of shock in STEMI is very short-lived; patients must be identified and measures should be taken within hours of presentation, including avoidance of measures that induce shock (Fig. 1.3). Very early reperfusion, which is the only therapy that prevents the development of shock in STEMI, is of paramount importance. The fact that cardiogenic shock develops later in NSTE ACS should not be interpreted as reflecting a more benign phenomenon; when it does occur, mortality is not lower than that seen among patients with STEMI complicated by shock (72.5% vs. 63.0% in the GUSTO IIb population, respectively, \(P = \text{NS}\)) [28]. Recognition of the risk factors for shock and prevention of reinfarction post NSTEMI are important.

The finding that cardiogenic shock complicates unstable angina or NSTEMI extends the current shock paradigm in two respects: (1) ACS with or without ST-segment elevation can be complicated by cardiogenic shock; and (2) myocardial ischemia alone (without infarction) can be complicated by cardiogenic shock. The difference in time to development of shock between patients with versus those without ST elevation suggests variation in the underlying mechanisms of the condition. Moreover, it may reflect differences in the baseline clinical and demographic characteristics, differences in antecedent cardiac function, and differences in the extent and nature of the coronary artery disease. It may also reflect the difference in the pathogenesis of the acute event, an abrupt closure of the coronary artery in STEMI versus a gradual and more diffuse compromise in coronary blood flow without total occlusion of the artery in NSTEMI.

Risk factors

Risk of development of cardiogenic shock

Timely recognition of a high-risk group of ACS patients prone to developing cardiogenic shock can be used as the central strategy for improving survival by avoiding measures that lead to iatrogenic shock (see below) and providing adequate therapeutic measures that can halt the deterioration that leads to this devastating condition.
Fig. 1.3 Iatrogenic shock [69]. 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 HF may induce shock. Tachycardia is often compensatory for lower SV but is not appreciated as such. Treatment with beta-blockade lowers HR and SV, leading to frank shock. Decompensation may also occur when patients who are reliant on compensatory vasoconstriction are treated with ACE-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 [63]. 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. (Reprinted with permission from Reynolds HR, Hochman JS. Circulation 2008;117(5):686–97.)
Certain demographic and clinical parameters are strongly associated with the development of shock. Leor and colleagues [25] reported that independent predictors for in-hospital shock were older age, female sex, prior angina, prior stroke, and peripheral vascular disease. Hands and colleagues [36] reported that the risk factors for developing cardiogenic shock were age >65 years, an LV ejection fraction <35%, larger infarct size (as estimated by serial cardiac marker measurements), prior MI, and diabetes mellitus. In these earlier studies, parameters from physical examination were not included in the analyses.

In an analysis of the GUSTO-I dataset [39] that included patients after fibrinolytic therapy, older age was the variable most strongly associated with the occurrence of shock; for every 10-year increase in age, the risk of developing shock was greater by 47%. Simple parameters derived from physical examination, such as systolic blood pressure, heart rate, and Killip class, among patients who did not present with cardiogenic shock were strong predictors for its subsequent development. The patient's age, combined with these physical parameters, provided 85% of the information needed to predict shock in this model.

Risk factors for cardiogenic shock have also been identified among patients with NSTE ACS in a retrospective analysis of the PURSUIT trial database [21]. In this trial, shock patients who received eptifibatide had a 50% reduction of 30-day mortality (58.5% vs. 73.5% for placebo; OR 0.51; 95% CI 0.28, 0.94; P = 0.03). Based on the scoring system developed for this analysis, cardiogenic shock was predicted primarily by age, the presence of ST depression in the initial ECG, and physical findings. Thus, despite the many differences between patients with or without persistent ST-segment elevation who develop shock, the baseline demographic and clinical variables associated with the development of the condition are similar.

The admission ECG along with relevant anamnestic and hemodynamic parameters can provide important information for quick risk stratification of acute MI patients. Retrospective analysis of the GUSTO-I clinical trial database aimed to determine the ability of initial ECG to predict all-cause mortality at 30 days following STEMI. After performing multivariable analysis, the sum of the absolute ST-segment deviation (both ST elevation and ST depression), heart rate, QRS duration, and ECG evidence of prior infarction (Q waves) appeared to be the strongest ECG predictors of mortality [40].

Bundle branch block on admission is relatively rare but carries important prognostic information. In the GUSTO-I trial, of all the 26,003 North American patients, 420 (1.6%) had left (n = 131) or right (n = 289) bundle branch block. These patients had higher 30-day mortality rates than matched control subjects (18% vs. 11%, P = 0.003, OR 1.8) and were more likely to experience cardiogenic shock (19% vs. 11%, P = 0.008, OR 1.78) [41].

Impaired fasting glucose, a state that precedes the development of diabetes mellitus, appears to increase the risk of shock in ACS patients. In the French RICO registry [42], 381 (38%) patients had diabetes mellitus, 145 (15%) had
impaired fasting glucose, and 473 (47%) had normal fasting glucose. The rate of mortality in the group with impaired fasting glucose was twice that observed in the normal fasting glucose group (8% vs. 4%, \( P = 0.049 \)). A significant increase in rates of cardiogenic shock (12% vs. 6%, \( P = 0.011 \)) and ventricular arrhythmia (15% vs. 9%, \( P = 0.035 \)) was observed in the impaired fasting glucose versus the normal fasting glucose group. After adjustment for confounding factors (age, sex, anterior location, and LV ejection fraction), impaired fasting glucose was a strong independent predictive factor for cardiogenic shock (\( P = 0.005 \)).

Women may have a higher incidence of cardiogenic shock than men. Data from the SHOCK registry [43] indicated a higher prevalence of mechanical complications as the cause of shock in women; severe MR occurred in 11.4% of women versus 7.1% of men with shock (\( P = 0.01 \)), and ventricular septal rupture developed in 7.7% of women versus 3.5% of men with shock (\( P = 0.003 \)). Women also tend to be older and have higher rates of prior hypertension and diabetes mellitus, and lower ejection fractions, than men with shock.

Outcomes in cardiogenic shock
The contemporary in-hospital mortality rate for cardiogenic shock remains extremely high at about 50–60% for all age groups. Patients with mechanical complications have even higher mortality rates, particularly without surgical intervention. Those with ventricular septal rupture have the highest mortality: 87% in the SHOCK Registry [24]. Papillary muscle rupture had a similarly high mortality before the era of surgical intervention, but with prompt surgical intervention, mortality is approximately 30% [44]. Surgical techniques for repair of free wall rupture are evolving with short-term survival approaching the survival after repair of papillary muscle rupture [45].

In the SHOCK trial registry examining cardiogenic shock caused by RV infarction, mortality was unexpectedly high in patients with predominant RV shock and similar to patients with predominantly LV failure shock—despite the younger age, lower rate of anterior MI, and higher prevalence of single-vessel coronary disease among RV compared with LV shock patients and their similar benefit from revascularization [46].

Predictors of death in cardiogenic shock once shock has developed
Demographics and hemodynamics
Older age has been associated with mortality in a number of trials and registries [12,29,47,48]. The apparent lack of survival benefit of early revascularization for the elderly in the SHOCK trial was found to be related to a chance imbalance in ejection fraction among elderly patients. Higher mortality rates among Hispanic and African American patients in the SHOCK registry (\( P = 0.05 \)) did not persist after adjustment for patient characteristics and use of revascularization (\( P = 0.26 \)) [49], with all race/ethnicity subgroups benefiting equally [50]. Female
sex was independently associated with outcome in one large registry (ACC-NCDR) [48]. Taking all of the evidence into account, female sex does not seem to be an independent predictor of poor outcome [29,43,51,52], although it should be noted that two larger registries did not report the independent effect of sex on outcome [5,30].

Diabetic patients with ACS complicated by cardiogenic shock had a higher risk profile than nondiabetic patients. In-hospital survival of diabetic patients in the SHOCK registry, however, was only marginally lower than that of non-diabetic patients after adjusting for risk factors [53].

The extent of LV injury that causes cardiogenic shock is generally large, and although ST elevation is the more common finding, mortality rates do not differ significantly by ST-segment status on the ECG [21,28,38].

Hemodynamic variables reflect the severity of the shock syndrome and have prognostic value. The hemodynamic measurements with greatest prognostic value appear to be cardiac output [12] or those measurements that incorporate cardiac output with systolic blood pressure, including stroke work [13] or cardiac power [14]. In the SHOCK trial, the strongest association with in-hospital mortality was found for cardiac power. Cardiac power was calculated as mean arterial pressure × cardiac output/451 [14]. Also in SHOCK, the presence of cardiogenic shock on admission appeared to be an independent predictor of in-hospital mortality as compared with cardiogenic shock that developed during hospitalization (68% vs. 49%, \( \text{P} = 0.039 \)), reflecting more deranged hemodynamics in those with shock at the time of admission [35].

**Angiographic and echocardiographic predictors**

Angiography in patients with cardiogenic shock most often demonstrates multivessel coronary disease (left main stenosis in 23% of patients, 3-vessel disease in 64% of patients, 2-vessel disease in 22% of patients, and 1-vessel disease in 14% of patients) [47]. In the SHOCK trial, angiography also revealed high rates of the left anterior descending coronary artery as the predominant culprit, as well as reduced coronary flow and complex lesion types [54]. Compensatory hyperkinesis is a favorable response, which develops in myocardial segments that are not involved in acute MI; this response helps maintain cardiac output. Failure to develop such a response, because of previous infarction, high-grade coronary stenosis, or metabolic abnormalities that develop remote from a large infarct zone, is an important risk factor for cardiogenic shock and death.

In a SHOCK trial substudy, 175 echocardiograms were performed within 24 hours of randomization to the early revascularization (ERV) or initial medical stabilization groups [55]. Median LV ejection fraction was 28%. MR of at least moderate degree was seen in 39% of patients; severe MR was an exclusion criterion for the trial. Short- and long-term mortality were independently associated with initial LV systolic function (EF) and mitral regurgitation (MR) as
assessed by echocardiography. LV volumes were not independently associated with death. The benefit of ERV was seen across the spectrum of baseline ejection fraction and MR (in a population that excluded shock due to severe MR).

**Risk models for shock mortality**

The large database of the American College of Cardiology–National Cardiovascular Data Registry (ACC-NCDR) [48] identified 483 patients who underwent PCI for cardiogenic shock secondary to acute MI among 326,369 consecutive PCI procedures, performed at 243 institutions between January 1, 1998, and September 1, 2002. Female sex, advanced age, baseline renal insufficiency (creatinine > 2.0 mg/dL), and total occlusion of the left anterior descending artery were identified as independent predictors of in-hospital mortality.

Although useful, this model does not address patients who were not selected for PCI or the benefit of PCI in patients at different levels of risk. A risk model using data from the SHOCK trial and registry has been developed and allows good discrimination of risk with and without use of early revascularization [56]. Two stages of risk assessment were identified: with and without invasive hemodynamic measurements. The model without invasive hemodynamics includes age, systolic blood pressure, anoxic brain injury, end-organ hypoperfusion, shock on admission, creatinine ≥ 1.9, prior CABG, and non-inferior location of MI. If EF was available, it replaced non-inferior MI as a marker of risk. In the model that includes invasive hemodynamics, older age, lower LV ejection fraction, anoxic brain damage, end-organ hypoperfusion, and lower stroke work are independent predictors of death. The addition of invasive hemodynamics reduced the number of terms in the model but added only modestly to risk discrimination.

Both of these risk models from the SHOCK trial and registry demonstrated better survival among patients undergoing emergency revascularization regardless of risk category.

**Improvement in survival of cardiogenic shock over time**

The outcome of cardiogenic shock seems to have improved slightly during a 23-year period with the greatest improvement in mortality during the 1990s [5]. From 1975 through 1990, the in-hospital mortality from cardiogenic shock averaged 77%, declining to 61% between 1993 and 1995 and further to 59% in 1997. Revascularization was strongly associated with survival [5] in this community-based sample. The SHOCK trial established the usefulness of an aggressive approach to cardiogenic shock patients [47,57]. Emergent coronary revascularization became the standard of care for cardiogenic shock due to pump failure and is highly recommended by American Heart Association and American College of Cardiology guidelines for the treatment of unstable angina and non-ST elevation as well as ST-elevation MI [58,59].
Implementation of the guideline recommendation for emergency revascularization in patients with acute MI and shock appears to have caused an additional decline in in-hospital mortality from 60% in 1995 to 48% by 2004 among patients in the US National Registry of Myocardial Infarction [30]. In the last decade, the in-hospital mortality rate in large “real-world” registries is remarkably consistent at 50–60%. In the Global Registry of Acute Coronary Events (GRACE), which enrolled patients between 1999 and 2001, the in-hospital mortality rate for cardiogenic shock patients was 59% [52]. In the Euro Heart Survey of ACS, the in-hospital mortality rate for cardiogenic shock was 52% in a period spanning 2000–2001 [22]. In-hospital mortality was 59.4% in 1998–2002 in the large database of the ACC-NCDR [48].

Iatrogenic shock
Medications often used in the early management of ACS, such as beta-blockers, angiotensin converting enzyme inhibitors, and morphine all exert a profound effect on systemic hemodynamics, and thus have been associated with the development of shock (Fig. 1.4) [60–62]. In the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) [60], cardiogenic shock was a secondary outcome. Unexpectedly, this mega-trial found no reduction in 30-day, all-cause mortality with the early use of IV followed by oral beta blockers. This was largely due to an increased risk of cardiogenic shock, especially during the first day, which offset a reduction in reinfarction and ventricular fibrillation. Therefore, in patients with high risk for the development of cardiogenic shock, early use of beta-blocking agents is a newly recognized iatrogenic risk factor. Variables that were determined to be independently associated with excess risk of cardiogenic shock are shown in Fig. 1.4.

Fig. 1.4 Excess risk of cardiogenic shock associated with medication use in randomized trials* and registry+.
shock were older age (>70 years), female sex, higher Killip class (>Class I), later time from symptom onset, definite ECG abnormalities, lower blood pressure (<120 mm Hg systolic), higher heart rate (>110 beats per minute), and previous hypertension.

The COMMIT findings demonstrate that early, IV beta blockade is contraindicated in patients with basilar rales or S3 gallop or pulmonary edema (Killip Class II–III). In contrast, it is strongly recommended to initiate low-dose oral beta-blockers prior to discharge with a gradual titration regimen, as used for chronic heart failure patients, for patients with MI and LV dysfunction.

As has been shown previously, medications that are beneficial in the long term after MI may be deleterious in some patients in the short term. A very large meta-analysis of early use of angiotensin-converting enzyme inhibition found an excess of cardiogenic shock of 4.6 patients per 1000 treated. In this study, older age, lower blood pressure, and higher heart rate at presentation were associated with the development of cardiogenic shock [62]. Interestingly, nitrate use was not associated with excess risk of cardiogenic shock in a randomized trial [63]. Given the widespread use of these medications, their potential deleterious effect is significant, and thus these agents should be used vigilantly in patients at risk.

In certain cases, depletion of intravascular volume with diuretics may also contribute to the development of shock (Fig. 1.3). The underlying mechanism entails decreased LV compliance caused by ischemia, and consequent redistribution of intravascular volume into the lungs leading to depletion of systemic intravascular volume. The administration of diuretics in this state may further deplete systemic intravascular volume, resulting in shock. Thus, when pulmonary edema complicates ACS, treatment with low-dose diuretics in conjunction with low-dose nitrate and positioning of the patient is preferable.

Conversely, volume loading may also cause shock in the case of RV infarction. In this clinical setting, the classical teaching is that RV pressure and thus cardiac output is maintained by volume supplementation. In fact, RV diastolic pressure is often high in the course of RV infarction, and excess fluid administration may lead to movement of the interventricular septum into the left ventricle, compromising LV systolic and diastolic function [64]. Invasive measurement or noninvasive estimation of right atrial pressure should be performed in cases of RV infarction with shock; the optimal range in most patients is 10–15 mm Hg, but there is variability among patients and the best range must be identified for the individual patient.

Long-term outcome
Available data regarding long-term outcome of patients with cardiogenic shock and acute MI show that, by far, the largest mortality risk is in the early period after infarction. In the SHOCK trial population, the 6-year survival rates for hospital survivors was 62.4% versus 44.4% for the early revascularization and initial medical stabilization groups, respectively, with annualized death rates
of 8.3% versus 14.3% and, for the 1-year survivors, 8.0% versus 10.7% [65]. Assignment to early revascularization was the only independent predictor of 1-year survival [66]. Singh and colleagues showed that, among patients with cardiogenic shock who survived 30 days after fibrinolytic treatment of STEMI in the GUSTO-I trial, annual mortality rates over the ensuing 15 years were 2% to 4%. These mortality rates approximate those of patients without shock [67]. Furthermore, patients who survive cardiogenic shock usually have good functional status, with up to 80% completely asymptomatic and most in functional class I or II [66].

Therefore, an aggressive approach to diagnosis and early treatment of cardiogenic shock is strongly recommended in all candidates.

References


