Cardiogenic shock in ACS. Part 1: prediction, presentation and medical therapy

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Abstract | Ischemic cardiogenic shock is a complex, self-perpetuating pathological process that frequently causes death irrespective of medical therapy. Early definition of coronary anatomy is a pivotal step towards survival. Those destined to develop shock are likely to have three-vessel or left main stem disease with previously impaired left ventricular function. Early reperfusion of the occluded artery can limit infarct size, but ischemia–reperfusion injury or the 'no-reflow' phenomenon can preclude improvement in myocardial contractility. Emergence of shock depends upon the volume of ischemic myocardium, stroke volume, and peripheral vascular resistance. If cytokine release triggers the systemic inflammatory response, systemic vascular resistance falls and inadequate coronary perfusion pressure heralds the downward spiral. Survival depends on early recognition of shock, followed by aggressive targeted treatment of left, right, or biventricular failure. The goal is to prevent end-organ dysfunction and severe metabolic derangement by raising mean arterial pressure, which is achieved with inotropes and vasopressors, often at the expense of tachycardia, elevated myocardial oxygen consumption, and extended ischemia. The value of intra-aortic balloon counter-pulsation is now questioned in patients with advanced shock. When mean arterial pressure is <55 mmHg with serum lactate >11 mmol/l, death is likely and mechanical circulatory support becomes the only chance for survival.

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Introduction

Cardiogenic shock is a complex, degenerating clinical spiral of multiorgan dysfunction that begins when the heart is no longer able to provide sufficient resting pressure and flow[1] (Figure 1). An estimated 500,000 ST-segment elevation myocardial infarctions (STEMIs) occur annually in the USA and 650,000 in Europe.[2] Given the 5–10% incidence of cardiogenic shock among patients hospitalized for myocardial infarction, these figures equate to as many as 50,000 and 65,000 cases of cardiogenic shock in the USA and Europe, respectively.[1] Without effective intervention, progression of shock is rapid and fatal.[3] In Part 1 of this Review, we examine the evolving clinical profile of cardiogenic shock, its prognostic importance, and progress in the medical management of this condition since the results of the SHOCK trial[4] were published in 1999.

Changes in incidence and mortality

Trials of thrombolytic therapy versus primary percutaneous coronary intervention (PPCI) in the 1990s, such as the GUSTO-IIb[5] and Primary Angioplasty in Myocardial Infarction studies,[6] were followed by massive economic investment in round-the-clock emergency revascularization. In the SHOCK trial, the difference in 30-day mortality between revascularized patients and those receiving medical therapy did not reach significance (47% versus 56%, $P=0.11$), but those who were discharged from hospital after PPCI or CABG surgery went on to show a survival benefit at 6 months when compared with those treated medically (50.3% versus 63.1%, $P=0.027$).[4] Since the SHOCK trial, hospital mortality has decreased steadily, now falling to below 50% in some studies.[7,8] This improvement is generally attributed to increased rates of PPCI for acute coronary syndromes (ACS), which logically might prevent progression to cardiogenic shock in those at risk.

This hypothesis is supported by the results of the long-term, population-based AMIS Plus Registry[7] of 23,696 patients with ACS. The overall incidence of cardiogenic shock between 1997 and 2006 fell from 12.9% to 5.5% ($P<0.001$). In the same period, the use of PPCI in patients with cardiogenic shock increased from 7.6% to 65.9% ($P=0.01$) and was associated with lower risk of hospital mortality (OR 0.47, 95% CI 0.30–0.73, $P=0.001$). Rates of cardiogenic shock on admission (28.5% of all cases; 2.3% of those with ACS) remained constant. By contrast, the incidence of shock developing in patients with myocardial infarction after hospital admission fell from 10.6% to 2.7% ($P<0.001$) and in-hospital shock mortality fell from 62.8% to 47.7% ($P=0.010$). Cardiogenic shock complicated STEMI more frequently than non-STEMI (10.7% versus 5.2%, $P<0.001$), but decreased similarly in both groups during the observation period (from 14.7% to 7.1% and from 8.9% to 3.4%, respectively, $P<0.001$). In

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response to progressive therapeutic regimens, the rate of in-hospital shock onset fell in both groups (from 11.9% to 3.6% and from 7.8% to 1.7% respectively, $P<0.001$). Similar proportions of patients with STEMI and non-STEMI received an intra-aortic balloon pump (IABP; 23% and 19%, respectively). Shock-related mortality was lower in STEMI than in non-STEMI (52.5% versus 58.0%, $P=0.041$) and was higher for patients aged ≥75 years (73.7% versus 42.8% for patients aged <75 years, $P<0.001$). Overall mortality for both older (≥75 years) and younger (<75 years) patients decreased over the study period (from 82.8% to 65.6%, $P=0.065$ and from 52.7% to 38.3%, $P=0.020$ respectively). Mortality for cardiogenic shock present on hospital admission in those aged ≥75 years was 90.9% in 1997 and had fallen, albeit nonsignificantly, to 64.3% by 2006 ($P=0.6$). Equivalent mortalities for younger patients with shock on hospital admission were 67.7% in 1997 and 38.3% in 2006 ($P=0.021$).[7]

These data are reinforced by findings from the US National Hospital Discharge Survey, which revealed decreasing incidence of cardiogenic shock from 1979 to 2004 corresponding with increased rates of PPCI and IABP use.[8] Thus, in the past decade, rates of cardiogenic shock present on hospital admission have remained constant, but the overall incidence has decreased because of improved rates of revascularization for ACS. Early shock-related mortality remains substantial, but with improving drug and device treatment the outlook for survivors of ACS is increasingly optimistic.[9,10] Indeed, the prognosis for patients who survive cardiogenic shock is now similar to that for patients without shock. In the GUSTO-I study,[11] 88% of patients who survived shock and were discharged from hospital were alive at 1 year. Heart failure, arrhythmias, and other events all occurred less frequently in those without transmural myocardial infarction.[11] Thus every effort should be made to revascularize then sustain the patient through the initial shock phase.

Clinical presentation

Typical presentation

Most randomized clinical trials have employed similar definitions of cardiogenic shock (Box 1).[4] Some investigators have used a range of decreased cardiac index from <1.8 l/min/m^2 to <2.2 l/min/m^2. Usually, the cut-off point for systolic blood pressure is <90 mmHg, although shock can also be recognized in patients with preserved systolic pressure (>100 mmHg) achieved through inotropic support or the use of an IABP. Hypoperfusion manifests as cool clammy extremities, poor capillary refill, loss of consciousness, disorientation or confusion, and urine output <30 ml/h. Elevated left atrial pressure causes pulmonary congestion and dyspnea, particularly in the presence of acute mitral regurgitation.

Some authors subdivide cardiogenic shock into 'acute transient shock' and 'protracted or refractory shock'.[12] In transient shock, hemodynamic function declines rapidly, but is promptly improved following PPCI, the administration of inotropes and vasopressors, or both. These patients have predominant myocardial stunning and inotropes can boost contractility in stunned myocardium. By contrast, those with refractory shock do not respond to intensive medical therapy and, without circulatory support, progress inexorably towards death. These patients are characterized by a left main stem lesion or severe three-vessel disease with previous myocardial infarction or CABG surgery. They often have extensive anterior infarction, pre-existing left ventricular (LV) dysfunction or stuttering progression of infarction owing to failure to reperfuse. Other authors differentiate between 'profound shock'—characterized by blood pressure <75 mmHg, cerebral dysfunction, and respiratory failure, (despite the use of inotropes and an IABP) —and 'nonprofound shock', where blood pressure remains >75 mmHg despite treatment with inotropes or an IABP.[13] Between these groups, a considerable difference in response to PPCI is evident, with 71% versus 22% mortality for profound versus nonprofound shock, respectively.[13]

In the randomized SHOCK trial, the median time between symptom onset and signs of shock was 5.0 h (interquartile range 2.2–12.0 h), and 74% of those who would eventually develop shock had done so by 24 h.[14] In the SHOCK registry, shock manifested at a median of 6.0 h (interquartile range 1.8–22.0 h) after presentation, and around 4 h following hospital admission.[15] Only 10–15% of patients with STEMI exhibit clinical signs of shock on admission to hospital. In the SHOCK registry,

Key points

- Cardiogenic shock complicates 5–10% of ST-segment elevation myocardial infarctions and 2–3% of non-ST segment elevation coronary syndromes, with mortality ranging from 40% to 80%
- Angiographic findings during primary angioplasty can predict cardiogenic shock, but early reperfusion has decreased the incidence of full thickness infarction and improved survival
- Ventricular septal rupture occurs in up to 0.5% of patients with ST-segment elevation myocardial infarction, whereas severe mitral regurgitation occurs in 10%, and free-wall rupture in 3%
- Cytokine release can trigger the systemic inflammatory response, causing low peripheral vascular resistance and profound refractory shock in around one-third of cases
- Management of primary left ventricular failure involves early reperfusion and administration of adrenergic inotropes and vasopressors; right ventricular failure is treated with volume loading, inotropes, and pulmonary vasodilators
- When mean arterial pressure is <55 mmHg, serum lactate >11 mmol/l, base deficit >12 mmol/l, and SvO_2 <65% despite medical therapy, recovery is unlikely without mechanical circulatory support

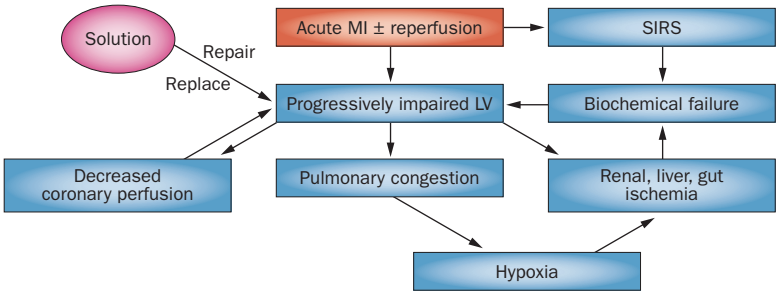

Figure 1 | Self-perpetuating mechanisms of cardiogenic shock. Only restoration of cardiac index and coronary perfusion to physiological levels can stop the vicious cycle. Abbreviations: LV, left ventricular; MI, myocardial infarction; SIRS, systemic inflammatory response syndrome.

Box 1 | Diagnostic criteria for cardiogenic shock

Systolic blood pressure <90 mmHg for ≥1 h that is:
- Not responsiveness to fluid administration alone
- Secondary to cardiac dysfunction
- Associated with signs of hypoperfusion, including cold clammy extremities, altered mental state, and urine output <30 ml/h, together with cardiac index <2.2 l/min/m^2 and pulmonary capillary wedge pressure >18 mmHg

Low cardiac output state, but with systolic blood pressure >90 mmHg in response to inotropes with or without the use of an IABP

Profound shock: cardiac index <1.8 l/min/m^2 with mean blood pressure <65 mmHg and unresponsive to inotropes with or without the use of an IABP

Abbreviation: IABP, intra-aortic balloon pump.

two temporal groups were identified with an overall mortality of 60%.[16] Early shock, affecting 74% of patients, presented <24 h after symptom onset, whereas late shock in the remaining 26% of patients presented >24 h after symptom onset. Relative mortality was 63% versus 54% for early and late shock, respectively. Median time to shock was 1.7 h for left main stem occlusion, 3.5 h for right coronary occlusion, 3.9 h for circumflex occlusion, and 11.0 h for left anterior descending occlusion. Although 78% of patients had multivessel disease, shock developed earlier in patients with single-vessel (5.5 h) or two-vessel disease (4.6 h).[16] Time from symptom onset to presentation was <6 h in 47% of patients with early shock and, for those who arrived at hospital already in shock, mortality was higher (SHOCK registry 64%, SHOCK trial 75%).[15,16] Late shock occurred at a median of 51 h with a frequent association between left anterior descending coronary occlusion and multiple new Q waves.[16]

Infarct extension can be the result of thrombotic reocclusion of a temporarily patent artery or propagation of thrombus into a distal vessel. Patients with shock are more likely than those with STEMI but no shock to have persistently elevated enzymes or reinfarction, suggesting ongoing ischemia. Shock usually presents later in patients with non-STEMI than in those with STEMI. In the GUSTO-IIb trial, shock emerged at around 76 h (interquartile range 20.6–144.5 h) for non-STEMI compared with 9.6 h (interquartile range 1.6–67.3 h) with STEMI (P = <0.001).[5] In the PURSUIT trial,[17] the median time between symptom onset and the development of shock was 94.0 h (interquartile range 38.0–206.0 h).

Variability in presentation

In the SHOCK registry, only 64% of patients presented with classical physical signs of shock, including pulmonary congestion.[16] A substantial minority (~20%) were in low cardiac output state with hypoperfusion, but without dyspnea or pulmonary edema. These 'silent lung' patients had elevated left atrial pressure (>20 mmHg), and mortality was higher than among patients with pulmonary congestion (70% versus 60%, P = 0.036).[16] Some patients with anterior STEMI present with clinical signs and biochemical parameters of shock while maintaining systemic pressure >90 mmHg. Urine production remains low in the face of fluid resuscitation, which can precipitate pulmonary edema. Sinus tachycardia (>100 bpm) compensates for the reduction in stroke volume. β-blockers given to reduce heart rate further can depress cardiac output. Invasive monitoring of these patients shows cardiac index to be <2.0 l/m^2/min, although cardiac output can temporarily increase with inotropic drugs or a fall in peripheral vascular resistance. Peripheral vasoconstriction is the normal physiological response to hypotension and is an intentional result of vasopressor therapy. However, 20% of patients have low systemic vascular resistance at the onset of shock, suggesting inappropriate vasodilatation.[18] Mismatch of depressed contractility with vasodilatation triggers severe hypotension, hypoperfusion, lactic acidosis, and profound shock.

Inflammatory mediators in shock

High levels of nitric oxide (NO) synthase expression follows the release of inflammatory mediators during myocardial infarction, which is consistent with the high body temperature, raised white-cell count, and elevated C-reactive protein (CRP) level among patients with extensive necrosis.[19,20] Geppert *et al.* performed a retrospective analysis of stored plasma samples from patients with postinfarction shock and found that those who did not survive already had high plasma concentrations of the inflammatory cytokine interleukin 6 (IL-6) by the time of presentation.[21] IL-6 levels >200 pg/ml were associated with increased mortality irrespective of whether the patient had successful PPCI.[21] Elevated IL-6 exerts a negative inotropic effect and predisposes the patient to multiorgan failure. In the study by Geppert and colleagues, patients with a high vasopressor need had 86% mortality, consistent with the fact that cytokine-induced release of NO within vascular cells causes reduced catecholamine responsiveness. Successful revascularization and an IL-6 level <200 pg/ml were associated with only 24% mortality compared with the overall series mortality of 47%.[21]

High levels of NO and peroxynitrites cause inappropriate vasodilatation and negate the reflex vasoconstriction during hypotension. NO has a biphasic effect on myocardium; low levels are positively inotropic whereas high levels negate inotrope responsiveness through suppression of mitochondrial respiration. This mechanism led Cotter and colleagues to propose that NO synthase inhibition could attenuate these effects and improve systemic blood pressure and coronary perfusion during the acute phase of shock.[22] These investigators randomly assigned 30 patients to full supportive care with or without the NO synthase inhibitor L-NG-monomethyl L-arginine (L-NAME) 30-day mortality was reduced to a remarkable 27% in the treated group versus 67% for controls. Patients with L-NAME infusion had better urine output and shorter time on ventilator and IABP support. Notably in this series, PPCI reduced target-vessel stenosis from a mean of 96% to 12% yet Thrombolysis In Myocardial Infarction (TIMI) grade 3 epicardial flow was obtained in only 53% of patients and blush score >1 in only 13%. The investigators concluded that a transient increase in

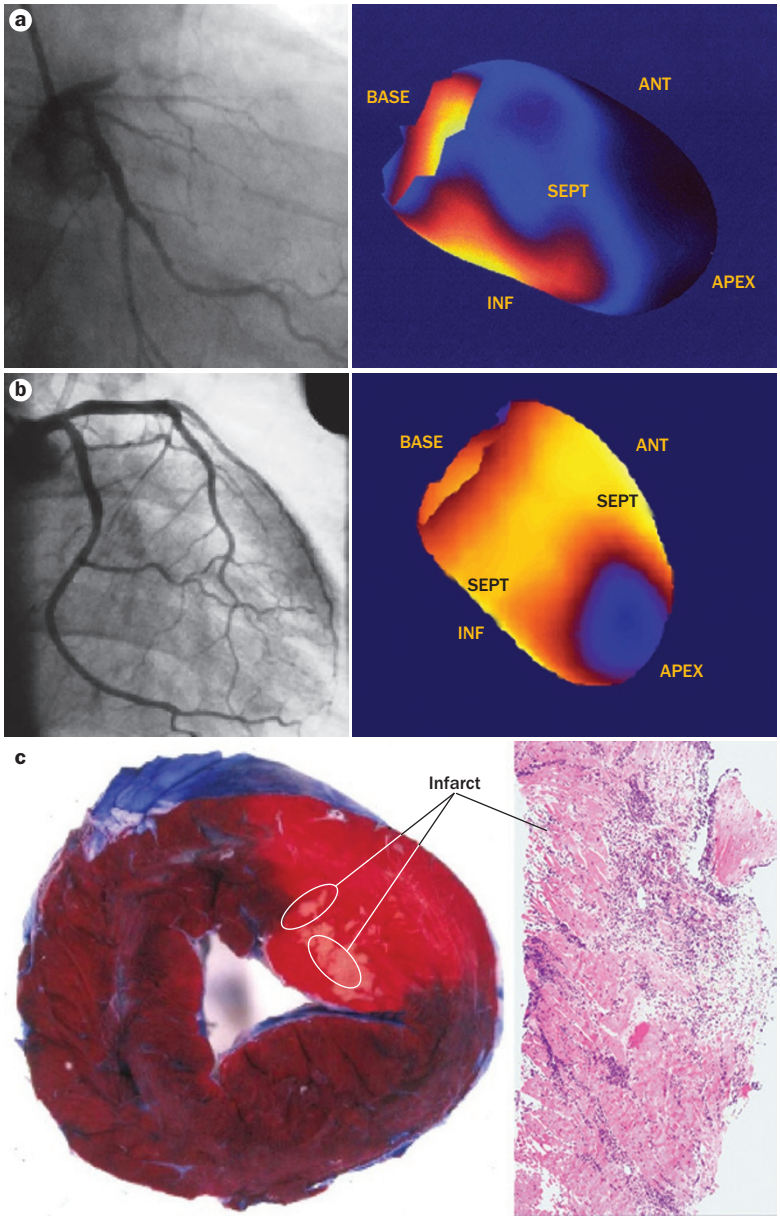

Figure 2 | Influence of PPCI on extent of myocardial infarction and stunning. After coronary reperfusion the area of myocardial infarction can be limited, but a much larger territory remains stunned with impaired contractility and compliance through reperfusion injury. **a** | A coronary angiogram from a patient with an anterior myocardial infarction and proximally occluded left anterior descending artery (left panel). A 3D MPS that demonstrates a large area of hypoperfusion in the anterior wall, anterior septum, and apex (right panel, blue areas). The inferior wall is perfused normally (yellow/red areas), which corresponds to the area at risk. **b** | A coronary angiogram after percutaneous intervention, with stent deployment in the proximal left anterior descending artery (left panel). A 3D MPS that demonstrates a small area of hypoperfusion at the apex (right panel, blue area). All other territories have normal perfusion (yellow/red areas), which corresponds to the final infarct size. Angiograms and MPSs courtesy of Professor Hans Erik Bøtker. **c** | Cross-section of a heart after experimental infarction showing the area at risk (bright red), area not at risk (blue/purple), and area of infarction (white) after Evans blue perfusion staining and Tetrazolium staining. The histology appearance of infarction with rich perivascular inflammatory infiltrate and myofibrillar disarray (inset). Abbreviations: ANT, anterior; INF, inferior; MPS, myocardial perfusion scintigram; PPCI, primary percutaneous coronary intervention; SEPT, septum.

systemic vascular resistance and myocardial contractility boosted mean arterial pressure and end-organ blood flow, thus preventing multiorgan failure. They also suggested that inhibition of NO synthase might attenuate stunning induced by toxic levels of NO.[22] A gradual increase in cardiac power index during the first 24 h of L-NAME infusion reinforced this hypothesis. Unfortunately, the findings from Cotter *et al.* were not confirmed by subsequent studies. TRIUMPH[23] showed that L-NAME (tilarginine) increased blood pressure, but without survival benefit.[23] TRIUMPH was the largest randomized study of L-NAME therapy attempted in patients with cardiogenic shock, but was discontinued after 398 patients were enrolled on the basis of a prespecified futility analysis.

Shock after coronary reperfusion

Epicardial patency does not necessarily reflect perfusion at the microvascular level.[24] Ischemic endothelial damage, impaired autoregulation, and coronary spasm can prevent microvascular reperfusion. Myocardial contrast echocardiography defines no-reflow in 16% of patients with TIMI grade 3 flow after PPCI.[25] The progression from myocardial ischemia to infarction and the effects of reperfusion are critically time-dependent. Thrombosis on an atherosclerotic plaque causes acute interruption of flow. Within minutes, ionized calcium rises in the ischemic myocyte, amino acid precursors fall, and ATP production stops. Sarcomeric contractile dysfunction prevents systolic shortening, which is superseded by passive lengthening. Myocardial stunning, followed by hibernation, ensues after 20–30 min of ischemia and takes days or weeks to recover.[26]

Early reperfusion by PPCI or thrombolysis can limit infarct size by prompt restoration of flow. PPCI delivers normal flow more predictably and has a lower reocclusion rate than thrombolysis (2% versus 20%, respectively).[27] The difference in lives saved (132 per 1,000 versus 70 per 1,000, respectively) is equivalent to the difference between medical management or surgery for left main coronary artery disease. However, PPCI must occur in little more than 120 min after symptomatic onset to provide substantial benefit.[28] Whereas restoration of flow within 40 min prevents necrosis in 60–70% of potentially viable myocardium, reperfusion at 180 min salvages only 10%.[28] After this time, reperfusion is associated with little functional improvement. Therefore, early thrombolysis might convey greater benefit than late PPCI.[29] Late reperfusion causes increased peri-infarction hemorrhage, edema, and contraction-band necrosis.[31] The 'no-reflow' phenomenon is more likely to occur if reperfusion is delayed and negates the benefit of epicardial vessel patency.[24] Myocardial stiffening then compounds stunning. Flow to the margins of the infarct is determined by perfusion pressure during

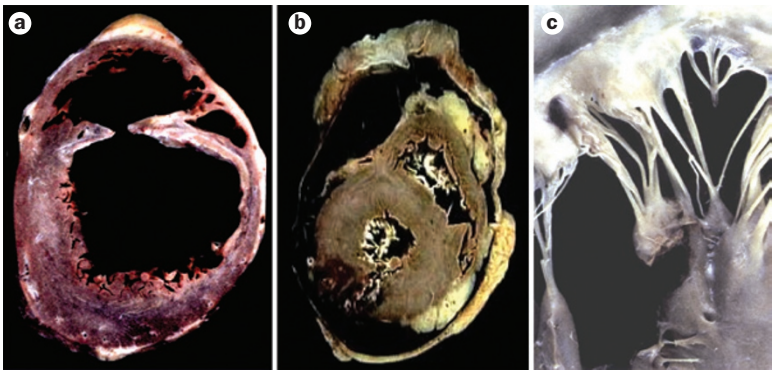

Figure 3 | Myocardial disruption after acute myocardial infarction. **a** | Ventricular septal rupture. **b** | Ventricular free-wall rupture. **c** | Papillary muscle rupture. See also Table 1.

diastole (mean aortic diastolic pressure minus LV diastolic pressure), coronary vascular resistance, and the presence of collateral circulation. As cardiac output falls and LV end-diastolic pressure rises, perfusion of the peri-infarct zone is further compromised. By 4–6 h after symptom onset, areas of transmural necrosis are found in some cases, depending on the severity of coronary disease and the presence of collateral flow. Metabolic acidosis contributes to global myocardial dysfunction and a critical low cardiac output state can cause irreversible end-organ failure within 24 h.

Even with restoration of TIMI grade 3 epicardial flow and endocardial perfusion, ischemia–reperfusion injury and stunning limit early improvement in contractility of the affected segments. The potential for global recovery in LV function remains, but stunned or hibernating muscle cannot sustain the patient through the rapid downward spiral of cardiogenic shock (Figure 2). Thus, potentially salvageable patients die if no effort is made to unload the distending ventricle and sustain blood flow to vital organs.

In routine clinical practice, patients present at hospitals with widely differing levels of care and, for many, the effort made to sustain life is limited. In the SHOCK trial,[4] 86% of patients received an IABP in an attempt to stabilize their condition and improve the safety of revascularization. A subsequent review by Babaev *et al.*[31] showed the registry intervention rate to be only 39% despite clear ACC/AHA guidelines.[32] Currently, doubts exist as to whether the IABP can influence outcome following acute myocardial infarction with or without cardiogenic shock. This issue is addressed in Part 2 of this Review.[33]

Cardiac disruption causing shock

Shock precipitated by myocardial disruption (manifesting as ventricular septal rupture, free-wall rupture, or papillary muscle rupture and mitral regurgitation; Figure 3 and Table 1) presents suddenly 1–7 days (median 2.4 days) after transmural infarction.[34] These presentations are discussed individually below.

Ventricular septal rupture

The median time from infarction to septal rupture (Figure 3a and Table 1) was 16 h in the SHOCK trial[4] and 1 day (range 0–47 days) in the GUSTO-I trial.[11] Although thrombolysis can limit infarct size, it can also promote hemorrhagic dissection into the necrotic myocardium and accelerate rupture.[35] Rapid access to surgical or catheter-based treatment is vital for these patients and outcomes are generally poor.[36] In the era before reperfusion therapy, ventricular septal rupture occurred in 1–3% of patients with STEMI.[34] Between 1990 and 2007 the MIDAS database recorded 408 cases of ventricular septal rupture from a total of 148,881 adults, an annual rate of 0.25–0.31%.[37] Patients with septal rupture were older, more likely to be female, and have chronic kidney disease, pre-existing heart failure, or cardiogenic shock. The incidence of septal rupture was similar for anterior and inferior myocardial infarction. Patients with hypertension, diabetes mellitus, chronic angina, or previous myocardial infarction were less likely to experience this complication, because prior ischemia leads to myocardial preconditioning, decreasing the likelihood of transmural myocardial necrosis and septal rupture.

Table 1 | Characteristics of myocardial disruption after acute myocardial infarction*

Parameter	Ventricular septal rupture	Ventricular free-wall rupture	Papillary muscle rupture
Incidence	3.9% in cardiogenic shock 1.0–3.0% without reperfusion therapy 0.2–0.3% after thrombolysis	0.8–6.2% PPCI seems to reduce risk Thrombolysis may increase risk	1% Predominately affects the posteromedial papillary muscle
Time course	24 h with thrombolysis 3–7 days without reperfusion therapy	2.7 days with thrombolysis 1–7 days without reperfusion therapy	24–36 h (range 1–14 days)
Clinical presentation	Chest pain Dyspnea Hypotension	Syncope Hypotension Chest pain Sudden death	Sudden dyspnea Hypotension Pulmonary edema
Findings	Harsh systolic murmur Thrill Pulmonary crepitations Cardiogenic shock	Venous distension (temponade) Pulses paradoxic Cardiogenic shock Electromechanical dissociation	Soft systolic murmur No thrill Cardiogenic shock Pulmonary edema
Echocardiography	Left-to-right shunt Right ventricular distension Apical or inferobasal septal defect	Pericardial fluid (>5 mm) Blood clot with signs of tamponade Tear might be visible	Flail papillary muscle Hypercontractile left ventricle with severe mitral regurgitation

*See also Figure 3. Abbreviation: PPCI, primary percutaneous coronary intervention.

Ventricular septal rupture is dependent on transmural infarction; therefore, fewer cases occur after early reperfusion. After thrombolysis, the rate of rupture is between 0.2% and 0.4% annually and is 0.2–0.5% for those undergoing PPCI.[38,39] Among the 41,021 patients in the GUSTO-I trial, septal rupture was suspected in 140 (0.34%) and confirmed by retrospective review in 84 patients (0.2%).[11] Thus reperfusion therapy has substantially decreased the incidence of septal rupture. In the SHOCK trial, in-hospital mortality was significantly higher for patients with septal rupture than among those with all other causes of shock (87.3% versus 59.2% for those with pure LV dysfunction and 55.1% among those with acute mitral regurgitation).[40]

The pathogenesis of septal rupture differs in patients with early (first 48 h) and later presentation of shock. Following thrombolysis, an intramural hematoma within the infarct may dissect and rupture.[35] In the absence of reperfusion, coagulation necrosis evolves over 3–5 days with acute inflammation and neutrophil infiltration around the necrotic zone.[41] The neutrophils undergo apoptosis and release lytic enzymes, which cause disintegration and rupture of the infarct. Propensity for rupture is reduced by collateral circulation in chronic myocardial ischemia complicated by infarction.[42] The septal defect is usually apical and simple after anterior infarction, but more-complex following posterobasal infarction where the right ventricle or papillary muscles can also be involved.[43] Rupture produces a sudden left-to-right shunt with right ventricular (RV) volume overload and increased pulmonary blood flow, which may be accompanied by chest pain, acute dyspnea, and low cardiac output state.[44] In contrast to acute mitral regurgitation, septal rupture produces a loud systolic murmur and thrill, but rarely pulmonary edema. When acute hemodynamic derangement progresses to cardiogenic shock, the thrill and murmur fade as turbulent transeptal flow decreases in response to poor LV function. Doppler echocardiography differentiates between septal or free wall rupture and mitral regurgitation. The sensitivity and specificity of color Doppler echocardiography are virtually 100% although, in ventilated patients, the transesophageal approach provides better definition of the site of rupture than the transthoracic approach.

Mortality for septal rupture without surgery is approximately 24% in 24 h, 46% at 1 week, and 82% within 2 months.[44] The ACC/AHA guidelines recommend immediate operative intervention regardless of clinical status.[45] Coronary angiography is used to direct concomitant coronary revascularization. Pending transfer to the operating room, medical management comprises hemodynamic support with an IABP, inotropes, and afterload reduction. Diuretics are used for pulmonary congestion and oxygenation is maintained using oxygen by mask, positive airway pressure, or mechanical ventilation. Maintenance of arterial blood pressure with vasopressors must be balanced against the need to moderate shunt fraction by reducing systemic vascular resistance. These patients are at very high risk and the surgical team must have appropriate experience. Intraoperative transesophageal echocardiography is used to ensure that the defect is closed yet a residual shunt is not uncommon.

LV free-wall rupture

LV free-wall rupture (Figure 3b and Table 1) complicates between 1% and 3% of all myocardial infarctions and accounts for death in 7–24% of patients in autopsy studies.[46] During thrombolysis, plasmin can break down myocardial collagen exposed by endocardial necrosis.[47] Cardiac rupture is the most-common cause of death in thrombolysed patients aged >75 years (54%).[48] In the elderly, the incidence of myocardial rupture associated with thrombolysis initiated more than 6 h after symptom onset is 17%, compared with 5% in patients who undergo PPCI and 8% for those who are not reperfused.[48] Rupture most-commonly occurs in the posterolateral free wall close to papillary muscle insertion (64%).[46]

Becker and van Mantgem classified cardiac rupture into three types; type I have an abrupt tear in the myocardium without thinning; in type II the infarcted myocardium erodes before dehiscence and is covered by thrombus; whereas type III ruptures have marked thinning of the walls, secondary aneurysm formation, and a perforation in the center of the aneurysm.[49] Type I often presents with electromechanical dissociation and sudden death whereas types II and III leak blood into the pericardium causing tamponade, hypotension, and low cardiac output state.[50] The pericardium may 'wall off' the leak producing a pseudoaneurysm.[51] Urgent pericardiocentesis followed by surgical repair provides the best chance of survival in patients with free-wall rupture.

Papillary muscle rupture and mitral regurgitation

Severe mitral regurgitation occurs in10% of patients with postinfarction cardiogenic shock and causes death in up to 70%.[52] The posteromedial papillary muscle is most frequently involved because of its single blood supply from distal branches of the posterior descending artery (from either right or circumflex coronary artery). The anterolateral papillary muscle has dual blood supply from both left anterior descending and circumflex coronaries making it less vulnerable. Thus mitral regurgitation is most common with inferior infarction followed by partial or total papillary rupture (Figure 3c and Table 1) in two thirds of cases.[52] Papillary muscle dehiscence presents with cardiogenic shock and pulmonary edema requiring early surgical repair. Chevalier *et al.* reported perioperative mortality of 24% in a consecutive series of 55 patients with ischemic mitral regurgitation and showed revascularization to have a protective effect.[53] Complete papillary rupture was present in 25 patients (posteromedial in 21, anterolateral in 4) with partial rupture in 12 (posteromedial in 10). Acute papillary muscle dysfunction without rupture was the cause of mitral regurgitation in 18 patients (posteromedial in 15). Papillary muscle dysfunction (in contrast to dehiscence) can be managed medically by reducing LV afterload with an IABP or vasodilators. When mitral regurgitation is severe, early surgery is preferable

using techniques to reimplant the flail papillary muscle. Prosthetic valve replacement is a less satisfactory, but frequently, necessary alternative.[54]

Predictors of shock and outcome

In 80% of patients with shock, primary LV failure follows the loss of around 40% of functional myocardium, either acutely during the first myocardial infarction or following repeated myocardial infarctions,[1,3] (STEMI or non-STEMI). The remaining 20% of patients develop shock through myocardial disruption (Figure 3 and Table 1) or predominant RV failure.[7,8] Acute RV failure can follow severe mitral regurgitation and pulmonary hypertension. Cardiogenic shock can also complicate non-ST-segment ACS. In the PURSUIT trial,[17] the incidence of shock was 2.9%, which was similar to the 2.5% incidence in the non-STEMI arm of the GUSTO-IIb study,[5] although 30-day mortality for shock in these trials was 66% and 73%, respectively. The 7.2% of patients who developed cardiogenic shock in the GUSTO-I trial accounted for 58% of the overall deaths by 30 days.[11] Interestingly, the average LV ejection fraction (LVEF) at onset of shock is 30%, a degree of impairment that causes only mild to moderate symptoms in chronic myocardial ischemia.

Given the imperative for specialized multidisciplinary management, including surgical input, early prediction of shock is vital. In the GUSTO-I[11] and GUSTO-III[55] trials, 85–95% of cases of shock were predicted by patient age, systolic blood pressure, heart rate, or presenting Killip class. Jolly *et al.* showed that the extent of troponin elevation was predictive of postinfarction shock, cardiac arrest, and heart failure in 16,318 patients with non-STEMI.[56] Coronary angiographic findings at presentation have strong predictive value for mortality. In the SHOCK trial registry, 53% of patients with cardiogenic shock had triple-vessel disease and 16% had a left main stem lesion.[57]For left main stem occlusion, hospital mortality was 79%. Occlusion of a saphenous vein graft after CABG surgery resulted in 70% mortality. For isolated occlusion of the left anterior descending, circumflex, and right coronary arteries, mortality was 42%, 42%, and 37%, respectively. With TIMI grade 3 flow, mortality was 26% and reached 47–49% for TIMI grades 0–2 flow, reflecting inadequate perfusion. The likelihood of sustained reperfusion was greater after PPCI with than without stent deployment and was further improved with the use of an IABP and antiplatelet medication.[58]

Garcia-Alveras *et al.* reviewed 74 consecutive patients with cardiogenic shock complicating STEMI (mean age 62 years) admitted to a Spanish tertiary-care center, of whom 55 (74%) had PPCI and 7 (9%) underwent urgent cardiac transplantation.[59] The mean time between symptom onset and PPCI was an excessive 6.3 h. Even so, with post-PPCI TIMI grade 3, 2, and 0/1 flows, 1-year mortality or need for transplant was 38%, 92%, and 90%, respectively ($P<0.001$). On multivariate analysis, the most important predictors of poor outcome were age >75 years, LVEF <25%, and TIMI grade <3 flow. The presence of multivessel disease and presentation of shock <6 h after symptom onset showed a trend towards worse prognosis. Surprisingly, delay between symptom onset and PPCI was less important as a prognostic indicator. A simple risk score allocating one point to each of the four variables effectively predicted outcome (without transplant). Survival for scores of 0, 1, and 2 was 83%, 19%, and 6%, respectively ($P=0.001$).[59] Thus, with two variables, death was virtually inevitable unless the patient underwent a heart transplant. None of the patients with an occluded left main stem or post-PPCI LVEF <25% survived.[59] Spain has the highest rate of organ donation in Europe, and urgent transplantation provided an effective solution for deteriorating patients.

In a single-center UK experience of 113 patients with shock undergoing emergency PPCI, Sutton *et al.* identified age >70 years, previous infarction, shock complicating failed thrombolysis treatment, and multivessel disease to be associated with adverse outcomes.[60] Hospital mortality was 51%, and each of the first three factors was an independent predictor of death. PPCI was unsuccessful in 27% of patients, with TIMI grade 0/1 flow and >50% residual obstruction. Mortality for this group was 84% compared with 39% for a good angiographic result (TIMI grade 3). In contrast to the Spanish study discussed above, none of the patients were offered an LV assist device (LVAD) or transplantation.[60]

In 2010, Sleeper *et al.* published a Shock Severity Scoring System from the original SHOCK trial data (Figure 4 and Table 2).[61] Mortality ranged from 22% to 88%, depending on score category. Early revascularization was of greatest benefit in moderate-to-high risk patients. The severity of clinical hypoperfusion was a powerful predictor of poor outcome. Correspondingly, shock present on admission and hypoxic cerebral injury were both independent predictors of death.[61]

Attempts have been made to define objective clinical markers that predict death in patients with cardiogenic shock. Den Uil *et al.* showed that impaired microcirculation measured using sidestream dark field imaging (MicroScan™, Microvision Medical, Amsterdam, Netherlands) of sublingual perfused capillary density could predict poor outcome in patients with cardiogenic shock from acute myocardial infarction.[62]

Cardiac power as a prognostic indicator

The concept of power reserve in cardiogenic shock was explored more than 20 years ago by Tan and Littler.[63,64] Cardiac power is the product of simultaneously measured cardiac output and mean arterial blood pressure. Coupling of these parameters provides a measure of cardiac hydraulic pumping ability and represents the energy input that the arterial system receives from the heart at the level of the aortic root. One Watt (W) is the normal resting cardiac power output (CPO) of an average-sized adult. During stress or exercise, the normal heart can generate up to 6 W.[64] In shock, the basal resting cardiac performance is depressed, but can be improved by boosting heart rate, preload, and contractility from resting valves.

Tan and Littler used dobutamine infusion to determine whether early assessment of cardiac pumping reserve and cardiac power could predict outcome for

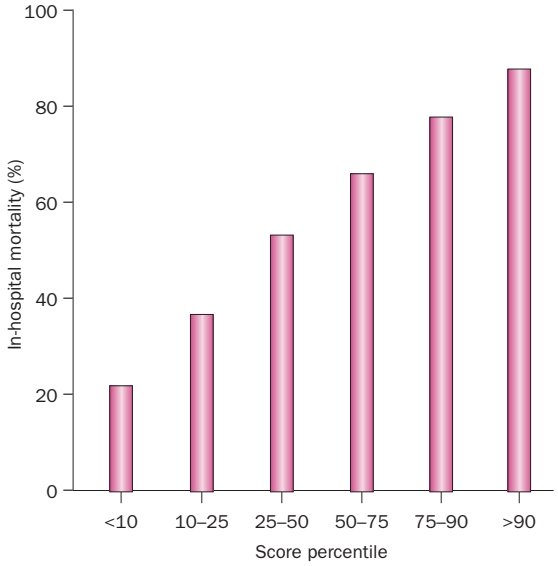

Figure 4 | In-hospital mortality in cardiogenic shock by stage I (clinical) severity category. See also Table 2. Reprinted from *American Heart Journal*, **160** (3), Sleeper, L. A. *et al.* A severity scoring system for risk assessment of patients with cardiogenic shock: a report from the SHOCK trial and registry. 443–450, © 2010, with permission from Elsevier.

Table 2 | Predictors of mortality in postinfarction shock*

Variable	Points
Anoxic brain damage	30
Cardiogenic shock on admission	6
Noninferior myocardial infarction	3
Hypoperfusion	14
Prior CABG surgery	7
Creatinine level ≥1.9 mg/dl	5
Age (years)‡	
≤45	0
46–50	2
51–55	5
56–60	7
61–65	10
66–70	12
71–75	15
76–80	17
81–85	20
86–90	22
>90	25
Systolic blood pressure (mmHg)§	
≤55	12
56–60	11
61–65	10
66–70	9
71–75	8
76–80	7
81–85	6
86–90	5
91–95	4
96–100	3
101–105	2
105–110	1
>110	0

*See also Figure 4. Stage 1 (clinical) scoring system without invasive hemodynamics. When left ventricular ejection fraction is added to this system, noninferior myocardial infarction has 0 points, and left ventricular ejection fraction has 10 points if ≤15%, 7 points if 16–25%, 5 points if 26–35%, 2 points if 36–45%, and 0 points if >45%. ‡When dichotomized to assess elderly risk, patients aged ≥75 years were assigned 0 points. §On support measures, including vasopressors, inotropes, and/or an intra-aortic balloon pump. Reprinted from *American Heart Journal*, **160** (3), Sleeper, L. A. *et al.* A severity scoring system for risk assessment of patients with cardiogenic shock: a report from the SHOCK trial and registry. 443–450, © 2010, with permission from Elsevier.

patients with cardiogenic shock.[63,64] In 28 patients with cardiogenic shock, the basal parameters of hemodynamic function were assessed using Swan–Ganz and radial arterial catheters.[64] Mean LVEF by echocardiography was 22%. All patients required inotropic support. Cardiac pumping reserve was determined by optimizing LV preload with fluid and evaluating the response to graded incremental dobutamine infusion (2.5–40 μg/kg/min) to a maximum of 15-40 μg/kg/min. None of the patients received an IABP. Maximum stimulation was assured when there was no further rise in CPO. Hemodynamic function was compared at basal resting state and during maximal dobutamine stimulation. Despite maximum medical therapy, 17 of the 28 patients died within 1 year. The average time between diagnosis of shock and death was 4 days. All 17 patients with a basal (predobutamine) resting cardiac index <1.3 l/min/m^2 and LV stroke work index <0.1 J/m^2 died, whereas all 11 with stroke work index >0.16 J/m^2 survived to 1 year. Survivors achieved maximal power output at lower rates of dobutamine infusion (18.2 μg/kg/min versus 25.6 μg/kg/min for those who died). Maximal dobutamine stimulation significantly increased heart rate, mean arterial pressure, stroke volume, cardiac index, and CPO for all patients. Right atrial pressure, and pulmonary and systemic vascular resistance all decreased. At basal resting heart rate, blood pressure, and central venous pressure did not differ between survivors and nonsurvivors. By contrast, all variables indicative of systolic cardiac performance (cardiac index, CPO, stroke volume, and stroke work indices) differed between survivors and nonsurvivors. The relationship between cardiac index and pulmonary artery wedge pressure, and between LV stroke work index and pulmonary artery wedge pressure, clearly defined survival potential from fatal outcome. All patients with basal resting CPO ≤0.35 W died, whereas those with cardiac reserve to generate peak power output >1 W with dobutamine survived. When reserve was limited so that maximal dobutamine produced ≤1 W, the patient died; thus, survival in cardiogenic shock is limited when peak power output in response to inotropic and chronotropic stimulation falls short of the normal value of the basal unstimulated state.[64] Cardiac

reserve estimated soon after the diagnosis of shock can, therefore, predict outcome.

In 2004, Fincke *et al.* published an analysis of 541 patients enrolled in the SHOCK trial, 406 (75%) of whom underwent right heart catheterization.[65] This study provided data that could be used to calculate basal CPO in 189 patients. By multivariate analysis, CPO was the strongest independent hemodynamic correlate of in-hospital mortality after adjusting for age and history of hypertension. An inverse correlation was observed between power index and patient age, and women had a lower power index than men (0.29 ± 0.11 W/m^2 versus 0.35 ± 0.15 W/m^2, $P = 0.005$). A CPO of <0.53 W was found to most-accurately predict in-hospital mortality.[65] The discrepancy between Tan's observed cut off for increased mortality (<1 W) and the cut off of <0.53 W demonstrated in the SHOCK trial can be explained by the fact that Tan used dobutamine to yield maximal power output. Subsequently Mendoza *et al.* reported a strong association between CPO and survival for other conditions, including ischemic cardiomyopathy, myocarditis, idiopathic dilated and Takotsubo cardiomyopathies, valvular heart disease, and arrhythmias. Cardiac power was a stronger predictor of poor outcome than cardiac index.[66]

This remarkable predictive capacity of cardiac power raises the question of futility of aggressive medical management for patients who cannot maintain sufficient cardiac power to sustain the circulation. For those with a basal cardiac index <1.3 l/min/m^2, LV stroke work index <0.1 J/m^2, or CPO <0.35W, death is inevitable unless the patient is supported by an LVAD or undergoes urgent cardiac transplant. If ineligible for either route, the patient should not be given medical treatment that might postpone death, but prolong suffering.

Medical management

Medical therapy for cardiogenic shock has been described in detail previously.[15,31,67] Most patients will have already undergone PPCI or thrombolysis and received antithrombotic therapy with heparin or antiplatelet agents. Thrombolysis provides lower rates of TIMI grade 3 reperfusion and is of no benefit in established shock. Optimal treatment is best achieved with invasive monitoring of arterial, central venous, and pulmonary arterial pressure, together with measurement of venous oxygen saturation and serum lactate. Echocardiography is used to evaluate ventricular function and screen for septal rupture, cardiac tamponade, or mitral regurgitation. Exclusion of endocarditis or aortic dissection is important. This approach allows careful manipulation of cardiac filling pressures and guides maximization of cardiac output in response to inotropes. Data derived from pulmonary artery catheterization allows prediction of risk and is advisable for all patients with cardiogenic shock.[68,69]

The goal of medical management is to rapidly restore cardiac output and prevent end-organ dysfunction. High-dose inotropes have potentially damaging effects when administered in the acute phase of shock—a time when LV unloading is preferable to reduce infarct size. Adrenergic inotropes elevate stroke work and wall tension, increase myocardial oxygen consumption, and deplete energy reserves. These changes can result in endocardial necrosis and impaired diastolic function with an overall negative effect on myocardial recovery. Nevertheless, because stunned myocardium remains partially responsive to inotropic support, these agents are first-line therapy during and after reperfusion.

For isolated LV failure, the ACC/AHA guidelines recommend beginning therapy with dobutamine unless profound hypotension is already present.[45] Dobutamine augments diastolic coronary blood flow to the ischemic area and boosts myocardial contractility, thereby increasing cardiac output and lowering LV filling pressure.[68] For more-profound hypotension (mean blood pressure <60 mmHg), dopamine or norepinephrine (norepinephrine) are employed early to rapidly restore cerebral and renal perfusion.[69] Dopamine's action is dose-dependent. Acting on both β-adrenergic and dopaminergic 1 receptors at low doses (1–4 μg/kg/min), the α-adrenergic effects escalate more rapidly than β-adrenergic effects as dose increases.[68,69] Dopamine raises blood pressure and cardiac output together with renal and hepatosplanchnic blood flow. However, dopamine also increases myocardial oxygen demand and exerts arrhythmogenic effects. Increasing the dose of dopamine to >20 μg/kg/min does not usually improve hemodynamic parameters further; this drug is more arrhythmogenic than norepinephrine.[69] For low systemic vascular resistance, the combination of dopamine and norepinephrine is usually effective. In the face of continued deterioration, other agents such as vasopressin, epinephrine, and phenylephrine are used pending insertion of a circulatory support system. High doses of α-adrenergic agents must be used with caution because of the risk of limb ischemia.

Acute RV failure can occur as a distinct entity through right coronary occlusion or secondary to abrupt worsening of ischemic LV failure with pulmonary hypertension.[70] Sudden deterioration in LV function, septal rupture, or papillary muscle rupture cause RV failure through increased afterload, displacement of the intraventricular septum towards the right, or pressure and volume overload. A right ventricle without pre-existing hypertrophy cannot generate pulmonary artery pressures exceeding 50–60 mmHg. If right atrial filling pressure is too low (<15 mmHg), RV ejection fraction (RVEF) will not be adequate. Positive pressure ventilation further impairs ejection and a fall in pulmonary artery pressure reflects worsening RVEF.[71]

Management of the acutely failing right ventricle or severe biventricular dysfunction is a complex process, based on optimization of volume status, reduction in RV afterload by selective pulmonary artery dilators, and inotropic support for both ventricles (Figure 5). Treatment is determined on the basis of invasive monitoring with a pulmonary artery catheter together with transthoracic or transesophageal echocardiography. In acute pulmonary hypertension, low-dose dobutamine (2–5 μg/kg/min) increases cardiac output and reduces pulmonary vascular resistance.[68,69] Higher doses induce tachycardia

and increase myocardial oxygen consumption without a further fall in pulmonary artery pressure.[68,69] Inhaled NO reduces pulmonary vascular resistance by increasing cyclic guanosine monophosphate and decreases pulmonary artery pressure.[72] Rapid inactivation by hemoglobin in the capillaries prevents systemic vasodilatation. The combination of dobutamine with inhaled NO increases cardiac output and the ratio of partial pressure of oxygen to fraction of inspired oxygen while reducing pulmonary vascular resistance.[73] The selective phosphodiesterase 3 inhibitor milrinone is an inodilator that decreases pulmonary vascular resistance and increases RVEF, but its use is limited by its systemic vasodilatory effect.[74]Milrinone can be combined with NO to augment pulmonary vasodilation while minimizing tachyarrhythmias.[70] Norepinephrine conveys inotropy via β-agonism, but is also an α1 agonist that elevates RV perfusion pressure and cardiac output.[69]

Levosimendan has global vasodilatory and anti-ischemic properties mediated by activation of adenosine-triphosophate-sensitive potassium channels in the mitrochondria of smooth muscle cells and by endothelial inhibition.[75] This drug sensitizes cardiac troponin C to the effects of intracellular calcium, thereby increasing contractility without an increase in myocardial oxygen consumption. The pulmonary vasodilatory effects lower pulmonary vascular resistance and increase cardiac output in acute heart failure.[75] By contrast prostacyclins, are not used in cardiogenic shock because of their systemic vasodilatory effects. Both inotropes and vasodilators are complemented by the use of an IABP. Through a reduction in pulmonary artery pressure, the IABP can improve systemic blood pressure, RV efficiency, and coronary blood flow. The use of the IABP is described in greater detail in Part 2 of this Review.[33] Both the IABP and optimum pharmacological therapy are required during the acute and postoperative management of ventricular septal and papillary muscle rupture.

When the patient is weaned from NO therapy, rebound elevation of pulmonary arterial pressure can prove problematic, particularly in those with an LVAD. In this case, sildenafil (a phosphodiesterase 5 inhibitor) can be used to block degradation of cGMP and selectively decrease pulmonary artery pressure with an increase in cardiac output.[76] The effects of sildenafil begin within 30 min of infusion, with a peak effect at around 60 min and a half-life of 4 h.

Owing to potential adverse effects, mechanical ventilation must be used carefully in patients with cardiogenic shock. The lowest tidal volume and positive end expiratory pressure are used to achieve oxygen saturations >92%.[71] Hypercapnia (or hypercarbia) can increase pulmonary artery pressure and worsen RV function through vasoconstriction. By contrast, hyperventilation decreases CO_2 level and pulmonary artery pressure. Hyperventilation is achieved by increasing the frequency of ventilation not the tidal volume.

For patients receiving medical therapy and an IABP, serum lactate level >11 mmol/l, base deficit of >12 mmol/l, mean arterial pressure <55 mmHg, urine output <50 ml

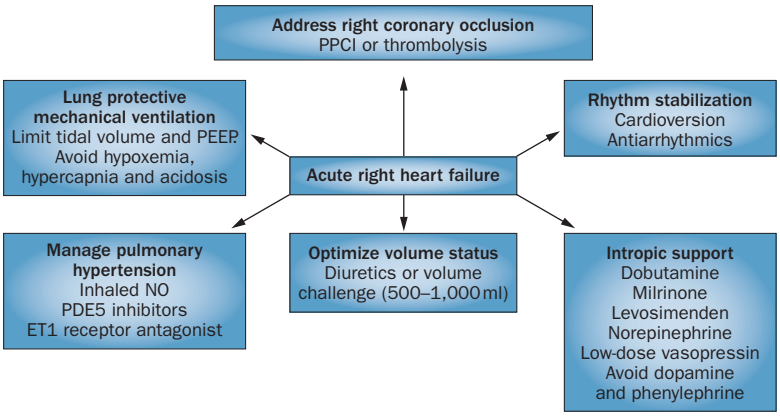

Figure 5 | Medical management of acute right ventricular dysfunction after myocardial infarction. Abbreviations: ET1, endothelin 1; NO; nitric oxide; PDE5, phosphodiesterase 5; PEEP, positive end-expiratory pressure; PPCI, primary percutaneous coronary intervention.

over 2 h, and infusion of epinephrine or norepinephrine >0.4 mg/kg/min herald impending death. Left atrial pressure >17 mmHg and mixed venous saturation <65% reinforce the likelihood of poor outcome. These patients have reached the stage of profound shock with little chance of recovery without urgent mechanical restoration of systemic blood flow. Patients with refractory or rapidly deteriorating shock should receive multidisciplinary care, the scope and outcomes of which are considered in Part 2 of this Review.[33]

Effects of statin therapy

In patients with shock, acute inflammation and stent insertion can cause platelet activation and propagation of thrombus.[77] As well as lowering lipid levels, statins are know to have favorable effects on platelet adhesion, endothelial function, inflammation, and thrombosis.[78,79] Garot *et al.* suggested that preinfarction treatment with statins might have a protective effect in patients with extensive infarction where shock seems inevitable.[77] Lipid lowering was already known to have a beneficial effect on early mortality after ACS and on myocardial perfusion during Q-wave infarction.[80] Statins reduce CRP level and can prevent vascular events in patients with elevated CRP.[81,82] Garot *et al.* retrospectively collected data from 111 consecutive patients who underwent emergency PPCI for STEMI complicated by cardiogenic shock between 2000 and 2008.[77] Thirty patients (27%) were receiving a statin at the time of the acute event and were more likely to have diabetes, hypercholesterolemia, hypertension, and prior STEMI or PCI. They were also more likely to be receiving β-blockers, an angiotensin-converting-enzyme inhibitor, aspirin, and clopidogrel. Prompt PPCI of the culprit artery was performed after a loading dose of ticlopidine (in 2000–1) or clopidogrel (after 2002) and full supportive medical treatment was provided for shock. The results were intriguing in that statin therapy at the time of the intervention was associated with a substantial in-hospital mortality benefit when compared with no statin therapy (46.7% versus 70.4%, $P = 0.027$). Comparison of the

groups showed no significant differences in other major clinical events. Collectively, the composite end point of death, STEMI, stroke and repeat revascularization was 56.7% for the statin group and 75.3% for the control group ($P = 0.056$). Statin therapy at the time of PPCI for STEMI with cardiogenic shock remained an independent predictor for 6-month survival (OR 0.32, 95% CI 0.11–0.89, $P = 0.029$).[77] The extent of mortality reduction exceeds that in statin-treated patients presenting with STEMI and ACS without shock.[83]

In support of these findings, the AMIS Plus Registry[7] showed that lipid-lowering treatment and PPCI were associated with lower mortality among all patients with ACS, and lower rates of in-hospital cardiogenic shock among patients who did not have shock on admission. The National Registry of Myocardial Infarction investigators reported that early postinfarction statin therapy was associated with a lower than expected incidence of cardiogenic shock, arrhythmias, cardiac arrest, and cardiac rupture in more than 300,000 patients with STEMI.[31] In addition, the PRISM investigators showed that the benefit of statin pretreatment in ACS was abrogated by discontinuing statin treatment in hospital soon after onset of symptoms.[84] By stark contrast, a meta-analysis of randomized trials encompassing 13,024 patients with ACS suggested that statin therapy is not associated with any reduction in mortality, STEMI, stroke, or repeat revascularization at 4 months.[85]

Therapeutic hypothermia

Ventricular fibrillation is a frequent terminal event in ACS with cardiogenic shock,[4] with <10% of resuscitated patients regaining an independent life style after the event.[86] The duration of unsupported 'cardiac arrest' and the effectiveness of resuscitative efforts determine the extent of immediate neuronal necrosis and influence the intensity of metabolic derangement, ischemia–reperfusion injury, and apoptosis, which cause delayed cerebral injury within 72 h.[87] The rationale for mild therapeutic hypothermia in patients resuscitated after ventricular fibrillation lies in the prevention of delayed reperfusion injury. Cooling reduces cerebral metabolism by 5% for every degree of temperature reduction.[88] Energy and oxygen consumption are decreased and high energy phosphates preserved. Release of excitatory amino acids and the oxygen free radical burst are attenuated. As a result, cytokine release, the inflammatory response, and calcium mediated activation of proteases and caspases are less severe. Brain swelling is reduced by a membrane stabilizing effect.[87]

Hypothermia was first applied after cardiac arrest in 1958[89,90] and is now used routinely to protect the brain during cardiac surgery. Evidence for clinical effectiveness emanates from two prospective randomized trials that focused on patients with out-of-hospital cardiac arrest. Published simultaneously in the *New England Journal of Medicine* in 2001, both were restricted to patients with ventricular fibrillation as the initial rhythm.[88,91] In both studies, the temperature of the patients was reduced to 32–34°C. The Hypothermia after Cardiac Arrest Study Group[88] in Europe reported a good 'cerebral performance category' rating in 55% of treated patients versus 39% of those kept normothermic. Mortality was 41% versus 55% at 6 months.[88] Bernard *et al.* reported survival to hospital discharge with "good outcome" in 49% of treated patients versus 26% of controls (OR for improved recovery was 2.65 [cardiac index 1.02–6.88]).[91]

Both studies support the use of hypothermia following resuscitation and neither reported adverse effects from the process. As a result, both the International Liaison Committee on resuscitation and the European Resuscitation Council recommend hypothermia for patients who remain comatose following resuscitation for ventricular arrhythmias.[92,93] Standard support measures, including positive pressure ventilation, optimal oxygenation and carbon dioxide elimination, maintenance of cerebral perfusion pressure (mean >90 mmHg), and blood glucose levels, are applied.[94] The patient is positioned at 30°, head up, with a central venous pressure of ≤12 mmHg. Mild acidosis and insulin resistance can occur; therefore, frequent assays of glucose, potassium, and magnesium levels are needed. A neuromuscular blocker can be used to prevent shivering and an inappropriate increase in metabolic rate. Theoretically, the faster hypothermia can be achieved the better, but rewarming must be performed gradually over 12 h.

Currently the indications (class I evidence) for therapeutic hypothermia after ventricular fibrillation are: witnessed, documented cardiac arrest with duration of resuscitation <30 min; return of spontaneous circulation to systolic blood pressure >90 mmHg with or without vasopressors; unresponsive after return of spontaneous circulation (Glasgow Coma Scale <10 without response to verbal commands); age >18; and endotracheal intubation and mechanical ventilation in place.[94] Clear contraindications are: an underlying condition that precludes intensive care, such as advanced malignancy; time to beginning resuscitation >10 min; time to return of spontaneous circulation >30 min; and time to initiation of hypothermia >6 h.[88,91]

Prediction of neurological outcome is particularly difficult for resuscitated patients with cardiogenic shock who remain unconscious. Clinical findings and CT have limited prognostic value within the first 72 h. Electroencephalography and somatosensory-evoked potentials are more informative.[94] With cerebral edema, persistent low cardiac output, arterial hypotension, and raised venous pressure, the outlook for the patient is grim. Only rapid restoration of cardiac (or LVAD) output and adequate cerebral perfusion pressure can provide the basis for recovery.

Conclusions

In the past 10 years, Europe and North America have diverted vast resources towards the provision of integrated and expedited systems of emergency care for patients with acute STEMI. Unfortunately a substantial gap persists between evidence-based recommendations and clinical practice. In particular, around 25% of patients do not benefit from reperfusion therapy and as few as 15%

receive PCI within 2 h of pain onset. As a result, cardiogenic shock still threatens life in 5–10% of patients with STEMI, particularly in the presence of inappropriately low peripheral vascular resistance. An aggressive management plan is necessary to interrupt the vicious cycle and prevent metabolic derangement and end-organ dysfunction.

Shock can be predicted. Accordingly, high-risk patients should be placed under the care of a multidisciplinary shock team as soon as possible, even when this involves interhospital transfer. Detailed management of primary left, right, or biventricular dysfunction requires invasive monitoring and access to pulmonary vasodilators. An IABP can improve borderline hemodynamics (a good prognostic sign), but is of dubious value in established shock. Some revascularized patients will recover as myocardial stunning resolves. For others, survival depends upon mechanical circulatory support or an urgent cardiac transplant. To realize substantial improvements in shock survival, the 'Heart Attack Center' concept must be expanded and focused on regional cardiac surgical units where expertise and invasive techniques are readily available.

Review criteria

We used PubMed to review English-language literature on cardiogenic shock complicating acute coronary syndromes published between 1995 and 2011. Search terms included "coronary syndromes", "myocardial infarction", and "cardiogenic shock" together with "primary angioplasty", "medical therapy", "SHOCK trial", "thrombolysis", "intra-aortic balloon pump", and "guidelines". The reference lists of identified articles were also reviewed.

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Author contributions

S. Westaby researched data for and wrote the article. All authors contributed to the discussion of content and reviewed the manuscript prior to submission.