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Primary angioplasty for patients in cardiogenic shock: optimal management

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Abstract:

Cardiogenic shock complicates approximately 5-10% of all myocardial infarction and remains the most common cause of death amongst these patients. Over the past few decades, the mortality associated with cardiogenic shock has improved with the introduction of early revascularization although there is limited data in patients with triple-vessel disease and left main stem disease. In more recent years, there have been a number of advances in the mechanical circulatory support devices that can help improve the haemodynamics of patients in cardiogenic shock. Despite these advances, together with progress in the use of inotropes and vasopressors, cardiogenic shock remains associated with a high morbidity and mortality. This review will outline the management of cardiogenic shock complicating acute myocardial infarction with major focus on revascularization techniques and the use of mechanical circulatory support devices.

Key Words: myocardial infarction; cardiogenic shock; coronary intervention; mechanical circulatory support

Introduction

Cardiogenic shock is a clinical condition of inadequate end-organ perfusion due to cardiac dysfunction (Table 1). It most commonly occurs in the setting of acute myocardial infarction with left ventricular failure (~80% cases)[1,2], but can also be caused by right ventricular infarction or late mechanical complications, such as acute mitral regurgitation or ventricular rupture (septal or free wall). Non-infarct related cardiogenic shock is comparatively rare, and may result from decompensated valvular heart disease and arrhythmias, to name a few mechanisms.

The pathophysiology of cardiogenic shock is complex and we will touch on this briefly here; myocardial ischaemia induces marked depression of myocardial contractility, which sets into motion a downward spiral of reduced cardiac output and hypotension, which in turn drives further myocardial ischaemia. This severe cardiac dysfunction causes tissue hypoperfusion and may eventually result in death if the vicious cycle is not adequately interrupted by timely treatment measures. In addition to the physiological impairment of myocardial function, cardiogenic shock also induces deleterious systemic responses including pathological vasodilation (after compensatory vasoconstriction), systemic inflammation with capillary leakage and impairment of the microcirculation[1,3].

This review will look at the optimal management of patients with cardiogenic shock complicating acute myocardial infarction with particular focus on revascularisation therapy and the use of mechanical circulatory support devices.

Incidence and prognosis of cardiogenic shock

Cardiogenic shock complicates 5-15% of cases of acute myocardial infarction, and despite advances in acute care there remains the same incidence (~60,000 – 70,000 patients per year in Europe) [2,4].

Historically, myocardial infarction complicated by cardiogenic shock was associated with a mortality rate of 80-90%[5]. However, with advances in coronary reperfusion techniques over the past few decades, especially with the introduction of primary percutaneous percutaneous coronary intervention, the mortality rate has improved to below 50%[4,6-12]. The trend toward better outcomes may also be due to greatly awareness of the need for timely treatment, improvements in the medical care of haemodynamically unstable patients as well as the use of mechanical support devices, though this has not yet been clearly demonstrated.

Despite this high mortality, it is important to note that patients with cardiogenic shock that survive to discharge have a long-term outcome similar to patients without cardiogenic shock, with a good functional outcome at one-year[13,14]. This highlights the importance of improving early survival of patients in cardiogenic shock.

Management

(a) Myocardial Reperfusion

There is evidence that the high mortality associated with cardiogenic shock has improved over time[7,9,11,15,16]. This benefit is thought to be due to increased use of coronary revascularisation strategies, which by restoring flow to the ischaemic myocardium, can limit infarct size, as well as interrupt the downward spiral that characterises cardiogenic shock[7,9,15].

As such, the cornerstone of management in cardiogenic shock complicating acute myocardial infarction is prompt revascularization as highlighted in the 'Should we emergently revascularize Occluded Coronaries for Cardiogenic Shock' (SHOCK) trial[17]. Patients with cardiogenic shock were randomly assigned to initial medical stabilization or early revascularization (PCI or CABG within 6 hours of randomization and 18 hours of onset of shock). The primary endpoint (all cause mortality at 30 days) did not differ between the initial medical stabilization and early revascularization group, however there was a significant decrease in mortality at one and six years in patients assigned to early revascularization[14,17,18]. The number needed to save one life at one year by early revascularization in comparison to initial medical stabilization is less than eight, and this benefit remained with long-term follow up (Figure 1).

The same trial also demonstrated the importance of timely revascularization, with an increasing long-term mortality as time to revascularization increased from 0 to 8 hours. However, the overall benefit of revascularization in cardiogenic shock may extend past the traditional 12 hour window post-myocardial infarction to

potentially as long as 54 hours after myocardial infarction and 18 hours after shock onset[18,19].

In current European Society of Cardiology guidelines, early revascularization by either PCI or CABG for cardiogenic shock is recommended[20] but despite general increased tends to perform early revascularization, real-world rates remain relatively low (50-70%)[2,14,21].

- Anti-platelet & anti-thrombotic medication

The clinical syndrome of cardiogenic shock impairs enteral absorption which may result in suboptimal bioavailability of oral agents[22]. In addition, patients in cardiogenic shock often require mechanical ventilation and this poses problems with oral medication (overcome with nasogastric tube insertion and delivery of crushed tablets) which further complicates matters[23]. In general, patients with cardiogenic shock should be loaded with aspirin as routinely recommended in acute coronary syndromes – however, administration of oral P2Y12 inhibitors should be deferred until coronary angiography as CABG may be immediately required[20]. Although not yet licensed, cangrelor (a fast-acting and rapidly reversable intravenous P2Y12 inhibitor) may prove to useful in these situations where oral anti-platelet administration may be delayed or unreliable[24].

Given the above problems with oral administration of anti-platelet agents, glycoprotein IIb/IIIa-inhibitors may be beneficial in cardiogenic shock. Observational data suggests a potential mortality benefit with their use in cardiogenic shock, but one randomised trial (of only 80 patients) did not

demonstrate any benefit of routine abciximab use compared to use at the discretion of the interventionalist[25]. As such, current guidelines recommend use of GP IIb/IIIa-inhibitors as bailout therapy for thrombotic complications during PCI and whilst limiting the recommendation for their routine use during PCI for STEMI[20,26].

During PCI, adjunctive anticoagulation with unfractionated heparin, low-molecular weight heparin or direct thrombin inhibitors should be co-administered with antiplatelet therapy. With a lack of specific randomised trials in cardiogenic shock, the same recommendations apply as for other types of acute coronary syndrome[20].

- What is the ideal method of early revascularization?

Coronary reperfusion can be achieved with thrombolytic therapy (in patients with STEMI), PCI, or emergency CABG. There is a paucity of randomized data assessing the efficacy of thrombolytic therapy compared to either placebo or PCI in patients who have cardiogenic shock at presentation. The available studies have demonstrated some benefit of thrombolytic therapy compared to placebo, but superiority of PCI or CABG compared to thrombolytic therapy[18,27,28]. Therefore, thrombolytic therapy is recommended only if PCI is not possible or if it is delayed (>90 min) and presenting early after symptom onset (<3 hours), followed by emergent transfer to a PCI facility[20].

The prognosis of patients with cardiogenic shock is related to the procedural success of PCI and importantly, patients with cardiogenic shock are less likely to

have successful PCI than patients without shock[16]. Since the recruitment of the SHOCK trial (where only 37% of patients undergoing PCI received stents) there have been many advances in PCI; first bare-metal stents and more recently drug-eluting stents have been associated with associated with a greater likelihood of complete revascularization, a higher incidence of TIMI 3 flow and improved survival in cardiogenic shock[29-31].

In the current European guidelines, infarct related cardiogenic shock is an indication for emergency revascularization with either PCI or CABG, if the patient has suitable coronary anatomy[26]. To date, there exist no randomized clinical trials that have compared PCI and CABG in patients with cardiogenic shock. In the SHOCK trial, the protocol recommended CABG in patients with a left main coronary stenosis of ≥ 50%, ≥2 total or subtotal occlusions, stenosis of >90% in two non-infarct-related major arteries, or stenosis unsuitable for PCI, as well as in patients whose PCI was unsuccessful[17]. However, this decision was made on an individual basis by site investigators and PCI was often performed in patients with three vessel disease. Among the 128 cardiogenic shock patients receiving emergency revascularization (63% PCI and 37% CABG) there was a similar mortality at 30 days, one year and six years regardless of method of revascularization[14,17,18]. However, in current practice, very few patients with cardiogenic shock and three-vessel disease are referred for CABG, ranging from 3.2% to 8.8%[32], possibly reflecting the real-world difficulties of arranging emergency CABG for patients with cardiogenic shock who often present overnight and at weekends.

In summary, in patients with cardiogenic shock complicating acute myocardial infarction PCI allows prompt restoration of coronary flow which may arrest the vicious cycle of myocardial ischaemia and reduced cardiac output. If there is likely to be a significant delay to PCI, thrombolytic therapy should be considered. Finally, urgent CABG should also be considered in the case of unsuccessful PCI, left main disease, three-vessel disease, or in the presence of severe valvular disease and mechanical complications of myocardial infarction[20,26].

- Revascularisation of multi-vessel coronary artery disease?

The majority (70-80%) of patients with cardiogenic shock complicating acute myocardial infarction have multi-vessel disease, which in itself is associated with a higher mortality compared to single vessel disease[4,33-35]. As discussed above, the current evidence does not clearly identify an optimal revascularisation strategy for cardiogenic shock patients with multi-vessel disease. There are four observational reports comparing PCI vs. CABG which suggest similar mortality rates[36]; however in current practice, CABG is rarely performed in patients with cardiogenic shock[2,33].

Due to the lack of reliable prospective clinical data, guideline recommendations have been based on physiological principles to arrest the downward spiral of myocardial ischaemia and reduced cardiac output. In contrast to the recommendations for haemodynamically stable patients, current guidelines recommend PCI to the culprit lesion followed by PCI to critical lesions (>90% stenosis) or those with unstable appearances (possible thrombus or lesion

disruption) if there is ongoing ischaemia or haemodynamic instability[20,26]. The ongoing prospective, multi-centre CULPRIT-SHOCK trial will company culprit-vessel treatment with complete revascularisation in cardiogenic shock.

- Revascularisation of left main stem disease?

There are no current guidelines on revascularisation for patients with left main coronary artery (LMCA) related myocardial infarction complicated with cardiogenic shock. In recent years, together with the increased use of PCI for LMCA in the stable setting, PCI has become the preferred method of revascularisation for patients with LMCA-related acute coronary syndromes[37]. The combined SHOCK trial and registry only include 21 patients with LMCA-related myocardial infarction and there is significant treatment bias in favour of PCI (as many severely unstable patients will be unsuitable for surgical revascularisation), as such it is not possible to draw any valid conclusion from their outcomes[14,38].

Given the paucity of evidence, the decision to perform CABG or PCI in patients with cardiogenic shock and LMCA disease should be taken on an individual basis taking into account the clinical stability of the patient, coronary anatomy, operator experience and potential risks of either strategy[20,26].

(b) Pharmacological Management

There have been recent summaries on the use of inotropes and vasopressor agents in cardiogenic shock[39,40], and a review of this is beyond the scope of this article. In brief, regardless of the decision to revascularise, pharmacological stabilisation of the patient in cardiogenic shock is a complex process which requires judicious use of fluids to obtain euvolaemia, vasopressors and inotropes with the aim of preventing multi-organ hypoperfusion and ultimately failure. Despite their almost ubiquitous use and clear effect on haemodynamics, there are no randomised data showing a prognostic benefit with the use of inotropes or vasopressors in the setting of cardiogenic shock. Furthermore, as catecholeamines increase myocardial oxygen consumption and vasoconstrictors may impair the microcirculation as well as tissue perfusion, their use should be restricted to the lowest possible dose for the shortest possible duration.

(c) Mechanical Circulatory Support

Mechanical circulatory support should be instituted in patients with cardiogenic shock who remain haemodynamically unstable despite revascularisation and inotrope therapy[41,42]. In general, mechanical circulatory support devices can potentially be of benefit in cardiogenic shock by maintaining organ perfusion whist reducing myocardial oxygen demand and augmenting coronary blood flow. Historically, the intra-aortic balloon pump has been the only mechanical circulatory support device available to interventionalists during high risk PCI such as with a patient in cardiogenic shock[33]. More recently, a number of new devices have recently become available which include axial flow pumps (e.g. Impella), left atrial to femoral artery bypass pumps (e.g. TandemHeart); and new devices for the implementation of extracorporeal membrane oxygenation (ECMO) (Figure 2).

- Intra-Aortic Balloon Pump (IABP)

The IABP remains the most commonly used form of circulatory support in cardiogenic shock. The IABP has two major components, a balloon catheter (filled with helium) and a pump console to control the balloon (Figure 2a). It is commonly inserted via the femoral artery, and the balloon inflates with the onset of diastole (around the middle of the T-wave) and deflates at the onset of left ventricular systole (at the peak of the R-wave)[41]. This mechanism provides haemodynamic support by increasing diastolic perfusion pressure in the coronary arteries and reducing left ventricular afterload, thereby reducing wall tension and

myocardial oxygen demand resulting in a modest elevation in cardiac output (0.3-0.5 l/min).

The first randomised controlled trial comparing IABP therapy to conservative management in 45 patients with cardiogenic shock found a reduction in BNP but no change in clinical outcomes (IABP SHOCK)[43]. This was followed with a larger trial of 600 patients with acute myocardial infarction complicated by cardiogenic shock and randomised patients to either IABP or standard therapy (IABP SHOCK II), which did not demonstrate a significant reduction in mortality at 30 days or 12 months (although 86.6% of IABPs were inserted post-PCI)[44]. Current ESC guidelines advise against the *routine* use of IABP during PCI in patients with cardiogenic shock, and limit their recommendations of its use to patients with cardiogenic shock due mechanical complications of myocardial infarction awaiting surgery[20,26].

- Left atrial to aorta assist devices (i.e. TandemHeart)

The Tandem Heart is a percutaneously inserted circulatory assist device that pumps blood extracorporeally from the left atrium to the iliofemoral arterial system via a transeptally placed atrial cannula, bypassing the left ventricle (Figure 2b)[41]. By working in parallel with the left ventricle, this results in a reduction of LV preload, filling pressures, wall stress and myocardial oxygen demand whilst increasing arterial blood pressure and systemic perfusion (increasing cardiac output up to 4 l/min).

A retrospective analysis of patients with refractory cardiogenic shock demonstrated that the TandemHeart improved haemodynamics[45]. This was following by two small randomised controlled trials which demonstrated that the TandemHeart improved haemodynamics to a greater extent than IABP, but at a cost of increased complications such as severe bleeding, limb ischaemia and arrhythmias[46,47].

- Left Ventricle to Aorta Assist Device (i.e. Impella)

The Impella is a non-pulsatile axial flow Archimedes-screw pump designed to propel blood from the LV into the ascending aorta in series with the LV(Figure 2c)[41]. This results in direct unloading of the LV, an increase in forward flow associated with reduction in myocardial oxygen consumption, improvement in mean arterial pressure and reduction in pulmonary capillary wedge pressure. A number of different version are available: the percutaneous 12-F (Impella 2.5) device and 21-F (Impella 5.0) surgical cut down device, which provide maximal flow rates of 2.5 and 5.0 l/min respectively. More recently, a percutaneous 14-F (Impella CP) device provides an intermediate level of support similar to the TandemHeart (up to 4 l/min). Complications of Impella support include bleeding at the vascular access site, haemolysis and pericardial tamponade, whereas use is contraindicated in patients with severe peripheral vascular disease, presence of a mechanical aortic valve or a severely calcified aortic valve.

There have been a number of studies demonstrating the safety and haemodynamic benefits of Impella insertion in cardiogenic shock. Recently, in the

Efficacy Study of LV Assist Device to Treat Patients with Cardiogenic Shock (ISAR-SHOCK) trial, the Impella 2.5 was associated with a larger increase in cardiac output and mean arterial pressure compared with IABP, however, the there was no difference in mortality between the two groups[48].

- Extracorporeal membrane oxygenation (ECMO)

The most comprehensive percutaneously inserted mechanical support is provided by ECMO, which can either provide oxygenation only (veno-veno [V-V] ECMO) or oxygenation with circulatory support (veno-arterial [V-A] ECMO). In cases of biventricular failure, V-A ECMO is the MCS of choice and is able to provide 7 l/min of non-pulsatile flow[41]. Similar to cardiopulmonary bypass circuits, V-A ECMO involves a circuit composed of a centrifugal pump, a heat exchanger and a membrane oxygenator. A venous cannula (20-F) drains blood from the right atrium into a membrane oxygenator for gas exchange, and then oxygenated blood is pumped into the patient via an arterial cannula (17-F) (Figure 2d).

The main limitation of ECMO is that the retrograde flow of the peripheral arterial cannulation increases afterload, increasing myocardial oxygen demand and can precipitate pulmonary oedema. Conversely, increasing ECMO flow rates in this situation will worsen the haemodynamic situation. A number of techniques can be used to improve LV emptying including concurrent Impella usage, or venting with a pigtail catheter in the LV, or creation of an atrial septal defect. Failing resolution, central ECMO can be used with direct cannulation of the LV, LA or pulmonary artery.

There are non-randomised data using historic controls suggesting that ECMO use for patients with myocardial infarction related cardiogenic shock can improve survival[49-51]. Although promising, using historic controls rather than a prospective randomised study does not account for other potential temporal advances in management.

Although ECMO may improve survival of patients in cardiogenic shock, there is significant procedural morbidity: common complications include limb ischaemia, renal failure, bleeding and infection[41].

Conclusion

Early revascularisation remains the cornerstone of management of patients with cardiogenic shock, although the optimal method remains unclear – patients who have the earliest revascularisation have the best outcomes. In addition to restoring myocardial perfusion, management of patients with cardiogenic shock requires haemodynamic stabilisation – predominantly through careful use of vasopressors and inotropes which may increase myocardial oxygen demand and thereby worsening ischaemia. In more recent years, a number of mechanical circulatory support devices have emerged that provide promising adjuvant therapies for patients in cardiogenic shock. These will allow for angioplasty to be performed in an improved haemodynamic setting and provide a bridge to potential recovery.

Table 1. The diagnostic criteria of cardiogenic shock

Cardiogenic Shock
Hypotension:
- **systolic blood pressure <90 mmHg for >30 min, or**
- **vasopressors required to achieve a blood pressure ≥90 mmHg**
Elevated Left Ventricular Filling Pressures:
- **Pulmonary Congestion, or**
- **Adequate or elevated filling pressures** (wedge pressure >20 mmHg)
Signs of impaired organ perfusion: (at least one of the following)
- **Altered mental status**
- **Cold, clammy skin**
- **Oliguria**
- **Increased serum-lactate**

Figure 1: Kaplan-Meier Long-term Survival of All Patients in the The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial modified from Hochman et al.[14]

Among all patients, the survival rates in the early revascularization (ERV) and initial medical stabilization (IMS) groups, respectively, were 41.4% vs 28.3% at 3 years and 32.8% vs 19.6% at 6 years (*P* = .03).

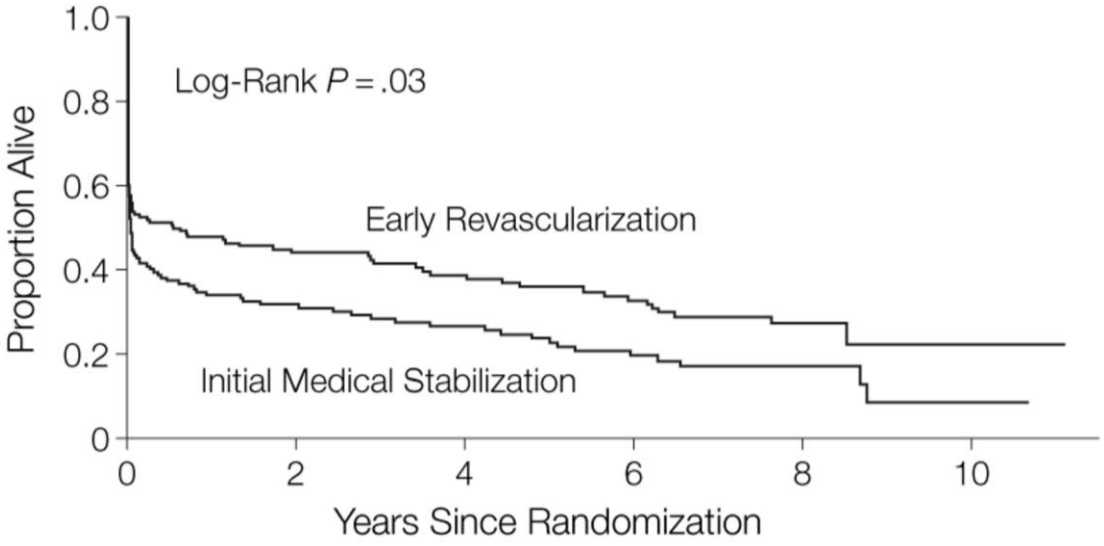
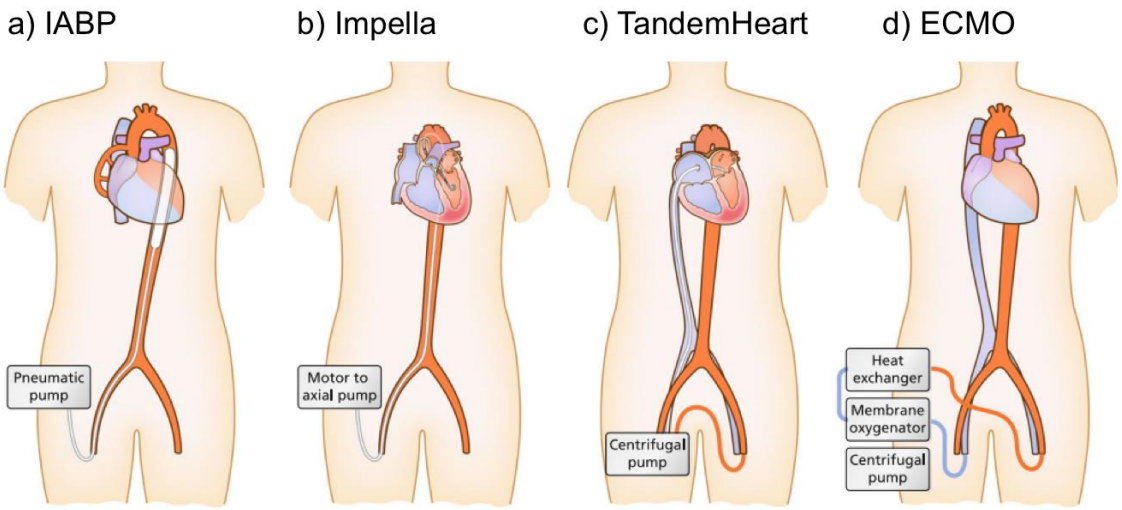


Figure 2: Peripheral ventricular assist devices, modified from Thiele et al.[52]
Schematic diagram to demonstrate the access site and mechanism of action of:

a) Intra-aortic balloon pump (IABP)
b) Impella
c) TandemHeart
d) Extracorporeal membrane oxygenation (ECMO)



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