DEBATES AND CHALLENGES IN THE MANAGEMENT OF CARDIOGENIC SHOCK DUE TO ST ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT

Cardiogenic shock is a complex hemodynamically complex syndrome characterized by reduced cardiac output that often culminates in multi-organ failure and death. Despite recent advances, clinical outcomes remain poor, with mortality rates exceeding 40%. Vascular remodeling, vasopressors, anticonvulsants, fluids, mechanical circulation support, and general intensive care measures are widely used for the management of CS. However, there is only limited evidence for any of the treatment strategies listed above except for remodeling and the relative ineffectiveness of intra-aortic balloon infusion. A few experiments were completed and a randomized clinical trial focused on these patients, reflecting the challenges of conducting trials in this severely ill population. We have little evidence to guide treatment. As a result, the controversy surrounding treatment strategies is more common in these patients than conclusions.
INTRODUCTION

Recent data suggests that mortality improvement among ST-elevation myocardial infarction (STEMI) have staggered in recent years (Shah et al., 2015). The incidence of CS complicating AMI is still in the range of 3–13% (Aissaoui et al., 2012; Jeger et al., 2008; Backhaus et al., 2018; Rathod et al., 2018). Recent registries showed contradictory data with a decreased, stable, or even increased incidence of CS (Aissaoui et al., 2012; Jeger et al., 2008; Backhaus et al., 2018; Rathod et al., 2018). STEMI complicated by CS remains one of the most challenging conditions to manage. Mortality rates are high with up to one half of all patients dying before hospital discharge (Anderson et al., 2013; Babaev et al., 2005). Timely reperfusion with primary percutaneous intervention (PCI) is a class I recommendation in the American college of cardiology foundation/ American heart association guidelines for the management of patients with STEMI complicated by CS (Yancy et al., 2013). Despite continued improvement in the door-to-balloon time since the implementation of the guideline (Menees et al, 2014); however, mortality rates remain high. We discuss different management strategies and challenges that limit progress in the treatment of CS. Ventricular failure subsequent to acute myocardial infarction (AMI) remains the most frequent cause of cardiogenic shock (CS) accounting for more than 80% of cases. Mechanical complications of AMI represent less common causes of CS (ventricular septal rupture (4%), free wall rupture (2%), and acute coronary regurgitation (7%) (Hochman et al., 2000).

DEFINITION OF CARDIogenic SHOCK

In general, CS is defined as a condition of hypovolemia and hypoxia of the critical end organ due to primary cardiac disturbances (Van Diepen et al., 2017). In practice, a diagnosis of CS can be made on the basis of clinical criteria such as persistent hypotension without adequate response to replace volume and clinical features associated with decreased blood flow in the end organ such as cold extremities, oliguria or altered mental state. In addition, biochemical features of tissue perfusion deficiency such as arterial lactate elevation are usually present (Table 1).

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<tr>
<td>Study arms</td>
<td>Emergent revascularization vs. initial medical stabilization in AMI-CS</td>
<td>IABP vs. optimal medical therapy in AMI-CS treated with early revascularization (PCI or CABG)</td>
<td>Impella CP vs. IABP in mechanically ventilated patients with AMI complicated by severe CS</td>
<td>Culprit lesion PCI (with option of staged revascularization) vs. Ad hoc multivessel PCI in AMI-CS with multivessel CAD</td>
</tr>
<tr>
<td>Sample size</td>
<td>302</td>
<td>600</td>
<td>48</td>
<td>786</td>
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### Clinical criteria

- SBP <90 mm Hg for 30 mins OR vasopressors to maintain SBP $90 mm Hg AND
- End-organ hypoperfusion (urine output <30 ml/h)

### Sustained SBP <90 mm Hg for 30 min or catecholamines to maintain SBP >90 mm Hg AND Clinical pulmonary congestion AND Impaired end-organ perfusion with 1 of the following criteria:

1. Altered mental status
2. Cold/clammy skin and extremities
3. Urine output <30 ml/h
4. Lactate >2.0 mmol/l

### Hemodynamic criteria

| CI #2.2 l/min/m2 and PCWP >15 mm Hg | - | - | - |

*Data was evaluated for 686 patients.

AMI ¼ acute myocardial infarction; CABG ¼ coronary artery bypass grafting; CAD ¼ coronary artery disease; CI ¼ cardiac index; CS ¼ cardiogenic shock; CULPRIT-SHOCK ¼ Culprit Lesion Only PCI versus Multi-vessel PCI in Cardiogenic Shock; IABP ¼ intra-aortic balloon pump; IABP-SHOCK II ¼ Intraaortic Balloon Pump in Cardiogenic Shock II; IMPRESS in Severe Shock ¼ IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK; PCI ¼ percutaneous coronary intervention; NA ¼ not applicable; PCWP ¼ pulmonary capillary wedge pressure;

RCT ¼ randomized controlled trial; SBP ¼ systolic blood pressure; SHOCK ¼ Should We Emergently Revascularize Occluded Arteries in Cardiogenic Shock.

In search of a common language for determining disease severity, the Society for Cardiovascular Imaging and Interventions (SCAI) recently developed a 5-stage (A - E) classification system for CS16 (Fig.1)
**Figure 1** Cardiogenic shock pyramid according to recent proposal. Five categories of cardiogenic shock. Stage A: At risk: Patients ‘At risk’ for cardiogenic shock development but not currently experiencing signs/symptoms of cardiogenic shock. Stage B: Patients with clinical evidence of relative hypotension or tachycardia without hypoperfusion being at ‘Beginning’ of cardiogenic shock. Stage C: Patients in the state of ‘Classic’ cardiogenic shock. Stage D: Cardiogenic shock signals deteriorating or ‘Doom’. Stage E: Patients in ‘Extremis’ such those experiencing cardiac arrest with ongoing cardiopulmonary resuscitation and/or extracorporeal membrane oxygenation cardiopulmonary resuscitation.

**MANAGEMENT AND TREATMENT**

a. **EMERGENCY DEPARTMENT**

Effective triage in the emergency department is fundamental to early recognition and treatment of CS. In AMI-CS, this means the timely acquisition and interpretation of a 12-lead ECG by emergency medical personnel and immediate transfer to a facility capable of percutaneous coronary intervention. In the emergency department, the diagnosis of CS may be facilitated by a physical examination, ECG, laboratory evaluation, and echocardiography (when available) at the point of care (Lancellotti et al., 2014). Although patients with pre-trauma may transfer directly to the cardiac catheterization laboratory, those with SCAI in stage C or D CS may first need initial fixation using vasocompression therapy and mechanical ventilation, albeit without much delay in pumping blood (Levy et al., 2018; van Diepen et al., 2020; Kochar et al., 2018). In patients with SCAI in stage E or end stage CS for whom aggressive treatments may not be feasible, palliative care counseling and discussions with healthcare alternatives regarding the goals of care may be warranted (Rogers et al., 2017).

Vascular remodeling based on trauma experience, early vascular remodeling is the most important treatment strategy in CS after myocardial infarction (Hochman et al., 1999)). However, there was a significant reduction in mortality at longer follow-up after 6 months, 1, and 6 years (Hochman et al., 1999; Hochman et al., 2006). Applying the current evidence-based standards together with the failed primary study endpoint, may presently lead to a different interpretation of the experiment. However, since the widespread use of early revascularization, multiple records have confirmed a significant reduction in mortality from the previous 70-80% to 40-50%. Therefore, the current Category 1B recommendation in the European Society of Cardiology (ESC) and principles American steering appears justified (Fig. 2) (Neumann et al., 2019; Ibanez et al., 2018; Kushner et al., 2009). Recent records indicate a detrimental effect of angiogenesis delays on outcome (Kochar et al., 2018; Scholz...
et al., 2018). Therefore, efforts should be directed towards immediate transfer to specialized 24/7 PCI care centers. Evidence is lacking to support fibrinolysis in CS. However, if an early invasive approach cannot be completed in time, then STEMI-associated fibrinolysis can be considered (Fig.2).

![Figure 2: Treatment algorithm for patients with cardiogenic shock and myocardial infarction complication. Category recommendation and level of evidence are provided according to the latest European Society of Cardiology guidelines if available. 15, 37, 38 Category 1 recommendations are outlined in green. Category IIa recommendations are shown in yellow. Category IIb recommendations are shown in orange. Category 3 recommendations are shown in red.](image)

b. REVASCULARIZATION STRATEGIES

Although more than 70% of AMI-CS patients have multivascular coronary disease, less than 4% undergo emerging coronary artery bypass grafting (Thiele et al., 2012). Monitoring data indicate that coronary artery bypass grafting and coronary artery bypass grafting share similar mortality rates in AMI-CS (Mehta et al., 2010). Despite the specific benefits of complete revascularization in AMI, optimal management of artery lesions not associated with infarction in AMI-CS remains unclear (Mehta et al., 2019). To date, the CULPRIT-SHOCK trial (Culprit Lesion Only PCI versus Multivascular PCI in Cardiogenic Shock) is the only study that has addressed this question, and has shown lower rates of 30-day death or renal replacement therapy using culprit vessel PCI versus a multivascular intervention (Thiele et al., 2017). A recent National Heart Trauma Initiative sub-study showed similar mortality, acute renal injury, and length of hospital stay between the two strategies when axial-flow MCSs were implanted before revascularization (Lemor et al., 2020), suggesting that revascularization of non-induced lesions may be possible when supported by MCS. AMI-CS custom multi-unit PCI is currently receiving a Class IIb guidance recommendation (Levine et al., 2016).
c. CICU MANAGEMENT OF CARDIOGENIC SHOCK

The treatment of CS is complex and cardiac intensive care units are best suited to deal with such a complication (van Diepen et al., 2017; Rab et al., 2018). Optimal MODS intensive care unit therapy is essential to treat patients with CS as it has a major influence on prognosis. Although CS has not been specifically investigated, multiple measures are generally accepted. If invasive ventilation is required, protective lung ventilation (6 mL / kg expected tidal volume of body weight) should be performed to prevent lung injury. Non-invasive ventilation with continuous positive airway pressure may be an option to prevent intubation in borderline respiratory conditions (Ponikowski et al., 2016). Urinary production as well as renal function should be measured by serial creatinine measurements and initiation of renal replacement therapy in acute renal failure with clinical signs of hematuria, irreversible overload, or metabolic acidosis (pH 6.0 mmol / L). Based on these criteria, renal replacement therapy was necessary in 14% of patients in the CULPRIT-SHOCK trial (Thiele et al., 2017). Initiation of renal replacement therapy had no effect on outcomes in ICU patients with acute renal injury (Gaudry et al., 2016).

High liver norms often follow poor circulation as a result of RV congestion. Liver function tests are altered in more than 50% of patients with CS (Jung et al., 2017). The elevated transaminases can be interpreted as a direct sign of decreased blood flow to the liver, associated with increased mortality (Jung et al., 2017). Hemodynamics must be stabilized to achieve optimal hepatic perfusion. Furthermore, it is recommended to adjust blood sugar to target blood glucose concentrations between 144 mg / dL and 180 mg / dL (8-10 mmol / L) while avoiding hypoglycaemia (Jacobi et al., 2012). Prevention of thromboembolism and stress ulcers should follow general recommendations for critically ill patients. Until recently the available evidence was insufficient for nutritional management in relation to enteral or parenteral administration. In a recent randomized trial including all-cause trauma (19% CS) requiring intestinal vascular pressures or parenteral nutrition initiated within 24 hours. Early parenteral parenteral administration compared with early parenteral parenteral nutrition did not reduce mortality but was associated with an increased risk of gastrointestinal complications. Therefore, no early stage feeding and possibly primary parenteral nutrition in CS should be preferred. There is no consensus on the optimal method of hemodynamic monitoring in the evaluation and treatment of patients in CS, including pulmonary artery catheterization. Current scientific guidelines and data take into account the use of PAC early in the treatment course in patients who do not respond to initial therapy or in diagnostic or therapeutic uncertainties (Figure 2) (van Diepen et al., 2017; Ponikowski et al., 2016). The understanding of the etiology of CS and RV failures has changed in the past decade. With PAC, several hemodynamic profiles were identified where the diagnosis is driven by RV performance that can be altered with RV MCS. These variables and calculations were recently revised (Kapur et al., 2017). Of them, the pulmonary artery pulse index (pulmonary artery systolic pressure - diastolic pulmonary pressure / right atrial pressure) 7 g / dL (> 4.3 mmol / L) unless there is no clinical bleeding problem (Hunt, 2014). Overall CICU management is summarized for CS in Figure 3.
Figure 3. This schematic illustrates the longitudinal and multidisciplinary care pathways for cardiogenic shock (CS) care in a contemporary level 1 cardiac intensive care unit (CICU). CI $\frac{1}{4}$ cardiac index; CO $\frac{1}{4}$ cardiac output; CPO $\frac{1}{4}$ cardiac power output; DNR $\frac{1}{4}$ Do Not Resuscitate order; dPAP $\frac{1}{4}$ diastolic pulmonary arterial pressure; L $\frac{1}{4}$ left; MAP $\frac{1}{4}$ mean arterial pressure; MCS $\frac{1}{4}$ mechanical circulatory support; PAPi $\frac{1}{4}$ pulmonary arterial pulsatility index; PCWP $\frac{1}{4}$ pulmonary capillary wedge pressure; pVAD $\frac{1}{4}$ percutaneous ventricular assist device; R $\frac{1}{4}$ right; sPAP $\frac{1}{4}$ systolic pulmonary arterial pressure.

**d. MECHANICAL CIRCULATORY SUPPORT**

Mechanical circulation support devices (MCS) are increasingly used in CS to stabilize hemodynamics (Helgestad et al., 2020), although exactly when and whether they are incorporated into trauma care remains controversial (Van Diepen et al., 2017; Thiele et al., 2019). The potential benefits of MCS include reducing stroke action and filling pressure within the heart, and enhancing perfusion of the coronary arteries and peripheral organs (Rihal et al., 2015). Device selection should be guided by disease severity, CS phenotype, degree of vascular and ventricular support required, vascular access or anatomy, size and procedural expertise of the operator or center (Fig. 4). Understanding how each platform changes ventricular pressure volume relationships is critical to implementing the optimal
strategy (Rihal et al., 2015). Although axial flow and centrifugation devices may improve circulation compared to an intra-aortic balloon pump, no survival benefit has been demonstrated to date (Thiele et al., 2017). In addition, recent monitoring data from CathPCI and Chest Pain records -MI as well as the Premier Healthcare database show wide variations in axial flow device use across the United States and raise safety concerns, particularly major bleeding, stroke, and deaths (Dhruva et al., 2020; Amin et al., 2020). Nevertheless, data emerging from records of dedicated trauma centers indicate that when MCSs are deployed selectively using early invasive hemodynamics and standard multidisciplinary treatment algorithms, improvements in survival can be achieved (Tehrani et al., 2019; Basir et al., 2019; Taleb et al., 2019). In patients with condylar femoral angiomas, experience with alternative access is key. The axillary artery, in particular, has been shown to be a suitable conduit for an intra-aortic balloon pump and Impella (Abiomed, Danvers, Massachusetts) in patients with CS, as it may also facilitate early ambulation and improve nutritional status in patients requiring prolonged circulatory support While awaiting alternative cardiac treatment (Tayal et al., 2019; Esposito et al., 2018). Our current practice is to selectively deploy MCS in appropriate patients with acute or refractory CS after urgent consultation with the multidisciplinary trauma team, which consists of an interventional cardiologist, cardiac surgeon, cardiac intensive physician and advanced heart failure specialist. Lactate levels, cardiac energy output, and the pulmonary arterial pulse index help facilitate both MCS and weaning strategies. MCS may be used as a bridge to myocardial recovery, heart replacement therapy, or as a temporary procedure to evaluate a patient's candidacy for a permanent ventricular assist device or heart transplant. Strict adherence to best practices for vascular access and closure, familiarity with device troubleshooting, and multidisciplinary care in PICU Level 1 are critical components of optimal care (Rab et al., 2018).
Figure 4. The hemodynamic profiles of the various circulatory support devices available for treatment of cardiogenic shock. ADHF ¼ acute decompensated heart failure; AMI ¼ acute myocardial infarction; AO ¼ aorta; Bi-V ¼ biventricular; CS ¼ cardiogenic shock; FA ¼ femoral artery; FDA ¼ Food and Drug Administration; HR-PCI ¼ high risk percutaneous coronary intervention; IABP ¼ intra-aortic balloon pump; IJ ¼ internal jugular; LA ¼ left atrium; LV ¼ left ventricular; LVAD ¼ left ventricular assist device; PA ¼ pulmonary artery; RA ¼ right atrium; RPM ¼ revolutions per minute; RV ¼ right ventricular; RVF ¼ right ventricular failure; VA-ECMO ¼ venoarterial extracorporeal membrane oxygenation. Adapted with permission from Thiele et al. 39

e. CONTROVERSIES OF MECHANICAL CIRCULATORY SUPPORT

Several open problems remain in mechanical device treatment such as the optimal timing of device insertion. Prevention of MODS could be a potential benefit of early use at the onset of CS. However, early use may lead to complications associated with invasive mechanical support devices, resulting in negative clinical outcomes in patients who still have non-surgical treatment options. Moreover, adequate patient selection is important and is currently often based on subjective criteria. Approximately 60% of CS patients will live without any active device as described in IABP-SHOCK II (Thiele et al., 2012). There may also be sterile situations where even the best will not be able. A device available to change the clinical outcome. Timing and appropriate patient selection is also influenced by the balance between the effectiveness of any device and its device-related complications. Devices with lower complication rates may be chosen more liberally in the early stage of CS, while more aggressive devices with higher flow rates may be reserved for more severe devices. The optimum support has also not been identified. A randomized, multicenter Danish trial (DanShock; Clinicaltrials.gov: NCT01633502) compares Impellaflow CP with standard treatment and may also answer if an active device implanted on a routine basis can reduce mortality. Several other devices are currently under investigation for CE approval in Europe such as HeartMate PHPTM (percutaneous heart pump; Thoratec, Pleasanton, CA, USA). Despite all these uncertainties, current European and American guidelines recommend considering the use of a percutaneous assist device to support circulation in refractory CS without any preference for device selection (IIa / C recommendation) (Windecker et al., 2014; Steg et al., 2012; O'Gara et al., 2013).

f. LV ASSIST DEVICES AND HEART TRANSPLANTATION

Early and ongoing evaluation of the potential need for cardiac replacement therapy, either with permanent MCS or heart transplantation, is essential for patients with refractory CS. Therapeutic considerations include traditional risk factors such as age, renal and hepatic function, blood clotting, aortic valve regurgitation, RV function, and compliance with drugs (Samsky et al., 2020). A thorough clinical and psychosocial evaluation is required. With an updated Heart Allocation Protocol of the United Network for Organ Participation that temporarily prioritizes patients with MCS for accelerated heart transplantation, an increasing number of patients with CS have used this pathway (Varshney et al., 2020). More research is needed to guide the patient's choice of such advanced therapies (Hanff et al., 2020).

g. SHORT REVIEW OF MANAGEMENT

Here are key points to remember from this recent review on cardiogenic shock management (Mukherjee, 2020):
i. Cardiogenic shock (CS) is a dynamically complex syndrome characterized by reduced cardiac output that often culminates in multi-organ failure and death.

ii. Despite recent advances, clinical outcomes remain poor, with mortality rates exceeding 40%. In the absence of sufficiently powered randomized controlled trials to guide treatment, best practices for managing trauma remain inconsistent.

iii. Data emerging from the North American records support the use of standardized protocols that focus on rapid diagnosis, early intervention, ongoing haemodynamic assessment, and interdisciplinary longitudinal care.

iv. Effective triage in the emergency department is fundamental to early recognition and treatment of CS. In the case of acute myocardial infarction (AMI)-CS, this means timely acquisition of a 12-lead EKG and interpretation by emergency medical personnel and immediate transfer to a facility capable of percutaneous coronary intervention.

v. Although there is no benefit from using routine pulmonary artery catheterization (PAC) for heart failure, mounting evidence supports the benefit of evaluating invasive hemodynamics in patients with CS. The use of PAC may lead to early and more accurate identification of the CS phenotype so that medical and device-dependent treatments can be applied in an ad hoc manner.

vi. Limited data support the use of norepinephrine as the preferred first-line agent, and retrospective analyzes indicate similar results with dobutamine and melrinone.

vii. In setting the dynamic and time-dependent complications associated with AMI-CS complex due to cardiac arrest, a multidisciplinary approach to management is recommended with an emphasis on assessing the patient's general prognosis, potential for meaningful neurological healing, and filtering for vascular and organ remodeling.

viii. Selective deployment of mechanical circulatation support (MCS) in appropriate patients with acute or refractory CS after urgent consultation with the multi-disciplinary trauma team, which consists of an interventional cardiologist, cardiac surgeon, cardiologist and advanced heart failure specialist, is reasonable.

ix. In some patients with a dominant left ventricle (LV) and hypotension, pure vasodilators such as nitroprusside may improve cardiac output by reducing subsequent pregnancy, while the vasodilating effects of melrinone and dobutamine can also be effective for high-pregnancy LV failure. Intravenous or inhaled pulmonary vasodilators reduce right ventricular postload (RV) for pulmonary arterial hypertension and RV failure.

x. There is a critical need for practical randomized clinical trials for current and emerging therapies to be adequately evaluated to further inform clinical practice including the optimal role of MCS.

**CONCLUSION**

The prognosis for ST segment elevation myocardial infarction has improved significantly since the introduction of coronary care units, revascularization and anticoagulant strategies, but CS remains a highly fatal condition. Despite efforts to improve results, the prognosis has not improved in recent decades. Controversies remain over optimal pharmacological treatments, remodeling strategies, the role of MCS, evidence-based patient selection and interactions between these parts of the path of care (Thiele et al., 2016; Moller, 2012; Brunner, 2015). The current informed consent model for clinical trials creates challenges in testing treatments for patients with CS who are too ill for consent and in need of
immediate treatment. Fortunately, several trials are underway comparing the remodeling strategies and MCS options (Thiele et al, 2016).

REFERENCES


