Controversies in cardiovascular medicine

Shock in acute myocardial infarction: the Cape Horn for trials?

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Despite therapeutic improvements, cardiogenic shock (CS) remains the most common cause of death in patients with acute myocardial infarction (AMI). In addition to percutaneous coronary intervention, inotropes, fluids, adjunctive medication, intra-aortic balloon counterpulsation, and also assist devices are widely used for treatment. However, currently, there is only limited evidence for any of the above treatments. This review will therefore outline the underlying causes, pathophysiology, and treatment of CS complicating AMI with major focus on interventional techniques and advancement of new therapeutical arsenals, both pharmacological and mechanical.

Keywords
Shock • Heart failure • Haemodynamics • Myocardial infarction • Assist device

Introduction

The incidence of cardiogenic shock (CS) in patients with acute myocardial infarction (AMI) differs depending on the definition of CS, but it has been estimated to range from 5 to 15% with some decline in the last years.1–4 Assuming a 5–8% incidence of CS of all hospitalized AMI, this translates in approximately 40 000–50 000 cases per year in the United States and approximately 60 000–70 000 cases in Europe.5,6 Numerous clinical complications are associated with the development of AMI, but none are more potentially devastating or carry a worse prognosis than CS.

Mortality of patients with AMI was reduced from 30% to 5% for non-CS patients during the last decades but in the subgroup of patients with CS, improvements were much less extensive. Despite advances in treatment during the last two decades leading to a steady reduction in mortality rates, CS remains to be the leading cause of death with hospital mortality rates still approaching 50%.6,7

This review will outline the underlying causes, the pathophysiology, and treatment of CS complicating AMI—excluding mechanical complications and CS from right heart failure—with major focus on interventional techniques and advancement of new therapeutical arsenals, both pharmacological and mechanical. Since studying the CS population in randomized trials remains very challenging, we will also focus on the challenges encountered in previous clinical trials and the implication for future research in CS.

Definition, diagnosis, causes, and pathophysiology

Definition and diagnosis

Cardiogenic shock is a state of impaired end-organ perfusion owing to a reduced cardiac output. It is characterized by hypotension and impaired tissue perfusion. It is therefore defined mainly by haemodynamic parameters such as (i) a systolic blood pressure of less than 90 mmHg lasting for more than 30 min (in the absence of hypovolaemia) or vasopressors required to achieve a systolic blood pressure ≥ 90 mmHg with (ii) a reduction of cardiac index (<1.8 L/min/m² without support and 2.0–2.2 L/min/m² with support, depending on the definition used); and (iii) with elevated left ventricular (LV) filling pressures (pulmonary capillary wedge pressure >18 mmHg).7,8 Evidence of vital organ hypoperfusion may be manifested clinically by (i) cool extremities owing to
centralization, (ii) decreased urine output, and/or (iii) alteration in mental status. In addition, serum lactate measurements may be used for the assessment of impaired peripheral microcirculation. However, CS diagnosis not necessarily needs invasive measurement of LV filling pressures and cardiac output by a pulmonary artery catheter. It can also be diagnosed clinically by blood pressure assessment in conjunction with clinical signs of pulmonary congestion and end-organ hypoperfusion. Haemodynamic abnormalities described above form a spectrum that ranges from mild hypoperfusion to profound shock, and the short-term outcome is directly related to the severity of haemodynamic derangement.

Causes
Acute myocardial infarction with subsequent LV dysfunction remains the most common cause of CS. The incidence of CS after non-ST-elevation MI (2.5%) seems to be lower than after ST-elevation MI. However, also mechanical complications, such as ventricular septal rupture, free wall rupture, and papillary muscle rupture or dysfunction contribute to CS after AMI. The underlying cause of CS can be easily evaluated by echocardiography revealing the LV dysfunction and associated mechanical complications.

Pathophysiology
The pathophysiology of CS is complex and has been reviewed previously. In brief, CS is the result of acute to subacute derangements in the entire circulatory system. Loss of LV function is the major cause in most CS forms with subsequent systolic and diastolic dysfunction, but other parts of the circulatory system may also contribute to shock with inadequate compensation or by contribution by additional defects. Extremity and vital organ hypoperfusion is the hallmark of CS, which is most sensitively measured by serum lactate. Compensation mechanisms by vasoconstriction lead to intermittent improvement in coronary and peripheral perfusion at the cost of increased afterload. However, vasoconstriction can be off-reverted by the systemic inflammatory response syndrome (SIRS) which occurs frequently with increasing duration of CS. In these patients, the systemic vascular resistance (SVR) is inadequately low despite treatment with vasopressors. Endothelial (eNOS) and inducible nitric oxide synthase (iNOS) may play a major role with the production of inadequately high levels of NO and also peroxynitrite, which has cardiac toxicity and is negatively inotropic. Other inflammatory markers such as interleukin-6 and tumour necrosis factor-α might contribute to this phenomenon.

Another important aspect in CS is bleeding which might also contribute to an increased mortality risk as shown previously in acute coronary syndrome trials with predominantly stable haemodynamic conditions. In particular, during CS, bleeding will trigger transfusion as it is generally believed to be beneficial that increasing haemoglobin levels via transfusion will increase oxygen delivery. However, blood transfusions in acute coronary syndromes itself increase the mortality risk. Alterations in erythrocyte nitric oxide biology in stored blood may provide a partial explanation, leading to initial vasoconstriction, platelet aggregation, and ineffective oxygen delivery. In addition, bleeding itself as well as transfusion contributes to inflammation. The mechanisms behind the associations of bleeding and also transfusions with mortality are likely complex and may relate to hypotension, anaemia, ineffective oxygen delivery, vasoconstriction, platelet dysfunction, or cessation of evidence-based antithrombotic or antiplatelet therapies.

Treatment
Revascularization
Because of its limited efficacy, fibrinolysis is only reserved for patients when percutaneous coronary intervention (PCI) is impossible or if there are significant treatment delays in the transport for PCI. The Should we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) trial is one of the rare adequately powered and most important randomized trials in CS complicating AMI. Although it failed to meet the primary endpoint—reduction of 30-day mortality by an early revascularization-based management either by PCI or coronary artery bypass grafting (CABG)—(46.7% vs. 56.0%, P = 0.11), there was a significant mortality reduction at 6 (50.3% vs. 63.1%, P = 0.027), 12 months (53.3% vs. 66.4%, P = 0.03), and long-term follow-up at 6 years (67.2% vs. 80.4%, P = 0.03). To save a life, less than eight patients need to be treated by early revascularization in comparison with initial medical stabilization. The Swiss Multicenter trial of Angioplasty for SHock (SMASH) trial, although stopped prematurely owing to slow enrolment, showed similar effects by early revascularization (Figure 2).

Since the widespread application of early revascularization in clinical practice mainly influenced by guideline recommendations, numerous registries have confirmed the survival advantage of early revascularization leading to a subsequent reduction of CS mortality in the young and also the elderly.

More than three-fourth of patients in CS present with multivessel disease. Current guidelines encourage multivessel PCI for patients in CS, which is in contrast to recommendations in haemodynamically stable patients. However, the optimal revascularization strategy—PCI vs. CABG—for patients with multivessel disease and CS is not clear. Furthermore, it is not clear whether multivessel PCI might be beneficial in CS. Any randomized clinical trials are missing for the CS subset. Nevertheless, multivessel PCI is performed in approximately one-third of CS patients with multivessel disease. As long as there are no randomized clinical trials, multivessel PCI in addition to culprit lesion PCI should be considered based on the morphology of the underlying lesions, predicted success rates, presumed ischaemia at rest caused by the lesions and also the haemodynamic stability. Otherwise, a staged procedure or also CABG should be considered.

Both randomized trials were performed before pharmacological strategies, such as loading with thienopyridines and glycoprotein IIb/IIIa inhibitors were commonly used. It is well known that early reperfusion by primary PCI and reperfusion success measured by TIMI-flow are major factors that are strongly
associated with mortality in CS.\textsuperscript{25} Therefore, efforts are necessary to improve the reperfusion success.

**Drug treatment**

Antithrombotic therapy with aspirin and heparin should be given as routinely recommended.\textsuperscript{13,26} Clopidogrel or prasugrel may be deferred because on the basis of angiographic findings, CABG may be immediately necessary. Clopidogrel/prasugrel is indicated in all patients undergoing PCI, and on the basis of extrapolation of data from MI patients who were not in shock, it should also be useful in patients with CS.

**Glycoprotein IIb/IIa inhibitors**

Glycoprotein IIb/IIa inhibitors improve the reperfusion success in PCI and reduce major adverse cardiac events in particular in high-risk patients.\textsuperscript{27} This might particularly be important for the highest risk group of CS patients which herald lower TIMI-3 flows (approximately 80%) after PCI in comparison with non-shock AMI patients.\textsuperscript{28} Observational data support a potential mortality benefit using glycoprotein IIb/IIa inhibitors in CS.\textsuperscript{29–31} However, in this specific setting, there is only one small, potentially underpowered, randomized trial in 80 patients (with 35% cross-over in the standard treatment group), which failed to confirm that routine upstream abciximab use is superior in comparison to standard treatment with abciximab use according to the discretion of the interventionalist.\textsuperscript{32} The primary endpoint (death/reinfarction/stroke/new renal failure) was reached by 42.5% in the up-stream abciximab-group and 27.5% in the standard treatment group ($P = 0.24$) and also in-hospital mortality did not differ (37.5% vs. 32.5%, $P = 0.82$; Figure 2).\textsuperscript{32} Given the potential higher bleeding risk with the use of these potent platelet inhibitors, the current role in cardiogenic shock cannot be finally determined without adequately powered clinical trials.

**Bivalirudin**

Given the strong influence of both AMI and major bleeding on subsequent risk of death in AMI and PCI, the optimal antithrombotic regimen would effectively suppress ischaemic complications while minimizing iatrogenic haemorrhagic risk. Bivalirudin reduces bleeding complications while being similarly effective in ischaemic event reduction. However, bivalirudin use in STEMI and non-ST-elevation acute coronary syndromes was mainly limited to patients without CS.\textsuperscript{33,34} Therefore, any conclusions

![Figure 1](image-url)
for CS patients are questionable given also the slightly higher risk of acute stent thrombosis for bivalirudin.34

Fluids, vasopressors, and inotropes
Irrespective of the underlying cause of CS, the treatment includes initial stabilization with volume expansion to obtain optimal filling pressures, vasopressors, and inotropes plus additional therapy for multiorgan system dysfunction.

Fluid administration in CS is mainly based on pathophysiological considerations and has not been studied in adequate randomized clinical trials.

Similar to fluid administration, the choice of vasopressor and inotropic therapy is mainly based on individual experience, institutional policy, pathophysiological considerations, and published American and European guidelines, where both recommend dopamine as inotropic as well as vasoconstrictive drug.13,26 These guidelines are challenged by a recent randomized clinical trial in 1679 patients with shock including 280 CS patients. Treatment with dopamine in comparison with norepinephrine was associated with significantly more adverse effects, mainly arrhythmic events for the overall study cohort and the predefined CS subgroup experienced higher death rates with dopamine (Figure 2).35 Therefore, when blood pressure is low norepinephrine should be the first choice because of its ability to act as a vasoconstrictor with less potential for tachycardia. It should be titrated until the systolic arterial pressure rises to at least 80 mmHg. Subsequently, intravenous dobutamine because of its β2-adrenergic effects may be given simultaneously in an attempt to improve cardiac contractility.

Despite the favourable haemodynamic effects of all catecholamines, none have produced consistent improvement in symptoms and many have shortened the survival.36 These findings may be related to the fact that these agents increase myocardial oxygen consumption and also the concentrations of cAMP, producing an increase in intracellular calcium that possibly leads to myocardial cell death and/or increases lethal arrhythmias. As a consequence, catecholamines should be used in the lowest possible doses. To overcome these problems inherited with catecholamines, in the last years there has been increasing interest in pharmacological agents acting on contractility without the drawbacks of catecholamines.
Levosimendan

Levosimendan is a relatively new calcium sensitizer and K-ATP channel opener, which improves myocardial contractility. It might be an ideal agent in CS, because in comparison with other inodilators it improves myocardial contractility without increasing oxygen requirements and induces peripheral and coronary vasodilatation with a potential anti-stunning, anti-ischaemic effect. The use of levosimendan and its clinical evidence in different clinical settings has been reviewed previously. Initial beneficial effects in small trials did not translate into a survival benefit in large-scale clinical trials. Although levosimendan is one of the best studied inotropic agents in acute heart failure, the clinical evidence in CS is limited. In view of its vasodilatory effects with subsequent blood pressure-lowering, it was not a drug of first choice in CS. There are, however, some clinical observations indicating that levosimendan can improve haemodynamics in CS when combined with catecholamines to maintain adequate perfusion pressures. Its current role in CS needs to be defined in further studies. However, to the best of our knowledge, there are no ongoing large-scale clinical trials assessing the clinical benefits of levosimendan in CS patients.

Nitric oxide synthase inhibitors

Pathophysiological observations that increased levels of NO in CS lead to inappropriate systemic vasodilatation, progressive systemic and coronary hypoperfusion, and also myocardial depression led to a small randomized clinical trial demonstrating improved haemodynamics by the administration of NO synthase inhibitors. This resulted also in a survival benefit. Subsequently, based on the dose-ranging SHOCK-2 study, the TRIUMPH trial (Tilarginine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock), the largest study in CS, investigated if tilarginine improves survival in CS. Despite an immediate increase in blood pressure, NO synthase inhibition did not result in a survival benefit, which led to discontinuation of the trial after inclusion of 398 patients based on a prespecified interim analysis. The results of the current evidence for NO synthase inhibition are displayed in Figure 2.

Mechanical support

Intra-aortic balloon counterpulsation

Intra-aortic balloon pumping (IABP) is a mature technology after approximately four decades of use in CS. By diastolic inflation and rapid systolic deflation in the aorta, it improves peak diastolic pressure and lowers the end-systolic pressure translating into an afterload reduction, improved coronary perfusion, and reduction in myocardial oxygen consumption. However, the effects on cardiac output are only modest. Nowadays, the IABP is the most widely used mechanical support device for the treatment of CS. According to guidelines, IABP use is highly recommended for patients in CS with a class 1B recommendation according to the AHA/ACC guidelines and a class 1C recommendation according to the ESC guidelines. The current evidence regarding IABP on CS outcome in the prefibrinolytic, the fibrinolytic, and also the primary PCI era has recently been reviewed. Because of a lack of randomized clinical trials, only registries were evaluated showing conflicting results for the three different eras with mortality risk differences of 29% and 18% in favour of the IABP in the pre- and fibrinolytic era. In contrast, there was a 6% mortality increase in the PCI-era, which was mainly influenced by the results of the National Registry of Myocardial Infarction-2.

However, these were observational studies, which are influenced by many confounders. For instance, those patients with IABP support in the fibrinolytic era were younger and more likely to undergo rescue-PCI or additional CABG. Thus, the observed mortality benefit might also be owing to these confounders. As a result of the lack of sufficiently powered randomized clinical trials and reimbursement policies, cardiologists often do not insert IABP in CS despite the high-class guideline recommendation. Current IABP use ranges from 11% in a German registry to 51% in the SHOCK registry and 86% in the randomized SHOCK trial. A recent analysis from the Euro Heart PCI survey revealed an average use of 24.8% in Europe. Figure 3 shows current IABP use in selected registries and trials.
Currently, there are only two randomized trials that have investigated IABP in haemodynamically unstable patients. The TACTICS (Thrombolysis And Counterpulsation To Improve Cardiogenic shock Survival) trial in the fibrinolytic era in patients with AMI complicated by sustained hypotension, possible CS, or possible heart failure was prematurely stopped owing to slow inclusion rates. Included patients were not necessarily in CS. This small study of 57 patients demonstrated no benefit on mortality from adding IABP to fibrinolysis for the overall study cohort, but a favourable decrease in 6-month mortality for patients with more severe haemodynamic impairment getting an IABP (80% vs. 39%, \( P = 0.05 \)). Another recently published small pilot trial in 40 patients with CS undergoing PCI showed beneficial effects on brain natriuretic peptide for the IABP group. However, for the primary study endpoint—change in serial APACHE-2 scoring—there was no statistically significant benefit. Based on this small randomized pilot study, a large properly powered, randomized, clinical trial has recently started (www.clinicaltrials.gov, NCT00491036), which will hopefully give the answer to whether IABP is beneficial for the treatment of CS in addition to PCI or alternatively CABG. The aim of this multicentre trial—Intraaortic Balloon Pump in cardiogenic shock 2 (IABP-SHOCK II)—is to randomize 600 patients within 2.5 years with the primary study endpoint 30-day mortality.

Percutaneous left ventricular assist devices

Left ventricular assist devices (LVAD) have been used in patients not responding to standard treatment including inotropes, fluids, and IABP, and also as first-line treatment. However, the current experience and evidence is limited. The current devices, mode of action, and evidence regarding percutaneous LVADs for the treatment in CS has been summarized previously. Table 1 provides an overview of the current percutaneous LVAD features.

Current devices include the TandemHeart\textsuperscript{TM} (Cardiac Assist, Inc., Pittsburgh, USA) which removes arterialized blood from the left atrium using a cannula placed through the femoral vein and into the left atrium via transseptal puncture. Blood is returned from the left atrium to the lower abdominal aorta or iliac arteries via a femoral artery cannula with retrograde perfusion of the abdominal and thoracic aorta (Figure 4B). A more detailed description of the mode of action and implantation has been described previously. Another percutaneous device, the Impella\textsuperscript{TM} 2.5 or 5.0 (Abiomed Europe, Aachen, Germany) is placed across the aortic valve using femoral access either percutaneously or by surgical cut-down (Table 1 and Figure 4C). This device has been tested in a small randomized clinical trial in 26 CS patients in comparison with IABP. Recently, the results of a multicentre registry in high-risk PCI have been reported. However, no CS patients were included in this registry.

A recent meta-analysis reported the results of three randomized trials comparing percutaneous LVADs vs. IABP treatment. Altogether, only 100 patients were included in these three trials of which two compared the TandemHeart\textsuperscript{TM} and one the Impella\textsuperscript{TM} 2.5 with IABP. Patients treated with active LVADs demonstrated improved haemodynamics as shown by higher cardiac index, higher mean arterial pressure, and lower pulmonary capillary wedge pressure when compared with IABP patients. On the other hand, there were differences observed in bleeding complications and also inflammation mainly in the TandemHeart\textsuperscript{TM} group. However, there was no sign of improvement in 30-day mortality (relative risk 1.06, 95% CI 0.68–1.66). Figure 5 shows the 30-day mortality rates based on an individualized patient-based meta-analysis of the three randomized clinical trials. Based on these results, percutaneous LVADs cannot be recommended as first-line treatment in CS. Although not entirely based on randomized trials, a treatment algorithm used in clinical practice—considering the individual patient age and comorbidities—is shown in Figure 6. Also, the combination of laminar flow assist devices with the pulsatile IABP might be beneficial from a pathophysiological point of view. However, this cannot be underlined by sufficient clinical data.

Currently, there are no meaningful ongoing trials powered to assess the effect of percutaneous LVADs on clinical endpoints, which might be able to change the current clinical practice. The RECOVER II trial, initially designed to include 346 patients comparing the Impella\textsuperscript{TM} 2.5 with IABP in CS, has recently been stopped because of slow inclusion rates and funding problems.
Although mechanical circulatory support with LVADs is theoretically appealing to interrupt the vicious spiral of ischaemia, hypotension, and myocardial dysfunction, allowing for recovery of stunned and hibernating myocardium, the extracorporeal support and contact with artificial surfaces of LVADs might further promote SIRS with subsequent deterioration to a multiorgan dysfunction syndrome (Figure 1). A second, potentially deleterious effect of extracorporeal circulation, besides the propagation of SIRS, is the activation of complement and the development of coagulation with subsequent fibrinolysis, which may progress to disseminated intravascular coagulation leading to severe bleeding complications (Figure 1). As long as there are no adequate clinical trials assessing meaningful clinical endpoints, percutaneous LVAD treatment will be restricted to the use on individual experience in dedicated centres for highly selected patients and will not attain broad acceptance.

In selected patients not responding to standard therapy, surgically implantable LVADs or extracorporeal life support involving membrane oxygenators might be considered as destination therapy or bridge to transplant. However, experience with these devices in CS after AMI is extremely limited. Additional randomized trials are needed for a more complete assessment of the role of different circulatory supportive strategies in CS.

Lessons learned and perspectives for future trials

Randomized clinical trials in CS are difficult to perform and are costly. Therefore, many believe that conducting a randomized study in this critically ill population is still a Cape Horn for trialists owing to difficulties of enrolling and randomizing these critically ill patients. However, as infarctions are frequent and CS inherited with high mortality, any intervention that reduces mortality is likely to have major public health implications and should be thoroughly tested. In the era of evidence-based medicine, such trials are therefore of paramount importance to achieve a
break-through in CS treatment. Several previous trials were stopped early because of enrolment difficulties. However, there are also several successful large-scale trials which contributed to the understanding and more importantly prognosis improvement in CS.

Conducting randomized trials in such population should require attention to methodology and the appropriate selection of the outcome parameters studied. Several trials have been published showing improved haemodynamics for drugs and also for active circulatory assist devices without effects on outcome. Therefore, we have to realize that an improved haemodynamic status might not be a suitable surrogate marker for survival. Future studies assessing any drug, intervention, or mechanical assist device need therefore to be judged according to their clinical efficacy. We need evidence from properly powered, randomized, controlled clinical trials with regard to their effect on outcome before any new drug, intervention, or device is heralded as a new therapeutic option. Assuming a current 45% mortality risk, the corresponding sample size can be depicted from Table 2 assuming an absolute mortality risk reduction of 2.5–20% with α of 5% and 80% power. In order to include such a large number of patients, the number of centres recruiting should be more than 30, and the selection should be based on their AMI annual recruitment (more than 200/centre/year). It is clear that to attain its objectives, such a study with a clinical endpoint should be conducted on a European, multinational scale.

Conflict of interest: H.T. has received lecture fees and is a consultant for Maquet, Cardiopulmonary AG, Hirrlingen, Germany.

Table 2  Sample size calculation using mortality as an endpoint

| Estimated mortality standard treatment group (%) | 45.0 | 45.0 | 45.0 | 45.0 | 45.0 | 45.0 | 45.0 | 45.0 |
| Estimated mortality new treatment group (%)     | 42.5 | 40.0 | 37.5 | 35.0 | 32.5 | 30.0 | 27.5 | 25.0 |
| Absolute mortality reduction (%)                | 2.5  | 5.0  | 7.5  | 10.0 | 12.5 | 15.0 | 17.5 | 20.0 |
| Power (%)                                       | 80.0 | 80.0 | 80.0 | 80.0 | 80.0 | 80.0 | 80.0 | 80.0 |
| Patients per group (n)                          | 6260 | 1574 | 702  | 396  | 254  | 176  | 129  | 98   |

Figure 6 Potential treatment algorithm for patients with CS complicating AMI (asterisks denote supported by randomized controlled trials). PCI, percutaneous coronary intervention CABG, coronary artery bypass grafting. Dotted line indicates alternative treatment.
References


