The ESC Textbook of Intensive and Acute Cardiovascular Care (2 ed.)

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Latest update

This online textbook has been comprehensively reviewed for the February 2018 update, with revisions made to 28 chapters. Find out more about the updates made.

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Cardiogenic shock in patients with acute coronary syndromes

Chapter: Cardiogenic shock in patients with acute coronary syndromes
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Update:

Update on prognosis estimation in cardiogenic shock.

Update on multivessel PCI versus culprit lesion only PCI and on the ongoing CULPRIT-SHOCK trial comparing culprit lesion only versus multivessel PCI in cardiogenic shock.

Update on levosimendan.

Update on percutaneous mechanical support devices.

7 new references

3 new figures (renumbering existing figures); slight modification to caption of existing Figure 49.4

Slight modification to title (and numbering) of Table 49.1

Updated on 22 Feb 2018. The previous version of this content can be found **here**.

Summary

Cardiogenic shock complicating an acute coronary syndrome is observed in up to 10% of patients and is associated with high mortality still approaching 50%. The extent of ischaemic myocardium has a profound impact on the initial, in-hospital, and post-discharge management and prognosis of the cardiogenic shock patient. Careful risk assessment for each patient, based on clinical criteria, is mandatory, to decide appropriately regarding revascularization by primary percutaneous coronary intervention or coronary artery bypass grafting, drug treatment by inotropes and vasopressors, mechanical left ventricular support, additional intensive care treatment, triage among alternative hospital care levels, and allocation of clinical resources.

This chapter will outline the underlying causes and diagnostic criteria, pathophysiology, and treatment of cardiogenic shock complicating acute coronary syndromes, including mechanical complications and shock from right heart failure.

There will be a major focus on potential therapeutic issues from an interventional cardiologist’s and an intensive care physician’s perspective on the advancement of new therapeutical arsenals, both mechanical percutaneous circulatory support and pharmacological support. Since studying the cardiogenic shock population in randomized trials remains challenging, this chapter will also touch

upon the specific challenges encountered in previous clinical trials and the implications for future perspectives in cardiogenic shock.

Contents

Introduction

The incidence of cardiogenic shock (CS) in patients with acute myocardial infarction (AMI) differs, depending on the CS definitions, but it ranges from 4% to 15%, with some decline in the last years [1–5]. Assuming a 5–8% incidence of CS in all hospitalized AMIs, this translates

in approximately 60 000–70 000 cases per year in Europe [6, 7]. Numerous clinical complications are associated with the development of AMI, but none is more potentially devastating for prognosis than CS.

The mortality of patients with AMI could be 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 impressive [4, 8–10]. Despite advances in treatment over the last decades, leading to a steady reduction in mortality, CS remains the leading cause of death, with hospital mortality rates still approaching 50% [1, 3–5, 11]. Some recent registries suggested an increase in the CS setting despite an increase in invasive measures and revascularization rates, which may be related to the higher age and the higher risk profile of patients [12, 13]. Other recent registries did not observe this increase in mortality and rather suggest a further decline in mortality [14, 15]. Interestingly, public reporting negatively affects the number of patients with invasive angiography in cardiogenic shock. Therefore, CS patients should be excluded from public reporting [16, 17]. Major efforts are still needed, and also intensified research should be directed, to improve the prognosis of CS.

Definition

CS of every cause is a state of impaired end-organ perfusion, due to a reduced cardiac output. It is characterized by hypotension, pulmonary congestion, and an impaired tissue and vital organ perfusion. In general, CS can be clinically defined. However, in particular, in some clinical trials, additional haemodynamic parameters, such as the assessment of left ventricular (LV) filling pressures or the cardiac index, were used to define CS [18, 19]. In the most recent IABP-SHOCK II trial, a clinical definition was used [20]. Generally, established criteria for CS definition are as follows:

- Systolic blood pressure <90 mmHg >30 min or vasopressors required to achieve ≥90 mmHg
- Pulmonary congestion or elevated LV filling pressures (e.g. PCWP >18 mmHg)
- Signs of impaired organ perfusion with at least one of the following criteria:
    - **a)** Altered mental status
    - **b)** Cold, clammy skin and extremities
    - **c)** Oliguria with urine output <30 mL/hour
    - **d)** Serum lactate >2.0 mmol/L
- Reduced cardiac index (<1.8 L/min/m^2 without support, and 2.0–2.2 L/min/m^2 with support) (optional)

Causes of cardiogenic shock

AMI with subsequent LV dysfunction is the most common cause of CS complicating ACS. The median time after STEMI for the occurrence of shock is in the range of 5–6 hours [21, 22]. Shock complicating UA or NSTEMI seems to occur at a later time period, with a median of 76 and 94 hours, respectively [23, 24]. In general, a loss of >40% of functional myocardium is required to cause CS, as shown in autopsy studies [25]. However, mechanical complications, such as acquired ventricular septal defect (VSD), free wall rupture (FWR), and papillary muscle rupture or dysfunction, with subsequent ischaemic mitral regurgitation (MR), also contribute to CS after AMI [26]. The incidence of CS causes has been described to be 78.5% for LV failure, 3.9% for VSD, 6.9% for ischaemic MR, 2.8% for right ventricular (RV) failure, and 1.4% for cardiac tamponade [26].

Pathophysiology

The CS pathophysiology is complex, and its understanding has emerged over the last decades [27–30]. In general, the underlying pathophysiology is a profound depression of myocardial contractility, resulting in a vicious spiral of reduced cardiac output, low blood pressure, further coronary ischaemia, and subsequent reduction in contractility and cardiac output, leading to death, if not interrupted by adequate treatment. Previously, the classic paradigm predicted that compensatory systemic vasoconstriction would occur in response to a cardiac functional depression [29]. Nowadays, it is well known that CS is the result of acute to subacute derangements in the entire circulatory system. Loss of LV function is the major cause, with subsequent systolic and diastolic dysfunction, but other parts of the circulatory system may also contribute to shock with inadequate compensation or by contribution of additional defects. Extremity and vital organ hypoperfusion is the hallmark of CS. Compensation mechanisms by vasoconstriction lead to an intermittent improvement in the coronary and peripheral perfusion, at the cost of an increased afterload. However, vasoconstriction can be off reverted by systemic inflammation, leading to subsequent pathologic vasodilatation which occurs frequently with increasing shock duration. Endothelial and inducible NO synthase may play a major role, with the production of inadequate high NO levels, and also peroxynitrite which has cardiac toxicity and is negatively inotropic. Other inflammatory markers, such as ILs and TNF, might also contribute to this phenomenon [28].

Another important aspect is bleeding which might also contribute to an increased mortality, as shown previously in trials with predominantly stable haemodynamic conditions [31, 32]. In particular in CS, bleeding will trigger transfusion, since it is generally believed beneficial that raising the haemoglobin levels via transfusion will increase O_2 delivery. However, blood transfusion itself increases the mortality risk [33]. Alterations in erythrocyte NO biology in stored blood may provide a partial explanation, leading to an initial vasoconstriction, platelet aggregation, and ineffective O_2 delivery. In addition, bleeding itself, as well as transfusion, contributes to inflammation [33]. The mechanisms behind the associations of bleeding and also transfusions with mortality are complex and may relate to several factors [34]. This complexity expands the current concept of the CS pathophysiology and its potential treatment options to interrupt the vicious shock spiral, as shown in Figure **49.1** [30].

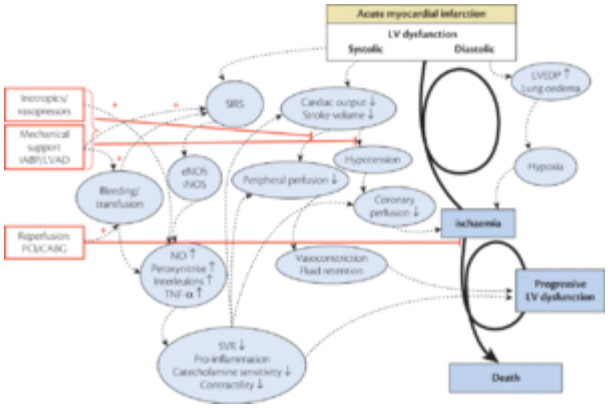


Figure 49.1
The pathophysiological concept of the expanded shock spiral. Treatment options, such as (1) reperfusion by PCI or CABG, (2) mechanical support by IABP or LVAD, and (3) inotropes or vasopressors, to reverse the shock spiral are shown on the left-hand side in red. Potential drawbacks of therapeutic interventions, including bleeding complications and influence on systemic inflammation, are shown. SIRS, systemic inflammatory response syndrome; LV, left ventricular; NO, nitric oxide; SVR, systemic vascular resistance; LVEDP, left ventricular end-diastolic pressure; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; TNF, tumour necrosis factor.
Adapted from Thiele et al. Shock in acute myocardial infarction: the Cape Horn for trials?, European Heart Journal, 2010, 31:15 by permission of Oxford University Press.

Risk factors and prognosticators

Because of the serious consequences of CS, the identification of patient subgroups with ACS at high risk for developing CS is important. In the fibrinolytic era, algorithms have been developed to predict the occurrence of in-hospital CS among patients with different types of STEMI and NSTEMI. These algorithms were validated in subsequent trials, with a high concordance index, indicating that these algorithms are applicable to both populations of ACS [35, 36]. In the PCI era, a recently validated algorithm the CardShock score has been proposed [37].

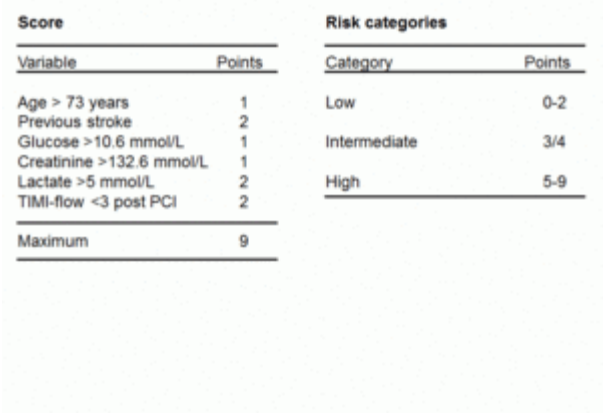
In case CS is present, it is also valuable to have prognostic markers for outcome prediction. In the fibrinolytic era, a score has been developed to predict mortality [38]. Adding variables, such as age, height, baseline heart rate and systolic blood pressure, the presence of VSD, the presence of FWR, prior infarction, prior angina, time to fibrinolysis, infarct location, Killip class, diabetes, smoking status, altered sensorium, cold and clammy skin, oliguria, and arrhythmia, led to a number of points predicting the 30-day death, ranging from 10% to 90%.

In the PCI era, CS mortality still can range from 10% to 80%, depending on demographic, clinical, and haemodynamic factors. These factors are similar in comparison to the pre-PCI era, including age, clinical signs of peripheral hypoperfusion, hypoxic brain damage, and LV function. In addition, initial haemodynamic parameters are predictive of short-term mortality. The strongest haemodynamic predictor is the cardiac power index which is derived from the product of the simultaneously measured cardiac index and the mean arterial blood pressure. Therefore, by coupling both pressure and flow domains of the cardiovascular system, this is a measure of cardiac pumping [39]. It is calculated by cardiac index × MAP × 0.0022 and is expressed as W/m^2. Among CS patients undergoing PCI, the time from symptom onset to PCI and the post-PCI TIMI flow grade are also independent predictors of mortality. Other prognostic parameters include the admission blood glucose, irrespective of diabetes status, creatinine clearance, the admission haemoglobin levels, and serum lactate [40–44]. More recently also, inflammatory markers, such as ILs and PCT, or the serum lactate clearance, as a marker of tissue hypoxaemia, have been predictive of CS survival [45–47]. In the CardShock score, adding the variables age >75 years (1 point), confusion at presentation (1 point), previous infarction or CABG (1 point), aetiology of ACS (1 point), ejection fraction <40% (1 point), serum lactate (<2 mmol/L [0 point], 2–4 mmol/L [1 point], >4 mmol/L [2 points]), and eGFR (>60 mL/min [0 point], 30–60 mL/min [1 point], <30 mL/min [2 points]) results in a maximum score of 9. The predicted mortality ranges from 15% for a score of 2 and close to 100% for a score of 9 [37].

The recently introduced IABP-SHOCK II score is the first score that has been validated against internal and external registry data. The score allows rapid prognosis estimation in the catheterization laboratory based on 6 variables including: [1]

1) Age >73 years
2) Previous stroke
3) Glucose at admission >10.6 mmol/L
4) Creatinine at admission >132.6 mmol/L
5) Arterial lactate >5 mmol/L
6) TIMI-flow <3 after PCI

Based on this, patients can be separated into low, intermediate and high-risk categories as shown in Figure **49.2**.



Score

Variable	Points
Age > 73 years	1
Previous stroke	2
Glucose >10.6 mmol/L	1
Creatinine >132.6 mmol/L	1
Lactate >5 mmol/L	2
TIMI-flow <3 post PCI	2
Maximum	9

Risk categories

Category	Points
Low	0-2
Intermediate	3/4
High	5-9

Figure 49.2
Based on 6 variables with a maximum of 9 points there are 3 risk categories. Patients in the low risk category bear a mortality risk of 20–30%, intermediate risk patients of 40–60%, and high-risk category patients of 70–90%. This score has been validated against an internal as well as external cohort [1].

Score	**Risk categories**
Variable	Points
Category	Points
Age > 73 years	1
Low	0–2
Previous stroke	2
Glucose > 10.6 mmol/L	1
Intermediate	3/4
Creatinine > 132.6 mmol/L	1
lactate >5 mmol/L	2
High	5–9
TIMI-flow <3 post PCI	2
Maximum	9

Treatment

Revascularization

Due to its limited efficacy, fibrinolysis (FL) is only reserved for STEMI patients when PCI is impossible, according to current ESC guidelines [2]. The SHOCK trial is one of the most important randomized trials in CS [22]. Although it failed to meet the primary endpoint—a reduction of 30-day mortality by an early revascularization-based management either with PCI or CABG—(46.7% vs 56.0%, $P = 0.11$) [22], there was a significant mortality reduction at 6 months [50] and long-term follow-up [51]. To save one life, <8 patients need to be treated by early revascularization, in comparison to initial medical stabilization.

Since the widespread application of early revascularization in clinical practice, mainly influenced by a class I B guideline recommendation [2, 48, 49, 51], 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 [4–7]. However, real-world revascularization rates range from 27% to 54% in the US [3] and 47% in the GRACE registry [53], and recently they have been reported to approach 70% in a Swiss, and 50% in a French registry [4, 5]. More efforts are needed to convince clinicians to recognize that benefits exist, despite the associated high risk. This is also important for the elderly patients. The apparent lack of benefit for the elderly in the SHOCK trial was likely due to imbalances between the groups. Several subsequent studies, including the SHOCK registry, have shown a consistent benefit of revascularization in elderly patients, which suggests that clinicians are capable of identifying those older patients who are appropriate for revascularization [54].

Revascularization strategy

Theoretically, there might be some influence by the revascularization type, i.e. PCI vs CABG, on outcome. Nevertheless, there is much uncertainty regarding the optimal revascularization type in CS [30], because all previous trials assessing the effect of revascularization on outcome did not specify the reperfusion type [18, 22, 55]. Given the current evidence from four observational reports, comparing PCI vs CABG, the type of revascularization does not influence the outcome of CS patients [56, 57]. In the current ESC revascularization guidelines, emergent surgery, after failure of PCI or FL, is only indicated in patients with persistent instability or life-threatening ventricular arrhythmia, due to extensive ischaemia such as left main or severe triple vessel disease (class 1 C recommendation) [49]. Furthermore, CABG is rarely performed, with only 4% of patients undergoing immediate CABG in the IABP-SHOCK II-trial and registry, which might represent current clinical practice [20]. (See also Chapter 48.)

More than 70% of CS patients present with multivessel disease or also left main disease [20, 58]. Current ESC STEMI guidelines encourage immediate multivessel PCI of all high-grade lesions, in addition to the culprit lesion, with a class IIa C recommendation. [2] with a class IIa B recommendation which is in contrast to recommendations in haemodynamically stable patients [48, 49]. These recommendations are mainly based on pathophysiological considerations. Current clinical evidence from registries, comparing multivessel PCI vs culprit-lesion-only PCI, does not support immediate multivessel intervention, with most of the trials showing an increased mortality with the multivessel PCI approach [59–62]. There is only one CS registry in patients after resuscitated cardiac arrest which showed an improved survival for the multivessel PCI approach [63]. The current evidence has recently been summarized in a meta-analysis showing an increased mortality at short-term follow-up with multivessel PCI and similar outcome at longer follow-up [3]. The results of short-term and long-term mortality are shown in Figure **49.3** However, non-randomized observational studies and registries are prone to treatment selection bias, precluding definitive conclusions. Therefore, the prospective randomized CULPRIT-SHOCK trial (Clinicaltrials.gov: NCT01927549) has been performed and recently finalized patient inclusion [74]. Results of this trial are anticipated by the end of 2017. (See also Chapter 47.)

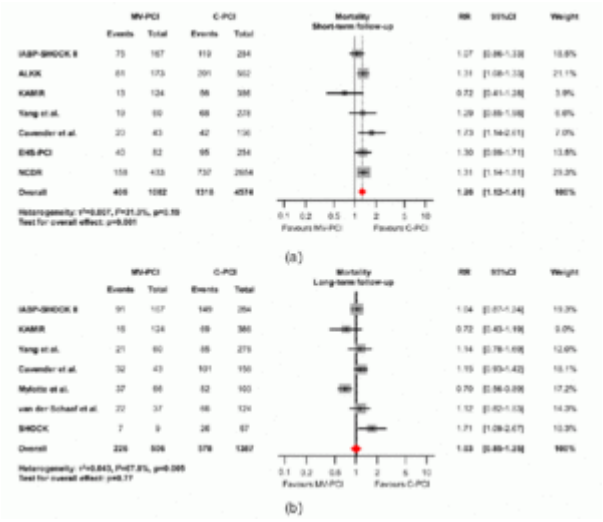


Figure 49.3
Forrest plot of short-term and long-term mortality comparing multivessel PCI versus culprit-only PCI in cardiogenic shock complicating acute myocardial infarction.
Reproduced with permisison from de Waha et al. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: A systematic review and

meta-analysis. European Heart Journal Acute Cardiovascular Care, *2017;epub ahead of print, Copyright 2017 Elsevier.*

In light of the limited evidence, it is not surprising that treatment modalities for multivessel disease in CS differ widely among different institutions, operators, and countries. Currently, multivessel PCI is performed in approximately one-third of CS patients with multivessel disease [20, 57].

Transradial versus transfemoral approach

In haemodynamically stable AMI patients, randomized data demonstrated superiority of transradial versus transfemoral access [75–77]. In CS, the benefit of transradial access is uncertain and has only been retrospectively investigated in registries and one small subanalysis of the RIFLE-STEACS trial [78]. Theoretically, the reduction of all-cause mortality driven by significant reduction of bleeding could also translate in improved prognosis in CS patients. A meta-analysis analysing data of 8131 patients demonstrated that transradial access was associated with a reduction in all-cause mortality as well as major adverse cardiac and cerebral events at 30-day follow-up in CS patients. The mechanisms behind this potentially improved outcome following transradial access have not been fully elucidated yet. Most likely, bleeding-related haemodynamic instability and other adverse influences such as blood transfusion-related oxidative stress may be especially critical in CS patients. Further, due to a lower rate of access site bleeding, patients undergoing transradial access could be more likely to receive aggressive antithrombotic therapy such as glycoprotein IIb/IIIa inhibitors. In general, in patients with palpable radial pulse the transradial access appears to be at least feasible. Radial access site may thus be used by experienced interventionalists in the shock setting. However, the radial route poses many potentially time-consuming technical challenges and the catheterization team should be prepared for a quick cross-over to transfemoral access in case of difficulties. Operators without extensive experience in transradial access are well advised to stick to a familiar (usually femoral) access or at least have a low threshold for crossover to a femoral approach.

Adjunctive medical treatment

Catecholamines

CS treatment includes initial stabilization with volume expansion, to obtain optimal filling pressures, vasopressors, and inotropes, plus additional therapy for multiorgan system dysfunction. Fluid administration is mainly based on pathophysiological considerations and has not been studied in adequate RCTs. The same applies to catecholamines, with pathophysiological considerations being based on the observation that stunned myocardium requires time until functional recovery after revascularization. This time should be bridged by inotropic and/or vasopressor support. The choice of catecholamine is mainly based on individual experience, institutional policy, and pathophysiological considerations. The mode of action of different inotropes and vasopressors has been reviewed previously [79]. ESC guidelines state that inotropic/vasopressor agents should be considered in CS, with IIa C recommendations for dopamine and dobutamine. In a RCT enrolling 1679 patients with shock of different causes, including 280 CS patients, treatment with dopamine, in comparison to norepinephrine, was associated with significantly more adverse effects—mainly arrhythmic events—for the overall study cohort, and the predefined CS subgroup experienced lower death rates with norepinephrine [80]. Therefore, when blood pressure is low and vasopressors are required, norepinephrine is preferred over dopamine, with a class IIb B recommendation in recent ESC STEMI guidelines [48]. This is somewhat confusing, given the higher class IIa C recommendation for dopamine which is also mainly a vasopressor. The recent Austrian/German CS guideline is more precise in stating that dopamine should not be used any more in the treatment of CS [73]. Norepinephrine should be titrated, until the systolic arterial pressure rises to at least 80 mmHg. Subsequently, IV dobutamine, due to its β2-adrenergic effects, may be given simultaneously, in an attempt to improve cardiac contractility [48].

Despite the favourable haemodynamic effects of all catecholamines, none has produced consistent improvement in symptoms, and many have shortened the survival [81]. These findings may be related to the fact that these agents increase myocardial O_2 consumption and also the concentrations of cyclic adenosine monophosphate (cAMP), producing an increase in intracellular calcium that possibly leads to myocardial cell death and/or increases lethal arrhythmias [79]. 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 [82].

Levosimendan

Levosimendan is a calcium sensitizer and a K^+–ATP channel opener, improving myocardial contractility. It might be an ideal agent in CS, because, in comparison to other inodilators, it improves myocardial contractility without increasing O_2 requirements and induces peripheral and coronary vasodilatation with a potential anti-stunning and anti-ischaemic effect. The use of levosimendan and its clinical evidence in different clinical settings have been reviewed in more detail previously [83]. Initial beneficial effects in small trials did not translate into a survival benefit in large-scale clinical trials [83]. Although levosimendan is one of the best studied inotropic agents in AHF, 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, when combined with catecholamines, to maintain adequate perfusion pressures [83]. Its current role in CS needs to be defined in further studies. In a recent large-scale randomized trial in septic shock comparing levosimendan versus placebo, there was no effect of levosimendan on severe organ dysfunction and mortality. However, there was a lower likelihood of successful weaning from mechanical ventilation [84]. This may influence the believe in this drug also in the CS setting, and a higher risk of supraventricular tachyarrhythmias; an increase is, however, some concern for the widespread use of this drug. Other recent trials in patients undergoing cardiothoracic surgery also failed to show a benefit for levosimendan once again supporting the lack of benefit of this drug on clinical outcome [4, 5].

A detailed overview on current and future inotropic agents has been published previously [82].

Adjunctive monitoring and treatment

Haemodynamic management

In addition to non-invasive monitoring by echocardiography, pulmonary artery catheters (PACs) are frequently used in heart failure to confirm the diagnosis of CS, to ensure that filling pressures are adequate, and to guide changes in therapy. The best use of this technique is to establish the relationship of filling pressures to the cardiac output in the individual patient and additional clinical assessment of responses. Haemodynamic data derived from PAC measurements, particularly cardiac power and stroke work index, have powerful short-term prognostic value [39]. In recent years, there has been a decline in PAC use, relating to controversy regarding the benefit, as shown in a meta-analysis [85]. Individualized PAC use is now recommended (IIb B ESC recommendation) for the monitoring of haemodynamic variables or to monitor treatment in patients with severe heart failure not responding to appropriate treatment [48, 73]. Clinical assessment with echocardiography is a

reasonable alternative. Both the pulmonary artery systolic pressure and PCWP can be accurately estimated with Doppler echocardiography, and, in particular, the finding of a short mitral deceleration time (<140 ms) is highly predictive of an increased PCWP of >20 mmHg in CS [86]. A recent consensus document gives recommendation on the use of haemodynamic monitoring in circulatory shock [87].

Glucose control

Patients in CS, as well as other patients in intensive care medicine, often develop hyperglycaemia as a result of a relative insulin resistance and accelerated glucose production. It is also well known that the glucose level at admission is a strong independent predictor for mortality in patients with and without the previous diagnosis of diabetes mellitus [43]. Based on a previous single centre trial in surgical intensive care patients showing a mortality decrease in patients with intensive insulin treatment, this has been adopted at many ICUs [88]. However, the NICE-SUGAR trial showed a mortality increase in patients with intensive insulin treatment, presumably caused by a higher incidence of hypoglycaemia [89]. Therefore, hypoglycaemia must be avoided in CS patients, and a moderate glucose control (≤180 mg/dL or 10.0 mmol/L) should be aimed for [73] (see Chapter 69).

Percutaneous mechanical support

Intra-aortic balloon pump

Intra-aortic balloon pump (IABP) is a mature technology after approximately five decades of use [90] (see Chapter 30). Through diastolic inflation and rapid systolic deflation in the aorta, it improves the peak diastolic pressure and lowers the end-systolic pressure. However, haemodynamic effects on the cardiac output are only modest [91]. Currently, IABP is the most widely used mechanical circulatory support (MCS) device for haemodynamic support [30]. Until recently, in American and ESC guidelines, IABP use in CS was a class I B and class I C recommendation, respectively [49, 92, 93]. This has been downgraded in the 2012 ESC guidelines to a class IIb B recommendation, and in the recent 2013 American guidelines to a class IIa B recommendation [48, 94]. This downgrading was mainly based on a systematic meta-analysis [95]. Due to a lack of randomized 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-fibrinolytic and fibrinolytic era [95]. In contrast, there was a 6% mortality increase in the PCI era [95]. This inconclusive evidence might be one reason why IABP in clinical practice is currently used in only 25–40% of CS patients [30, 96].

Based on a small pilot trial in 40 patients with CS, the large randomized multicentre IABP-SHOCK II trial has been conducted [97, 98]. IABP-SHOCK II randomized 600 patients with CS complicating AMI and early

revascularization to IABP or conventional treatment. There was no difference in the primary study endpoint 30-day mortality between the two treatment groups, and these results were confirmed by a lack of beneficial effects for any of the secondary study endpoints [20]. On the other hand, there were no safety issues with the use of the IABP [20]. The influence of these negative results led to a further downgrading in the ESC Revascularization guidelines and the most recent NSTE-ACS guidelines with a current class IIIB recommendation for the routine use of the IABP in cardiogenic shock [2, 99, 100]. The impact on clinical practice of the IABP-SHOCK II results has also recently been shown in a US registry, with a steady decline in the IABP use, since the publication of the IABP-SHOCK II trial.

Percutaneous left ventricular assist devices

Active percutaneous MCS devices have been used in patients not responding to standard treatment, including catecholamines, fluids, and IABP, and also as a first-line treatment (see Chapter 30). However, the current experience and evidence with MCS is limited [101]. Current devices, mode of action, and evidence regarding percutaneous MCS for treatment in CS have been summarized previously [102] and also recently in an updated review [103]. Figure **49.4** shows current devices, and Table 49.1 provides an updated overview of current percutaneous MCS features, including the Impella® CP, the paracorporeal pulsatile device iVAC 2L® (PulseCath BV, Arnhem, The Netherlands), the most recently introduced HeartMate percutaneous Heart Pump™ (HeartMate PHP™, St. Jude Medical, Pleasanton, CA, USA), and ECMO.

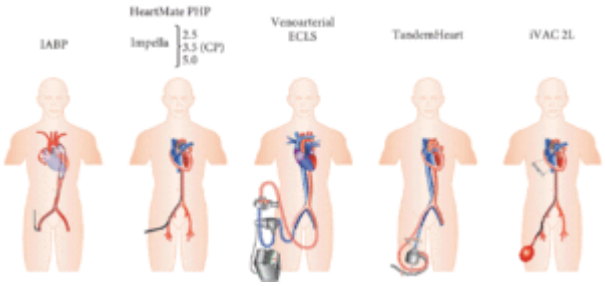


Figure 49.4
Schematic drawings of current percutaneous mechanical support devices: IABP, Impella®, venoarterial ECLS, TandemHeart™, iVAC 2L.

Table 49.1 Technical features of current percutaneous circulatory support devices

	iVAC 2L®	Tandem Heart™	Impella® 5.0	Impella® 2.5	Impella® CP	Heartmate PHP	ECLS (multiple systems)
Catheter size (F)	11 (expandable)	–	9	9	9	14	–
Cannula size (F)	17	21 venous 12–19 arterial	21	12		13	17–21 venous 16–19 arterial
Flow (L/min)	Max. 2.8	Max. 4.0	Max. 5.0	Max. 2.5	3.7 – 4.0	>4.0 (Max. > 5.0)	Max. 7.0
Pump speed (rpm)	Pulsatile, 40 ml/beat	Max. 7500	Max. 33 000	Max. 51 000	Max. 51 000	Max. 20 500	Max. 5000
Insertion/ Placement	Percutaneous (femoral artery)	Percutaneous (femoral artery + vein for left atrium)	Peripheral surgical (femoral artery)	Percutaneous (femoral artery)	Percutaneous (femoral artery)	Percutaneous (femoral artery)	Percutaneous (femoral artery + vein)
LV unloading	+	++	++	+	+	++	–
Anticoagulation	+	+	+	+	+	+	+

Recommended duration of use	–21 days	–4 days	10 days	10 days	10 days	6 hours	–7 days
CE-certification	+	+	+	+	+	+	+
FDA	–	+	+	+	+	–	+
Relative costs	++	+++++	++++	+++	++++	++++	+(+)

ECLS, extracorporeal life support system; LV, left ventricular; CE, conformité européenne; FDA, Food and Drug Administration.

Current devices include the TandemHeart™ (Cardiac Assist, Inc, Pittsburgh, US) which removes arterialized blood from the LA and returns it to the lower abdominal aorta or iliac arteries, via a femoral artery cannula, with retrograde perfusion of the abdominal and thoracic aorta. A more detailed description of the mode of action and implantation has been described previously [102, 104]. Another percutaneous device the Impella® 2.5, CP, or 5.0 (Abiomed Europe, Aachen, Germany) is placed across the aortic valve, using the femoral access, either percutaneously or by surgical cut-down. This device with the 2.5 L version has been tested in a small RCT in 26 CS patients, in comparison to IABP, showing an improved cardiac index with the use of the Impella® device.

HeartMate PHP™

This new axial flow device system consists of a covered nitinol cannula with integrated impeller that is introduced percutaneously over a 13 French introducer into the femoral artery (Figure **49.4**). The major design feature is a collapsible elastomeric impeller and nitinol cannula, which renders this device to the lowest profile insertion cannula with the highest flow. Once placed across the aortic valve, the cannula can be expanded to 24 French and allows for a continuous mean flow of >4 L/min at modest operating speeds (Table **49.1**). For removal, the system can be collapsed to the initial 13 French. Currently, data are limited for this device with only a small registry trial with 46 patients undergoing high-risk PCI (SHIELD-I) [105].

iVAC 2L®

The iVAC 2L® system is introduced percutaneously through the femoral artery and can provide a pulsatile support of approximately 2 L/min using an extracorporeal membrane pump via a 17 French cannula (Figure **49.4**, Table 49.1). In the systolic phase of the heart, blood is aspirated from the left ventricle through the catheter lumen into the membrane pump. During the diastolic phase the pump ejects the blood back through the catheter, subsequently opening the catheter valve and delivering the blood to the ascending aorta through the side outflow port, thereby creating an ‘extra heart beat’. Data are limited to small case series and the clinical impact of this device needs to be further investigated [106].

A meta-analysis reported the results of three randomized trials comparing percutaneous MCS devices vs IABP treatment [101], of which two trials compared the TandemHeart™ and one the Impella® 2.5 with IABP [107–109], altogether only 100 patients were included. Patients treated with active MCS demonstrated improved haemodynamics, as shown by a higher cardiac index, higher MAP, and lower PCWP, compared with IABP patients. On the other hand, there were differences observed in bleeding complications and also inflammation, mainly in the TandemHeart™ group.

However, there was no sign of improvement in 30-day mortality (relative risk 1.06, 95% CI 0.68–1.66) [30].

In the recent IMPRESS in Severe SHOCK trial 48 patients with CS complicating a STEMI and the need for mechanical ventilation underwent randomization to Impella CP versus IABP [110]. This trial had 30-day mortality as a primary endpoint. However, this trial was based on a power calculation with non-realistic mortality rates and thus this trial is markedly underpowered. The patients included were not in severe CS and mortality rates at 6-month follow-up very similar to other much larger trials. It is thus not surprising that there was no difference in the primary endpoint all-cause mortality after 30 days; however, the lack of benefit in any of the other parameters including serum lactate is a concern with respect to the efficacy of the device and the concept of mechanical circulatory support. Being largely underpowered, IMPRESS in Severe SHOCK can thus only be regarded as a feasibility trial. Reasons for the failure of this concept can be found in the accompanying editorial for IMPRESS in Severe SHOCK [111].

A most recent meta-analysis including the IMPRESS in Severe SHOCK trial showed no difference in mortality, some improvement in arterial lactate and also MAP. On the other hand, there were no significant improvements in cardiac index and also PCWP and significantly more bleeding complications [6]. The summary of the results are shown in Figure **49.5**

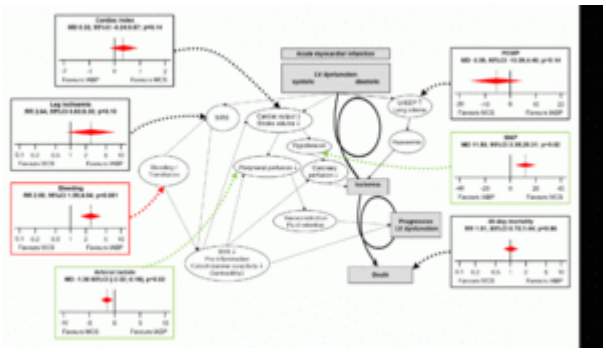


Figure 49.5
The pathophysiological concept of the expanded shock spiral and potential beneficial and negative effects of mechanical support devices based on a recent meta-analysis. IABP, intra-aortic balloon pumping; MCS, active mechanical support device; MD, mean difference; PCWP, pulmonary capillary wedge pressure; 95% CI, 95% confidence interval; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; SIRS, systemic inflammatory response.
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review and collaborative meta-analysis of randomized trials, European Heart Journal, *2017; epub ahead of print, Copyright 2017 Oxford University Press.*

Based on these results, percutaneous MCS cannot be recommended as first-line treatment in CS and are currently only considered in refractory CS with a class IIb C recommendation in ESC guidelines [2, 112]. Currently, there is another ongoing Danish randomized trial with the newly introduced Impella® CP, in comparison to standard treatment, with or without IABP.

Extracorporeal membrane oxygenation (ECMO)

After the introduction of the first cardiopulmonary bypass (CPB) system in 1953, further developments led to percutaneous applicable devices [113]. These systems consist mainly of a blood pump and an oxygenator. After pump priming, blood is withdrawn from the right atrium and pumped through a heat exchanger, through a membrane oxygenator, and ultimately returned into the femoral artery. There are several drawbacks to these devices such as large cannulae sizes, with subsequent lower limb ischaemic complications, often requiring perfusionists, the lack of direct unloading, afterload rise, and a limited support time [114]. There are only limited experiences in CS, with one single centre, non-randomized retrospective analysis showing an improved survival with ECMO support, in comparison to historical control [115]. In a recent prospective report, ECMO in-hospital mortality was as high as 63.2%. Patients with age >62 years and with prior resuscitation even had a mortality of 100%, questioning the use of ECMO in unselected patients [116]. In another recent registry, mortality for patients with ECMO was also extremely high and the recent data suggest that only younger patients may have a benefit from ECMO [117]. In a recent meta-analysis based on observational registry data ECMO was associated with a 33 % higher 30-day survival compared with IABP (95% confidence interval 14–52%; $p<0.001$) but no difference when compared with TandemHeart/Impella (−3%; 95% confidence interval −21 to 14%; $p=0.70$) [7].

Taken together, although mechanical circulatory support with LVADs or ECMO is theoretically appealing to interrupt the vicious spiral of ischaemia, hypotension, and myocardial dysfunction, allowing for the recovery of ischaemic myocardium, the extracorporeal support and contact with artificial surfaces of LVADs might further promote SIRS. A second, potentially deleterious, effect of extracorporeal circulation, besides the propagation of inflammation, is the activation of complement and the development of coagulation with subsequent FL, which may progress to DIC, leading to severe bleeding complications. Currently, percutaneous LVAD treatment should be restricted to the use in refractory CS and will rely on individual experience in dedicated centres for highly selected patients. Additional randomized trials are needed for a

more complete assessment of the role of different circulatory supportive strategies in CS.

Treatment of mechanical complications

Ventricular septal defect

VSD complicating AMI is a relatively rare event associated with high mortality (see Chapter 45). The incidence of infarct-related VSD without reperfusion ranged from 1% to 2% [118, 119], with a decrease to 0.2% in the era of reperfusion [120]. The median time from infarction to rupture is usually 24 hours but may occur up to 2 weeks. Without surgical repair of post-infarction VSD, 90% of patients die within 2 months [121].

Surgical VSD correction was first described in 1957 [122]. The current mortality of surgical post-infarction VSD closure is as high as 50% [123, 124]. In two prospective registries, the mortality rates were as high as 81–100% for patients with VSD and CS [120, 125]. Current guidelines recommend immediate surgical VSD closure, irrespective of the patient's haemodynamic status, to avoid further haemodynamic deterioration [48, 49]. Nevertheless, a subgroup of patients with VSD exists, for whom surgery is futile, because mortality approaches 100%; this includes the very elderly and patients with poor RV function. In general, implantation of an IABP before surgery is recommended [48, 49].

As a result of the high mortality and suboptimal surgical results with a post-operative residual shunt found in up to 20% of treated patients [120, 124, 126], the technique of percutaneous VSD device closure has been developed [127]. Such less invasive approach with a catheter-based intervention may offer improved survival or provide haemodynamic stabilization as a bridge to surgery. Furthermore, it might be used as an adjunctive therapy for residual post-surgical shunts. Currently, data are limited for post-infarction VSD interventional closure. The largest single-centre experience in 29 patients reported a survival rate at 30 days of 35%, with much higher mortality in CS, as opposed to non-shock patients (88% vs 38%, $P < 0.001$) [127]. Procedure-related complications are frequent which further demonstrates the requirement of technical improvement. An overview on potential technical improvements and outcomes has recently been published [128]. Furthermore, a metaanalysis on all published reports with percutaneous VSD closure has recently been published [129].

Free wall rupture

Since many patients with FWR present with sudden profound CS, often rapidly leading to PEA caused by pericardial tamponade, there are limited treatment options. However, there might also be subacute presentations in cases of a covered rupture. an immediate pericardiocentesis can confirm the diagnosis, in addition to echocardiography which is the cornerstone of the diagnostic work-up. Pericardiocentesis (see Chapter 27) relieves pericardial tamponade at least momentarily for an immediate surgical repair, if available. In a less acute clinical course, this allows for potentially lifesaving therapeutic interventions. In the SHOCK trial registry, 28 patients presented with pericardial rupture or tamponade. The overall in-hospital mortality for this specific cohort, of which 75% underwent surgery, was as low as 39% [130]. However, this was a selected patient group, with not all having an overt clinical FWR.

Acute ischaemic mitral regurgitation

In acute ischaemic MR, only papillary muscle rupture needs immediate repair. Other causes, such as LV global or regional remodelling or ischaemic papillary muscle dysfunction, may resolve after revascularization and recovery of the LV function. Accordingly, only 46% of the patients in the SHOCK trial registry underwent mitral valve surgery [131]. In contrast to VSD repair, surgery of papillary muscle rupture does not involve necrotic myocardium in suture lines. Therefore, the mortality associated with this repair is lower [131]. The unpredictability of a rapid deterioration and death with papillary muscle rupture makes early surgery necessary, even though there may be an initial apparent haemodynamic stabilization with initial IABP therapy which is highly recommended by guidelines as a bridge to surgery, although no randomized data are available for this condition [48, 49]. Recently also, the first percutaneous approaches with the MitraClip system have been reported for the treatment of acute ischaemic mitral regurgitation with cardiogenic shock. However, current evidence is very limited [132].

Treatment of right ventricular failure

A detailed review of the pathophysiology and the treatment of CS from RV failure has been published previously [133, 134]. It is of paramount importance to establish early reperfusion to reverse RV ischaemia, to maintain an adequate RV preload with volume loading, to preserve synchrony (possibly using dual-chamber temporary pacing or even biventricular pacing), and to reduce the RV afterload with IABP and potentially inotropes. Traditionally, the treatment of patients with RV dysfunction with CS focused on ensuring adequate right-sided filling pressures to maintain the cardiac output and an adequate LV preload. However, often patients with shock due to RV dysfunction have relatively high end-diastolic pressure, often exceeding 20 mmHg. This may result in the shifting of the interventricular septum towards the LV, impairing LV

filling and systolic function [135]. Therefore, the common practice of aggressive fluid resuscitation for RV dysfunction in CS can be misleading. Inotropic therapy is therefore indicated for RV failure when CS persists after preload optimization. In extreme cases, both pericardectomy and the creation of atrial septal defects have been used [133]. CS due to isolated RV dysfunction carries nearly the same mortality risk as left-sided CS, and the benefit of revascularization is similar, as shown in the SHOCK trial registry [136].

Personal perspective

The mortality of CS patients is still unacceptably high. The incidence of CS, however, is slightly declining, due to more rapid and efficient reperfusion by primary PCI. In cases where CS has developed, there is crucial importance for a multidisciplinary team and a specialized centre in its management to improve the clinical outcome of these patients. If patients are treated according to guidelines, with an early reperfusion for all patients and an optimal intensive care treatment, the mortality of CS may be reduced to 40%, as shown in a recent randomized trial [20].

Currently, there are many unsettled issues, such as the type of reperfusion (culprit-lesion-only PCI vs multivessel PCI), the optimal inotrope or vasopressor support, the role and potential treatment options of concomitant inflammation, the selection and timing of patients for mechanical support with LVADs, the type of LVAD, the optimal mechanical ventilation, the treatment of bleeding complications, among many others. Some of these open questions are addressed by ongoing trials, such as the CULPRIT-SHOCK trial, the Danish shock trial, or trials assessing the effect of mild induced hypothermia on haemodynamic improvements and outcome [137].

In general, RCTs in CS are difficult to perform and are often more costly than trials in other clinical conditions, due to the complexity of the studies. Therefore, many believe that conducting a randomized study in this critically ill population is still not possible, due to difficulties of enrolling and randomizing these critically ill patients. However, as infarctions are frequent, and CS inherited with high mortality, any intervention which reduces mortality is likely to have major public health implications and should therefore be thoroughly tested.

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