Management of cardiogenic shock complicating myocardial infarction

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ABSTRACT

Up to 10% of acute coronary syndromes are complicated by cardiogenic shock with contemporary mortality rates of 40-50%. The extent of ischemic myocardium has profound impact on the initial, in-hospital, and post-discharge management and prognosis in this patient population. Individualized patient risk assessment plays an important role in determining appropriate revascularization, drug treatment with inotropes and vasopressors, mechanical circulatory support, intensive care support of other organ systems, hospital level of care triage, and allocation of clinical resources. This review will outline the underlying causes and diagnostic criteria, pathophysiology, and treatment of cardiogenic shock complicating acute coronary syndromes with a focus on potential therapeutic issues from an interventional cardiologist's, an emergency physician and an intensive care physician's perspective on the type of revascularization, new therapeutic advancements in pharmacologic and mechanical percutaneous circulatory support.

Abbreviations

AHA	American Heart Association
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
AST	Aspartate Aminotransferase
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CCU	Coronary Care Unit
CI	Cardiac Index
CVP	Central Venous Pressure
CS	Cardiogenic Shock
ECG	Electrocardiography
ECLS	Extracorporeal Circulatory Life Support
ECMO	Extracorporeal Membrane Oxygenation
ERC	European Resuscitation Council
ESC	European Society of Cardiology
ESICM	European Society of Intensive Care Medicine
IABP	Intra-aortic Balloon Pump
ICU	Intensive Care Unit
KDIGO	Kidney Disease: Improving Global Outcomes
LV	Left Ventricle
MAP	Mean Arterial Pressure
MCS	Mechanical Circulatory Support
MV	Mechanical Ventilation
NE	Norepinephrine
NIV	Non-invasive Ventilation

NSTE-ACS	Non-ST-Segment Elevation Acute Coronary Syndrome
OHCA	Out-of-hospital cardiac arrest
PAC	Pulmonary artery catheter
PCI	Percutaneous Coronary Intervention
RCT	Randomized Controlled Trial
RRT	Renal Replacement Therapy
RV	Right Ventricle
ST2	Suppression of Tumorigenicity 2
STEMI	ST-Elevation Myocardial Infarction
TIMI	Thrombolysis In Myocardial Infarction
TTM	Targeted Temperature Management
VA-ECMO	Veno-arterial Extracorporeal Membrane Oxygenation
VSD	Ventricular Septal Defect
VSR	Ventricular Septal Rupture

INTRODUCTION

Cardiogenic shock (CS) as defined by the European Society of Cardiology (ESC) and the American Heart Association (AHA) is a state of critical end-organ hypoperfusion due to primary cardiac dysfunction. [1-3] Diagnostic criteria include hypotension (i.e. systolic blood pressure <90 mmHg, or vasopressors required to achieve a blood pressure ≥90 mmHg), and signs of impaired organ perfusion (e. g. central nervous system abnormalities including confusion or lack of alertness, or even loss of consciousness; oliguria; cold, clammy skin and extremities, increased arterial lactate >2 mmol/L) in the state of normovolemia or hypervolemia. Some clinical trials criteria also included hemodynamic parameters such as reduced cardiac index (CI, i.e. <1.8 L/min/m^2 or <2.2 L/min/m^2 with cardiac support), or elevated left-ventricular filling pressures (i.e. pulmonary capillary wedge pressure >15 mmHg). [4] However, CS is a clinical diagnosis and does not require pulmonary artery catheterization. The clinical severity ranges from mild hypoperfusion to a pulseless state. [5] Of note, some described a “pre-shock state” that includes patients at risk for CS.[6] In addition, patients can have normotensive CS where hypoperfusion is present without hypotension. In a cohort of 49 patients, even in the presence of normal blood pressure, clinical signs of peripheral hypoperfusion, which may be subtle, are associated with a substantial risk of in-hospital death following acute myocardial infarction (AMI). [7] The most severe form of CS is also named “refractory CS” defined as a persisting shock despite the administration of volume, inotropes, vasoconstrictors.

CS following acute myocardial infarction (AMI) has an incidence of 5-10% and is the leading cause of mortality in patients with AMI.[8] Half of the cases of CS are present at hospital admission and the other half is develops following hospital admission. [8] Among patients with AMI, the SHOCK trial registry reported that predominant left ventricular failure (78.5%) was the most common etiology of CS, followed by severe mitral regurgitation (6.9%),

ventricular septal rupture (VSR) (3.9%), right ventricular failure (2.8%), and cardiac tamponade (1.4%). [9]

Short-term mortality in CS complicating AMI is 40-60% and even more than 80% in case of ventricular septal rupture. [9] Mortality in CS is mostly seen in the intensive care unit (ICU). [10] However, post-discharge mortality and symptomatic heart failure in CS patients is still higher than after AMI without CS. [11]

Several clinical and biological factors have been used for prognosis assessment. Those factors have been recently regrouped on scores combining independent parameters – the Sleeper score (8 items; score from the SHOCK trial 2010), [12] the CardShock risk score (7 items as prior infarction and coronary artery bypass grafting are taken as one; 2015), [13] and the IABP-SHOCK II risk score (6 items; 2017) (**Table 1**)**.** [14] Based on 6 variables with a maximum of 9 points there are 3 risk categories in the IABP-SHOCK II score. Patients in the low, intermediate, and high risk categories have an in-hospital mortality risk of 20-30%, 40-60%, and 70-90%, respectively. This prediction model is the first CS score with both internal and external validation.[14]

CONTEMPORARY MANAGEMENT OF CARDIOGENIC SHOCK AND AMI

CS patients may benefit as early as possible from pre-hospital management (**Figure 1**), coronary revascularization, hemodynamic resuscitation and optimization, and the assessment and treatment of end-organ dysfunction. Notably, revascularization is the only well study evidence-based therapy with proven survival benefit. To provide benefit from this contemporary management of CS due to AMI, individual hospitals should be part of a regional network that includes a tertiary cardiogenic shock center.

Revascularization

Due to its limited efficacy, fibrinolysis should be reserved for ST-elevation myocardial infarction (STEMI) patients when timely percutaneous coronary intervention (PCI) is not

feasible.[15] The SHOCK trial is one of the milestone randomized trials in CS.[16] 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),[16] there was a significant mortality reduction at 6 months and at long-term follow-up.[17]

Since the widespread application of early revascularization in clinical practice, mainly influenced by a class I B guideline recommendation,[15, 18, 19] 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.[8, 20] Real-world revascularization rates range from 27% to 54% in the US,[20] 47% in the GRACE registry,[21] 70% in a Swiss registry,[8] and 50% in a French registry.[22] This finding suggests knowledge translation and implementation of early revascularization, despite the associated high risk, are a clinical priority.

Up to 85% of CS patients present with multivessel coronary artery disease or left main disease.[23] Patients presenting with multivessel coronary artery disease have higher mortality compared to patients with single vessel disease. 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.[18] These recommendations are mainly based on pathophysiological considerations. The current evidence has recently been summarized in two meta-analyses showing an increased mortality at short-term follow-up with multivessel PCI and similar outcome at longer follow-up.[23, 24] Recently, the randomized, multicenter Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial showed a significant clinical benefit of a culprit-lesion-only strategy with a reduction in the primary endpoint of 30-day mortality or severe renal failure requiring renal replacement therapy (45.9% culprit-lesion-only PCI versus 55.4% immediate multivessel PCI group; relative risk 0.83; 95% confidence interval 0.71-0.96; P=0.01) which was mainly driven by an absolute 8.2% reduction in 30-day mortality (43.3% versus 51.5%; relative risk 0.84; 95% confidence interval 0.72-0.98, P=0.03).[25] The CULPRIT-SHOCK results were consistent across all predefined subgroups. Thus,

revascularization should be limited to culprit lesion only with possible staged revascularization. Intuitively, some angiographic subgroups, such as occluded right coronary artery culprit lesion with a concomitant high-grade proximal left anterior descending coronary artery or additional non-culprit subtotal lesions with Thrombolysis In Myocardial Infarction (TIMI) flow 1 or 2 may call for immediate multivessel PCI. However, this should be considered on an individual basis.

There may also be a role for emergent coronary artery bypass grafting; however, there is little evidence to guide surgical versus PCI revascularization. Current evidence from four observational reports, comparing PCI vs coronary artery bypass grafting (CABG), the type of revascularization did not influence the outcome of CS patients. [26, 27] In current clinical practice, immediate CABG is only performed in less than 4% of patients. [8, 28]

The ESC STEMI and NSTE-ACS guidelines recommend radial access (class 1 A) in stable patients if performed by experienced radial operators. [2, 29-31] In CS, the benefit of radial access is less evidence-based. A meta-analysis analyzing data of 8131 registry patients demonstrated that radial 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. [32] We propose to favor the radial access in case of experienced radial operators and in patients with a palpable radial pulse. Otherwise the femoral access may be chosen.

Platelet inhibitors, anticoagulation

Antithrombotic therapy including antiplatelets and anticoagulation is key during and after PCI. There are no specific trials in CS for oral antiplatelets, however it is well known that in CS enteral resorption is impaired. Besides impaired enteral perfusion mechanical ventilation with inability to swallow oral P2Y12 inhibitors plays a major role for the bioavailability of these drugs. Prasugrel/ticagrelor or clopidogrel in case of contraindications for the newer oral antiplatelets is indicated in addition to aspirin in all patients undergoing PCI. In intubated patients crushed tablets need to be administered through a nasogastric tube. In stable infarction patients crushed ticagrelor improved platelet inhibition in comparison to non-crushed tablets.[33] Because of the late and impaired onset of oral antiplatelets glycoprotein

IIb/IIIa-inhibitors or cangrelor may be more liberally used in CS. During PCI, adjunctive anticoagulation including unfractionated heparin or low molecular weight heparin should be co-administered with antiplatelets. With a lack of specific randomised trials in CS the same recommendations apply as for other types of acute coronary syndrome.[15, 19]

Mechanical complications

The incidence of infarct-related VSR without reperfusion ranged from 1-2%with a decrease to 0.2% in the era of reperfusion. [34] The median time from infarction to rupture is usually 24 hours but may occur up to 2 weeks. Without surgical repair of post-infarction VSR, 90% of patients die within 2 months. [35] Current mortality of surgical post-infarction VSR closure is as high as 50%. However, in two prospective registries, mortality rates were as high as 81–100% for patients with VSR and CS. [34, 36] Current guidelines recommend immediate surgical VSR closure, irrespective of the patient's hemodynamic status, to avoid further hemodynamic deterioration. [37] Nevertheless, a subgroup of patients with VSR exists, for whom surgery is futile, because mortality approaches 100%; this includes the very elderly and patients with poor right ventricular function. 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, the technique of percutaneous VSR device closure has been developed. Though data are limited for post-infarction VSR interventional closure. A meta-analysis on all published reports with percutaneous VSR closure has recently been published showing similar mortality data compared to surgery. [38]

In acute ischemic mitral regurgitation, only papillary muscle rupture needs immediate repair. Other causes, such as left ventricular global or regional remodeling or ischemic papillary muscle dysfunction, may resolve after revascularization and recovery ventricular function. Accordingly, only 46% of the patients in the SHOCK trial registry underwent mitral valve surgery. [39] In contrast to VSR repair, surgery of papillary muscle rupture does not involve necrotic myocardium in suture lines. Therefore, mortality associated with this repair is lower.

[39] The unpredictability of a rapid deterioration and death with papillary muscle rupture makes early surgery necessary.

Regional cardiogenic shock center network

Regional systems of care coupled with treatment algorithms have improved survival in MI. As recently suggested by American Heart Association (AHA), applying a similar framework to CS management may lead to similar improvements in survival, and CS systems of care are emerging within existing regional cardiovascular emergency care networks (AHA guidelines). [3]

In a regionalized system of care for CS, individual hospitals would have CS treatment algorithms according to onsite capabilities, in relation with the leadership of regional “cardiac shock” center(s). In order to allow continuity in CS management, “cardiac shock” centers would require to create mobile multidisciplinary CS teams available 24 hours a day, 7 days a week for onsite or offsite consultation, referral, and extracorporeal membrane oxygenation (ECMO)/ mechanical circulatory support (MCS) insertion (**Figure 2**). In addition, cardiogenic shock centers would have therapeutic technologies, including PCI and temporary MCS.

HEMODYNAMIC MANAGEMENT IN THE ICU

Recognition of CS should trigger a swift assessment of the etiology and hemodynamic profile based upon history, physical examination, laboratory investigations, electrocardiogram (ECG) and echocardiography. Although initial assessment and management does not require invasive hemodynamic monitoring, **Table 2** provides an overview of the main indications for advanced hemodynamic monitoring.

Arterial line

Arterial blood pressure should be monitored using a continuously transduced arterial line and more advanced invasive hemodynamic monitoring may be considered in severe refractory

cases and/or when mechanical complications supervene. The initial target mean arterial blood pressure should be in the range of 60-65 mmHg. However, this blood pressure target has not been validated in randomized clinical trials. [40] An arterial line also allows regular blood gas analysis and arterial lactate monitoring. Devices based on arterial waveform analysis through proprietary algorithms have been developed to measure a number of hemodynamic parameters, including cardiac output. Despite their widespread use, a number of studies have shown inconsistent performance of these devices in the setting of acute/very low cardiac output states and CS. [41]

Central venous catheter

The central venous waveform allows visualization of an elevated pressure (in the context of respiratory support), or abnormal waveform should trigger further evaluation of both, heart and lungs/ventilatory parameters. The insertion of a central venous catheter also allows to analyze $ScvO_2$ for the assessment of the ratio of global oxygen demand and supply, hence response to therapy. The central line also represents the preferential route for the administration of inotropes and/or vasopressors. [42] Finally, central line trajectory monitory may help to estimate congestion of extrathoracic organs such as the kidneys as it directly translates to output pressure of intra-abdominal organs. Hence, all efforts should be made to keep the central venous pressure <12 mmHg.

Echocardiography

In the context of CS, transthoracic echocardiography has strengths and weaknesses. Indeed, echocardiography is recommended repeatedly during ICU stay for evaluation of left and right ventricular function, valve dysfunction and exclusion/diagnosis of mechanical complications. Echocardiography is also emerging as a hemodynamic monitoring tool in ICUs to estimate cardiac output, cardiac filling pressures, predict volume responsiveness and determine response to critical care interventions. [43] Its use in monitoring patients with CS, however, can prove challenging. First, there are a number of intensive care interventions that may

fundamentally alter echocardiographic findings, and every study must be interpreted in the pharmacopathological context. Second, few parameters validated in either the outpatient or general cardiology setting have been validated in CS complicating AMI. Third, unlike invasive monitoring, echocardiography cannot measure intracardiac pressures, merely provide an estimate of pressure differences between different chambers. The intelligent application of physiological echocardiography (i.e. stroke distance, pulmonary vascular resistance, cardiac electromechanics including ventricular-ventricular interactions and heart-lung/ventilator interactions), interpreted in the clinical context can, however be used to monitor and guide ongoing interventions, including requirement for pacing interventions, vasoactive drug therapies and ventilatory settings. [44] Further, echocardiography is mandatory for the use of mechanical circulatory support in order to assess contraindications, inform the type and level of support required, guide and monitor institution of support, assess complications and predict potential for weaning. [44] Ultrasound also provides information on lung congestion and pleural effusion.

Pulmonary artery catheter (PAC)

Randomized studies and several meta-analyses have failed to confirm a clinical benefit of the PAC in a wide range of critically ill patient pathologies. [45-47] Current recommendations of the European Society of Intensive Care Medicine still consider PAC as a useful tool in some patients with severe CS, especially in case of right ventricular dysfunction or CS unresponsive to initial therapies, reflecting standard practice in expert centers in the management of this condition. [13, 40]

Laboratory testing

In case of CS related to AMI we recommend performing full laboratory testing, ideally twice a day, until restoration of stable hemodynamic parameters. Laboratory testing can indicate in the first hours the extent of organ injury and the prognosis of the patients while serial measures give information on the aggravation or recovery of organ functions. Laboratory

testing should include troponin, natriuretic peptides (and ST2 for prognosis [48]), lactate (mostly in the first days [49]), renal, liver, and basic coagulation function tests as well as blood count.

Inotropes and vasopressors

Hemodynamic alteration in CS complicating AMI includes cardiac impairment with or without low vascular resistance. [50] In addition to timely revascularization, vasopressors and/or inotropes are required to restore systemic perfusion in the pre-hospital setting, in the catheterization laboratory, or in the ICU. In general, inotropes and vasopressors should be used at the lowest dose and the shortest time possible. Furthermore, these agents have different effects at different doses making interpretation of the evidence even more difficult. In addition, we suggest that clinicians integrate clinical, laboratory, and hemodynamic variables to determine response to therapy to determine appropriate vasoactive drug dosing and titration based on clinical, laboratory, and hemodynamic multimodal monitoring.

When blood pressure needs to be rapidly restored, norepinephrine may be a reasonable first line agent. Various studies showed that norepinephrine is safer than dopamine, [49] vasopressin, [51] or epinephrine, with a lower risk of atrial arrhythmias. [48]

Given the reduced cardiac output in CS, the addition of an inotropic agent may help to improve stroke volume after hemodynamic stabilization with an inopressor. In case of evidence of predominant low cardiac output and preserved perfusion pressure, dobutamine is the initial therapy and (starting dose 2.5 µg/kg/min) may act rapidly to restore stroke volume.

Concerning inotropic agents associated with vasodilator properties, levosimendan may also be used in particular in patients on chronic beta-blocker therapy given its inotropic effect being independent of beta-adrenergic stimulation. [1] However, further studies are needed.

The following agents are generally not considered first-line therapies in CS: 1) Dopamine was shown to be associated with increased 28-day mortality as compared to norepinephrine although this effect may be explained by play of chance. [52] In the same study, dopamine

showed also higher number of arrhythmias. [52] 2) Epinephrine led to higher lactate levels in a small randomized trial in CS. [53, 54] This is supported by a retrospective analysis of the Cardshock cohort revealing that epinephrine use was associated with higher short-term mortality. [48] A prospective double-blind multicenter study confirmed detrimental effect of epinephrine on outcome in CS patients. [55] 3) Vasopressin is also not preferred because this drug did not change cardiac power index and cardiac index while norepinephrine increased it.[51]

Mechanical circulatory support

Recommendations on the use of intraaortic balloon pump (IABP) and extra-corporeal life support in CS will be described below. A consensus nomenclature of various extra-corporeal life supports was recently described.[56]

Intraaortic balloon pump

The IABP-SHOCK II randomized 600 patients with CS complicating AMI and early revascularization to IABP or conventional treatment and found no difference in the primary study endpoint 30-day mortality between the two treatment groups. [28] The results of the primary study endpoint were confirmed by a lack of beneficial effects for any of the secondary study endpoints and also through longer follow-up. [28, 57] These results led to a downgrading of the IABP in the ESC guidelines with a current class IIIB recommendation for the routine use of the IABP in cardiogenic shock. [15, 19] The 2017 ESC STEMI guidelines now recommend IABP consideration only in patients with mechanical complications (class IIa, level C).[15]

Percutaneous active mechanical circulatory support devices

Partly a result of the lack of benefit of IABP, active MCS are increasingly used.[58, 59] However, the current evidence to support the routine use of MCS is limited. [60] Current devices, mode of action, and evidence regarding percutaneous MCS for treatment in CS

have been summarized previously. [61] **Table 3** gives an overview over current devices and technical features.

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. Another percutaneous device is the Impella® 2.5, CP, or 5.0 (Abiomed Europe, Aachen, Germany) which is placed across the aortic valve, using the femoral access, either percutaneously or by surgical cut-down.

In the recent IMPRESS-in-Severe-SHOCK trial 48 patients with STEMI associated CS requiring mechanical ventilation were randomized to Impella CP versus IABP.[62] The 30-day mortality primary endpoint was based on a power calculation with non-realistic mortality rates and thus this trial is markedly underpowered. 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 arterial lactate may be a concern with respect to the efficacy of the device.[63] A trial adequately powered for trial of in patients with CS is required before routine therapy with this device can be recommended.

A most recent meta-analysis including the IMPRESS-in-Severe-SHOCK trial showed no difference in mortality for overall 148 included patients. There was some improvement in arterial lactate and also MAP. On the other hand there were significantly more bleeding complications. [60] Some registry data suggest a benefit for MCS insertion before revascularization. [64, 65] However, these data need to be confirmed in randomized trials.

VA-ECMO

Extracorporeal circulatory support (ECLS) with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is another potential first-line device in CS since it provides both respiratory and cardiac support. [66] VA-ECMO bypasses the heart and/or the lung due to extraction of blood from a venous inflow cannula and return to the arterial system via an outflow cannula after decarboxylation and oxygenation. [67] It may be the preferred option in cases of CS because of few major advantages: 1) the possibility of rapid application, 2) the

applicability in case of malignant arrhythmia due to lack of alteration of flow condition and 3) rapid improvement in oxygenation. On the other hand, VA-ECMO carries a relevant risk of thromboembolic events and limb ischemia. It increases left ventricle afterload, which may impair heart function recovery and aggravate hydrostatic pulmonary edema. [68] Furthermore, it requires a specialist team to insert and run ECMO such as perfusionists or ECMO specialists. Strategies combining IABP or IMPELLA and VA-ECMO to decrease LV pressures have suggested a clinical benefit which should be evaluated in specific trials.[69, 70] In a recent meta-analysis based on observational registry data VA-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).[71]

Taken together, although MCS are theoretically appealing devices that may interrupt the vicious spiral of ischemia, hypotension, and myocardial dysfunction and allow for the recovery of ischemic myocardium, the extracorporeal support and contact with artificial surfaces of these devices might further promote the systemic inflammatory response. A second potentially deleterious effect is severe bleeding.

Currently, percutaneous MCS should be restricted to the use in refractory CS (class of recommendation II b C) and will rely on individual experience in dedicated centers for selected patients.[15] Additional randomized trials are needed for a more complete assessment of the role of different circulatory supportive strategies in CS. [72]

MANAGEMENT OF ORGAN DYSFUNCTION (Figure 2)

Respiratory distress

Chest X-ray at admission allows assessing pulmonary congestion, cardiac size and the position of endotracheal tube and supportive devices (pacing wires and MCS).

CS related to LV failure is usually complicated by pulmonary edema associated with impaired gas exchange. [73] Metabolic acidosis increases the compensatory respiratory load. Most

CS patients may need respiratory support to provide adequate gas exchange and to relieve the work of breathing. The majority of guidelines and reviews recommend invasive ventilation in CS, and its use ranges from 60 to 80%. In isolated right ventricular failure, whether those patients are mechanically ventilated or on non-invasive ventilation (NIV), caution is advised due to undesirable effect of positive end-expiratory pressure on right ventricular afterload and function. [73] In few patients with acute pulmonary edema and mild metabolic and hemodynamic alterations, NIV can be installed and seems a safe option. [74]

Acute kidney injury

The incidence of acute kidney injury (AKI) – defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria – is roughly one third in CS patients [68]. Increased creatinine levels and anuria – but not oliguria - was associated with increased mortality. The development of AKI seemed at least partly associated with persistent decrease in CI and MAP and elevated central venous pressure. In case of AKI, we recommend a rapid restoration of renal perfusion pressure and avoiding the use of nephrotoxic agents. Data supporting those recommendations are needed.

Acute liver injury

Overall, elevated liver parameters can be interpreted as generally poor hemodynamic status. Liver function tests are altered in over 50% of patients suffering from cardiogenic shock. [75] Elevated alanine transaminase (ALT) and aspartate transaminase (AST) may be interpreted as a direct sign of liver hypoperfusion, associated with increased mortality. Hemodynamics should be stabilized as in renal dysfunction.

Brain injury due to resuscitated cardiac arrest

Registries and trials have reported a 29-41% incidence of cardiac arrest in patients with CS following MI. [76-79]. The optimal brain management of these patients has not been well studied. The European Resuscitation Council and the European Society of Intensive Care

Medicine guidelines for post-resuscitation care suggest multiparametric monitoring of hemodynamics (blood pressure, cardiac index, central venous oxygen saturation, lactate), oxygenation, and ventilation, to avoid secondary brain injury. [80] Benefits of the optimization of cerebral blood flow using transcranial Doppler and/or cerebral NIRS should be evaluated in further studies. Targeted temperature management (TTM) has been shown to improve neurologically intact survival in cardiac arrest patients, [81, 82] though data in CS following cardiac arrest are missing. The ongoing HYPO-ECMO study (NCT02754193) will evaluate the effect of moderate hypothermia and normothermia in CS patients treated with VA-ECMO. In the meanwhile, we may recommend, if possible, TTM for 24 hours in patients with MI associated with CS and an out-of-hospital cardiac arrest who remain unresponsive. By contrast, in patients in CS and no cardiac arrest, there is insufficient data to support the use of targeted temperature management (see Supplementary material).

Right ventricular infarction

Acute right ventricular (RV) infarction usually occurs in relation to acute inferior wall MI caused by occlusion of the proximal right coronary artery. [83] It is an independent, strongly age-dependent predictor of short-term mortality in patients with inferior MI. The anatomic occlusion of the infarct-related artery and functional impairment of the right ventricle are poorly correlated. Unlike the left ventricle, the right ventricle may remain viable for days after an infarct. Therefore, late reperfusion is an option that may be considered in patients with inferior MI complicated by RV dysfunction. Despite younger age, less multivessel disease, and better left ventricular ejection fraction, prognosis is no different in cardiogenic shock patients with or without acute RV failure. [84]

FUTURE DIRECTIONS

Future directions address many aspects of CS management. An overview is provided in **Table 4.**

CONCLUSION

Despite early revascularization the mortality of patients with CS is still high. In cases where CS has developed, we advocate for multidisciplinary care in a specialized center. Patients who are treated according to clinical practice guidelines, with early reperfusion for all patients and an optimal supportive intensive care treatment have a mortality rate of approximately 40%, as shown in recent randomized trials.

Currently, there are many unresolved issues, such as the access site for reperfusion, type of reperfusion (culprit-lesion-only PCI with staged revascularization versus immediate CABG in severe coronary artery disease), the optimal inotrope or vasopressor support, the role and potential treatment options of concomitant inflammation, the selection and timing of patients for MCS, optimal mechanical ventilation strategy, treatment of bleeding complications, among many others. Some of these open questions may be addressed by ongoing trials.

In general, randomized controlled trials 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; however, identifying interventions that improve survival in this high morbidity and mortality condition is likely to have major public health implications and should therefore be thoroughly tested.

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TABLES

Table 1 – Risk scores in cardiogenic shock.

	Sleeper (2010)	**CardShock (2015)**	**IABP-SHOCK II (2017)**
Systolic blood pressure	X		
Arterial lactate		X	X[1]
Glucose (>10.6 mmol/l or 191 mg/dl)			X
Creatinine	X[2]		X[3]
eGFR		X	
Confusion		X	
Higher age	X	X[4]	X[5]
Shock on admission	X		
Clinical signs of end-organ hypoperfusion	X		
Anoxic brain damage	X		
Prior myocardial infarction		X	
Prior coronary artery bypass grafting	X	X	
Non-inferior myocardial infarction	X		
ACS etiology		X	
LVEF <40%		X	
Prior stroke			X
TIMI flow grade <3 after PCI			X
MAXIMUM SCORE	*	9	9

[1]>5 mmol/l; [2]≥1.9 mg/dL; [3]>132.6 µmol/l or 1.5 mg/dl; [4]>75 years; [5]>73 years
*two different scoring systems (i. e., with and without invasive monitoring)

Table 2 – Most common indications for advanced hemodynamic monitoring in cardiogenic shock.

Indications for advanced hemodynamic monitoring
Differential diagnosis of shock
Management of mechanical complications of acute myocardial infarction
Management of severe valvular disease
Management of selected patients following cardiac surgery
Guide to pharmacologic therapy
Guide to fluid management
Guide to invasive ventilation management in selected patients

Table 3 Technical features of current percutaneous circulatory support devices

	iVAC 2L®	Tandem Heart™	Impella® 2.5	Impella® CP	Impella® 5.0	Heartmate PHP	VA-ECMO
Catheter size (F)	11 (expandable)	–	9	9	9	14	–
Cannula size (F)	17	21 venous 12–19 arterial	12		21	13	19–25 venous 15–19 arterial
Flow (L/min)	Max. 2.8	Max. 4.0	Max. 2.5	3.7 – 4.0	Max. 5.0	>4.0 (Max. > 5.0)	Max. 7.0
Pump speed (rpm)	Pulsatile, 40 ml/beat	Max. 7500	Max. 51 000	Max. 51 000	Max. 33 000	Max. 20 500	Max. 5000
Insertion/Placement	Percutaneous (femoral artery)	Percutaneous (femoral artery + vein for left atrium)	Percutaneous (femoral artery)	Percutaneous (femoral artery)	Peripheral surgical (femoral artery)	Percutaneous (femoral artery)	Percutaneous (femoral artery + vein)
LV unloading	+	++	+	+	++	++	–
Anticoagulation	+	+	+	+	+	+	+
Maximum recommended duration of use*	tbd	2-3 weeks	7-10 days	7-10 days	2-3 weeks	tbd	3-4 weeks
CE-certification	+	+	+	+	+	+	+
FDA	–	+	+	+	+	–	+
Relative costs in comparison to IABP	++	+++++	++++	+++++	+++++	++++	+(+)

VA-ECMO, veno-arterial extracorporeal membrane oxygenation; LV, left ventricular; CE, conformité européenne; FDA, Food and Drug Administration. Tbd: to be determined. *: according to general product information

Table 4 – Future directions for outcome improvement.

GOAL	RESEARCH QUESTIONS
Prediction of patients at high risk of cardiogenic shock (CS)	-Which patients with MI are at high risk of developing CS -How to manage such patients
Early recognition of CS (ED/In-hospital)	- Early identification of patient with shock at presentation - Recognition of CS developing in patients in-hospital - Standardized assessment and "red flags"
Define optimal hemodynamic monitoring	- Need for right heart catheterization - ECHO parameters - Better clinical profiling of CS
Characterize different clinical trajectories in CS	- Are there different clinical and hemodynamic profiles in CS? - How to define and characterize these? - Clinical trajectories and management of CS with specific etiologies such as stress cardiomyopathy, post-resuscitation CS
Define hemodynamic targets	- Which hemodynamic parameters and specific treatment targets
Pharmacological management	- Safety and benefit of vasopressors and inotropes - Titration of vasoactive medication - Use as single or in combination? - Use, timing and appropriate doses of cardiovascular medications
Optimal access site, revascularisation strategy and anti-thrombotic therapy in patients with ACS	- Radial or femoral access - Culprit vessel with staged revascularization or immediate CABG - Anti-platelet and anticoagulant therapy
Pathophysiologic mechanisms of shock	Define the pathophysiology of CS in more detail to help develop targeted therapies
Appropriate tools for monitoring organ function	Define critical organs, monitoring tools, threshold for organ dysfunction and management strategies
Ventilation	- Mechanical ventilation or non-invasive pressure ventilation (CPAP/BiPAP)?
Treatment options in "refractory shock"	- Benefit of MCS? - Novel approaches such as end-organ support, anti-inflammatory therapy
Markers and risk prediction tools for patient selection for advanced mechanical therapies.	- Assess the utility of current risk scores (CardSHock, IABP-SHOCK II, SAVE) in various CS cohorts to select patients for MCS or other advanced therapies
Evaluation of novel therapies for CS	Temperature management Anti-inflammatory therapy
Incorporate biomarker profiling in CS	Utility in diagnosis, risk profiling, response to management and assessing prognosis
Assessment of prognosis at different stages of shock	- Selection of patients who will benefit from advanced therapies - Develop better tools for timely identification of patients candidates for palliative care
Optimal systems of care for patients with CS	-Specialized centers - Multidisciplinary and multilevel organisation - Reporting quality of care and patient outcomes

FIGURE LEGEND

Figure 1. Algorithm of management of cardiogenic shock prior to cardiac shock center admission. AMI, acute myocardial infarction; ECG, electrocardiography; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Figure 2. Algorithm of management of cardiogenic shock during the first period after cardiac shock center admission. VA-ECMO, veno-arterial extra-corporeal membrane oxygenation; BP, blood pressure; CCU, coronary care unit; ECG, electrocardiography; IABP, intra-aortic balloon pump; ICU, intensive care unit; LV, left ventricle; MV, mechanical ventilation; NE, norepinephrine; PAC, pulmonary artery catheter; PCI, percutaneous coronary intervention; RRT, renal replacement therapy; RV, right ventricle.

Supplementary materials

Targeted Temperature Management in Cardiogenic Shock and Out of Hospital Cardiac Arrest

Large-scale randomized trials in CS have reported an incidence of up to 55% of resuscitated patients.[21, 24] The optimal treatment of these patients has not been well studied, but we recommend that hemodynamic resuscitation and neurologic protection measures protection should be given equal priority. Multiparametric monitoring of hemodynamics, oxygenation, and ventilation, to avoid secondary brain injury may be useful. In normothermic patients, a loss of cerebral autoregulation has been demonstrated, thus the use surrogate of cerebral blood flow monitoring such as transcranial Doppler and/or cerebral near infrared spectroscopy are promising ancillary monitoring techniques that have not been shown to improves outcomes in this population. Target Temperature management (TTM) has been shown to improve outcomes in cardiac arrest patients, however, there are no clinical practice guidelines that address TTM in patients with CS. The largest published experience of therapeutic hypothermia in patients with CS stems from a secondary analysis of the TTM trial. In 1939 patients (50% with STEMI), no differences in 180-day survival were observed between patients cooled to 33°C versus 36°C.[60] Therefore, TTM for 24 hours is reasonable in patients with MI associated with CS and an OHCA remaining unresponsive.

Targeted temperature management in patients without cardiac arrest

Experimental trials suggested a possible hemodynamic benefit of hypothermia in CS by demonstrating an increase in myocardial contractility and cardiac output as well as stroke volume using MTH.[61] Possible effects of hypothermia on the heart in CS include i) a reduction in the overall metabolic rate by 5-7% per 1°C decrease of body temperature, ii) a reduction of the myocardial metabolic rate influencing reperfusion injury positively, and iii) an increased contractility of cardiac myocytes without increase of oxygen consumption.[61] Retrospective human registry data in 20 resuscitated CS patients found a higher relief of

arterial lactate and reduced need for catecholamine support with hypothermia versus historical control.[62] The SHOCK-COOL trial prospectively included 40 patients that underwent randomization to moderate hypothermia for 24 h or control in patients with CS after AMI. Hypothermia ailed to show a beneficial effect in patients with CS after AMI on hemodynamic parameters.[63] The ongoing HYPO-ECMO study (NCT02754193) will address the effect of moderate hypothermia and normothermia in cardiogenic shock patients treated with VA-ECMO. In conclusion, there is currently no sufficient data to support the use of moderate hypothermia during cardiogenic shock.

Supplementary figure: Structured approach to neuroprognostication (from [80] with authorization)