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"Therapeutic Advances in the Management of Cardiogenic Shock"

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Abstract

Background: Cardiogenic shock (CS) is a life-threatening state of tissue hypoperfusion, associated to a very high risk of mortality, despite intensive monitoring and modern treatment modalities. Present review aims to describe the therapeutic advances in the management of CS.

Areas of Uncertainty: Many uncertainties about CS management remain in clinical practice, and these relate to intensity of invasive monitoring, the type and timing of vasoactive therapies, the risk-benefit ratio of mechanical circulatory support (MCS) therapy and optimal ventilation mode. Furthermore, most of the data is coming from CS in setting of acute myocardial infarction (AMI), while for nonAMI-CS patients there are very few evidences for etiological or MCS therapies.

Data Sources: The prospective multicentric acute heart failure registries that specifically presented characteristics of patients with CS, distinct to other phenotypes, were included in the present review. Relevant clinical trials investigating therapeutic strategies in post AMI-CS patients were added as source information. Several trials investigating vasoactive medications and meta-analysis providing information about benefits and risks of MCS were reviewed in the manuscript.

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Therapeutic Advances: Early revascularization remains the most important intervention for CS in settings of AMI, and in patients with multivessel disease, recent trial data recommends revascularization on a “culprit-lesion-only” strategy. Although diverse types of MCS devices improve hemodynamics and organ perfusion in patients with CS, results from almost all randomized trials incorporating clinical endpoints were inconclusive. However, development of the new algorithms of utilization of MCS and progresses in technology showed benefit in selected patients. A major advance in the management of CS is development of concept of regional CS centers based on the level of facilities and expertise. The modern systems of care with CS centers used as hubs integrated with emergency medical systems and other referee hospitals has the potential to improve patient outcomes.

Conclusions: Additional research is needed to establish new triage algorithms, and to clarify intensity and timing of pharmacological and mechanical therapies.

Keywords

Cardiogenic Shock; risk stratification; inotropes; circulatory support

Background

Cardiogenic shock (CS) is the most severe manifestation of acute heart failure (AHF) (1), with in-hospital mortality between 30 and 60% (2–7). As a distinct clinical phenotype, it accounts for 2–5% of AHF presentations (2–7). (Table 1). Regardless of etiology, CS manifests with severe and persistent hypoperfusion due to cardiac dysfunction, and results in multi-organ dysfunction syndrome (MODS) (8–10). Acute myocardial infarction (AMI) is the most frequent cause of CS, accounting for 60–80% of cases (2–7,11,12). Despite the increasing use of early revascularization, percutaneous mechanical circulatory support (MCS), and potent anti-thrombotics, CS remains the most common cause of in-hospital death in the setting of AMI, with mortality rates between 40 and 50%(13,14).

There are several definitions of CS, all including presence of clinical signs of hypoperfusion and systolic blood pressure (SBP)<90mmHg. One definition, based on the SHOCK trial (11), included hemodynamic parameters, such as reduced cardiac index (CI < 2.2 L/min/m2) and elevated pulmonary capillary wedge pressure (PCWP>15mmHg). However, CS is a clinical diagnosis and does not require invasive measurement of the hemodynamic data (10). CS is defined in the 2016-ESC-HF-Guidelines (1) as SBP <90 mm Hg despite adequate filling status and clinical signs of hypoperfusion (cold extremities, oliguria, mental confusion, dizziness, narrow pulse pressure) and/or biological markers of hypoperfusion (metabolic acidosis, elevated serum lactate>2mmol/L, elevated serum creatinine).

The clinical picture and pathophysiological stages of CS were extensively described in previous manuscripts (8–10). Inadequate circulatory compensation represents the key factor in progression of CS (Figure 1). Compensatory vasoconstriction is reversed by inflammatory mediators, which determine nitric oxide (NO) dependent pathological vasodilation (15). The occurrence of the systemic inflammatory response syndrome (SIRS) contributes to the further worsening of hypoperfusion and development of MODS through excessive vasodilation, capillary leakage, and impairment of microcirculation. In addition, bleeding,

transfusion and even hemolysis induced by some MCS further contribute to the inflammatory response (8). Development of SIRS and MODS are considered to be major contributors to the high in-hospital mortality beyond hemodynamic abnormalities (8–12).

The main goal of this review is to summarize therapeutic advances in the management of CS, with a major focus on risk-stratification models, vasoactive medications, revascularization techniques and MCS.

Area of uncertainty

Despite numerous studies documenting extremely high mortality, contemporary management of CS remains unstandardized. Although some consensus-driven algorithms (9,10) have been proposed, many uncertainties about CS management remain in clinical practice Table 2.

Data sources

Historically, the first robust evidence about the management and outcome of CS was provided by large observational studies evaluating critically ill patients admitted to the ICU, including patients with CS (16,17). The large prospective multi-centric AHF registries (2–7) that specifically presented epidemiology, in-hospital management and outcomes of patients with CS, were included in the present review. Three pivotal randomized clinical trials, SHOCK (11) IABP-SHOCK II (18) and CULPRIT SHOCK (19), investigating therapeutic strategies in post AMI-CS patients, were added as source information. Other contemporary registries or longitudinal cohorts including CS patients treated with various types of MCS were used as source information. Although RCTs investigating the benefit of temporary MCS (20) had small sample size and were not adequately powered to assess the differences between therapeutic interventions, several meta-analysis provided relevant information about benefits and risks of MCS.

A recent AHA scientific statement presented a contemporary perspective on the pathophysiology and in-hospital management of CS and suggests a stepwise management algorithm that integrates medical, surgical, and MCS therapies (9).

Therapeutic Advances

Phenotyping patients with CS

Phenotyping patients with CS may have potential clinical impact on management, since classification would support initiation of appropriate therapies according to the stage of severity. Although US (14) and European Guidelines (1) describe a singular CS presentation as part of AHF Syndromes, several trials and registries have identified a larger spectrum of CS presentations (21).

One of the most commonly used classifications is based on clinical severity, where the most severe form of CS is named “refractory CS”(10), defined as persistent shock despite the administration of inotropes and vasoconstrictors.

Dividing CS patients in, AMI-related vs no-AMI related, is clinical relevant because the two entities are very different in terms of clinical characteristics and management. For AMI-CS patients, early revascularization is the most important evidence based etiological treatment, while for nonAMI-CS patients there are very few evidences for etiological treatment or for MCS, since the trials of temporary MCS have mainly focused on AMI-CS.

Furthermore, a recent AHA statement (9) suggests the existence of the diverse clinical and hemodynamic presentations of CS. CS caused by predominantly LV failure may present as “wet and cold” (hypoperfused and congested) with high LV filling pressure (2/3 of clinical presentations in SHOCK trial). Patients treated with vasodilators or diuretics may present “dry and cold” (hypoperfused without congestion) with relatively normal LV and RV filling pressures, or as “wet and warm” (well perfused and congested) with high LV filling pressure but low systemic vascular resistance, as seen in the later stages of CS when SIRS and vasodilation can occur (21). In a minority of cases CS patients may present normotensive, with peripheral hypoperfusion despite a SBP >90 mm Hg. This group had comparable CIs and PWCPs, but higher systemic vascular resistance (SVR) compared with hypotensive patients with CS, thus highlighting the risk of relative hypotension and the potential for hypoperfusion without profound hypotension (22).

CS caused by predominantly RV failure may present as “wet and cold” or “wet and warm”. These patients have high RV filling pressure, low pulmonary artery pressure and different values of SVR according to the extent of systemic inflammatory response. More often, CS is caused by biventricular failure, clinical settings where solely clinical examination may lead to erroneous interpretation and requiring invasive assessment of hemodynamics via PAC.

The utility of PAC use for medical decision in patients with severe heart failure has been downgraded by the results of the ESCAPE trial (23). However, the conclusion that PAC is not useful in patients with CS, represents an overinterpretation, since the patients with CS have been excluded from ESCAPE trial. PAC may be a useful tool in some patients with severe CS, especially in cases of RV involvement or CS unresponsive to initial therapies (24).

Risk stratification and prognostic models

In patients with CS, an early and objective risk stratification would allow potentially life-saving interventions to arrive early in the course of the disease and to avoid the high rate of death seen in the first hours after admission. In two large registries (5,7) enrolling patients with CS, 50% of in-hospital deaths occurred within the first 24 hours of presentation, raising the hypothesis that early identification and treatment of hypoperfusion may be potentially life-saving in this setting.

Several biological factors have been used for prognostic assessment in CS, but their value was reduced by the presence of multiple confounders, their limited ability to predict prognosis, or to identify the candidates for therapies.

Although, in CS elevated levels of NT-proBNP are impacted by impaired renal function, NT-pro-BNP remains a good indicator for prognosis in patients with CS by its dependency on

organ dysfunction (25). Lactate, measured from either venous or arterial blood, remains an important indicator of tissue hypoperfusion (26). Lactate concentration >2 mmol/L is one of the diagnostic criteria for impaired end-organ perfusion, and is associated with higher mortality in CS (20). Serial measurements of arterial lactate may assist to monitor responses to therapeutic interventions and lactate levels that do not decrease following appropriate treatments are associated with a poor outcome (26,27).

Many studies aimed to identify predictors for adverse outcome, but only a few studies have proposed a risk score. In TRIUMPH trial (Tilarginine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock), the authors identified predictors for worse outcome but did not develop a risk-scoring model (28). The SBP, creatinine clearance, and number of vasopressors were significant predictors of mortality in patients with postAMI-CS despite a patent infarct artery.

Several risk models assessing organ dysfunction were derived in the general ICU population and include the APACHE II (Acute Physiology and Chronic Health Evaluation)- score (16) and SAPS (Simplified Acute Physiology Score)-II scoring systems(29). Both scores were used to predict in-hospital mortality in critically ill patients admitted to the ICU for cardiac and non-cardiac causes, and also predicted mortality in a cohort of patients with CS enrolled in one tertiary hospital (17).

One of the first risk score obtained from a CS specific population was the *Sleeper risk score* (30), derived from postAMI-CS patients enrolled in the SHOCK trial. However, the main goal of this score was to evaluate the potential benefit of early revascularization on mortality in different risk strata, rather than to evaluate overall mortality risk. A multivariable modeling identified 8 risk factors for increased mortality: increased age, shock on admission, clinical evidence of end-organ hypoperfusion, anoxic brain damage, low SBP, prior coronary artery bypass grafting, non-inferior MI, and creatinine ≥ 1.9 mg/dL.

The most recent scores specifically used in CS population are IABP-SHOCK II Risk Score (31) and the CardShock risk score (32) (Table 3).

IABP-SHOCK II risk score (31) was obtained in patients with AMI-related-CS undergoing PCI, enrolled in the largest randomized CS trial to date. It is a simple tool that can be rapidly calculated in the catheterization laboratory setting.

The CardShock risk score (32,33) was developed in 219 patients with CS of any etiology enrolled in a prospective registry. The score includes 7 variables stratifying the risk of short-term mortality and may facilitate early decision-making in the ICU.

The development of accurate risk stratification tools to guide MCS treatment decisions is also clinically important. Extracorporeal membrane oxygenation (ECMO) initiation too early in a patient's course may lead to an uncontrolled use of this, increasing resource consumption, while exposing patients to unnecessary complications. However, this must be balanced with initiating ECMO too late, which has not been associated to improving outcomes (8). The SAVE-score (34) includes 12 pre-ECMO variables independently associated with in-hospital mortality assembled in a 5-level risk score. Discriminatory

performance of the SAVE score was greater than APACHE II, APACHE III, and SOFA scores at ICU admission or at ECMO cannulation. The SAVE-score is a potential tool to predict in-hospital survival for patients receiving ECMO for refractory CS and highlights the need to target the 'right time window' for ECMO initiation.

ORBI score (35) was designed to assist prediction of the development of in-hospital CS in patients with ST-segment elevation MI treated with primary PCI. Eleven variables were independently associated with the development of in-hospital CS. The score derived from these variables allowed the classification of patients into four distinct risk categories.

Revascularization

Coronary reperfusion is the main evidence-based therapeutic intervention for patients with acute MI presenting with CS (36). The SHOCK trial demonstrated that early revascularization is the most important treatment strategy in post-AMI-CS (11). Although, the 30-day all-cause mortality was non significantly lower in the invasive arm, either PCI or CABG, (46.7% versus 56.0%; p =0.11), mortality was significantly lower at, 12 months (37), and through long-term follow-up (6 years)(38). Also, an early invasive treatment approach had consistent benefits across multiple subgroups determined by ethnicity, age strata, sex, or diabetic status (39–41). At present, early revascularization has a class I B Guideline recommendation (42). Even though application of early revascularization has markedly increased in clinical practice, rates are still unsatisfactory ranging from 50 to 70% in registries (13,43).

Approximately 80% of patients who have CS present with multivessel coronary artery disease, and mortality is higher with multivessel disease than with single-vessel disease (44). The prognostic value of performing immediate PCI for clinically important stenosis of major non-culprit coronary arteries is controversial, and current guidelines recommendations (42) are mainly based on pathophysiological considerations. Recently, the randomized, multicenter Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial (31) 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. This endpoint was mainly determined by an absolute 8.2% reduction in 30-day mortality (43.3% vs 51.5%). The higher dose of contrast medium in the immediate multivessel PCI group may have led to acute LV volume overload with a negative effect on myocardial function and recovery (19). The prolonged duration of the multivessel PCI procedure may be hazardous at a time when the patient is hemodynamically unstable, leading to potentially more bleeding and inflammation. (19,45). The results of CULPRIT-SHOCK may lead to a Class I, Level of Evidence B recommendation, to limit PCI to the culprit lesion only on a routine basis, with possible staged revascularization. The results of CULPRIT-SHOCK trial were confirmed in two recent meta-analysis (44,46) showing an increased short and long-term mortality with multivessel PCI.

Types of stents appear to not impact outcomes in CS patients, as there are no differences in outcomes between DES and bare metal stent (47–49).

A meta-analysis analyzing data of 8131 registry patients demonstrated that radial access was associated with a reduction in all-cause mortality and a reduction of cerebral events at 30-day follow-up in CS patients (50). However, some important practical consideration are that the radial access may be challenging in hypotensive patients with CS and radial access cannot be used to place temporary MCS.

In the SHOCK trial (11), the mortality rate at 1-year was similar among those

treated with PCI (48%) and those treated with CABG (53%) when randomized to an early revascularization strategy (51). Furthermore, a meta-analysis (52) including four observational studies suggests similar mortality rates with CABG and PCI in patients with STEMI and multivessel coronary disease complicated by CS.

Vasoactive pharmacological management

Despite the frequent use of catecholamines, which are administered in >80% of patients in CS, few clinical outcome data are available to guide the initial selection of vasoactive therapies in patients with CS, or to support a distinct inotropic or vasopressor as a superior solution to reduce mortality in patients with CS (53,54). Vasopressors and/or inotropes are required to restore systemic perfusion, but the haemodynamic benefits appear to be counterbalanced by catecholamine related adverse effects, such as increased myocardial oxygen demand, arrhythmogenicity, and compromise of tissue microcirculation. These adverse effects are time and dose dependent and are associated to increased mortality risk (8), thus all inotropes and vasopressors should be used at the lowest dose and the shortest time possible (8–10).

Confirming past information, more recent registry and trial data demonstrate the negative effects of certain inotropic agents. The SOAP II trial (Sepsis Occurrence in Acutely Ill Patients) (55) evaluated first-line vasopressor selection in patients with generalized shock and included a pre-specified CS subgroup. In the CS subgroup, dopamine was associated with higher risk of 28-day mortality as compared to norepinephrine. Also, in a recent meta-analysis comparing the clinical outcome of dopamine to norepinephrine in CS (56), norepinephrine was associated with a lower 28-day mortality and a lower risk of arrhythmic events, regardless of CS etiology.

In a recent analysis from ESC-HF –LT registry (57), dopamine was associated with worse short- and long-term outcomes when compared to other inotropes and/or vasopressors, such as dobutamine and levosimendan.

Although, epinephrine is mainly recommended for resuscitation (1), this agent is still used as an inotrope (2–7), despite of its cardio-toxic effects (53).

In the CardShock registry (58), epinephrine was associated with increased 90-day mortality independent of prior cardiac arrest, and even after multivariable adjustment. Compared to other vasopressors, epinephrine was associated with marked aggravation of myocardial and renal injury (58), and led to higher lactate levels (59).

Mechanical Circulatory Support

MCS represent the most important therapeutic option to obtain hemodynamic stability and to prevent, or to reverse MODS in patients with refractory CS (8–10).

MCS improves systemic blood flow while avoiding the possible adverse effects of catecholamines (8). The goal of MCS is to bridge to recovery or to definitive therapy, or alternatively to LVAD and/or to cardiac transplantation, making patient selection crucial (8–10).

While device therapy has been shown to improve hemodynamics, no adequately powered trial has so far been able to demonstrate outcome benefit in patients with CS. To date, the most rigorously studied device is the IABP, which failed to demonstrate benefit in the IABP-SHOCK II (Intra-Aortic Balloon Pump in Cardiogenic Shock II) trial (18,60). Other recent observational studies (61,62) have also suggested limited utility and potential harm of IABP therapy in CS. These studies have clearly impacted clinical practice, as there has been an observed decline in IABP use, accompanied by an increase in Impella, TandemHeart, and VA-ECMO use (63,64). The 2017 ESC STEMI guidelines (42) gave IIIB recommendation for the routine use of the IABP in CS, and consider IABP only in patients with mechanical complications post AMI (class IIa, level C).

The individual trials comparing different types of MCSs were underpowered to adequately evaluate a potential mortality benefit. In the IMPRESS trial (20), Impella CP was not associated with better survival when compared with IABP therapy in patients with CS complicating AMI, but the study was underpowered to ascertain the outcome difference between the two interventions. Also, in a meta-analysis comparing diverse MCSs (Impella and Tandem Heart) to a control arm (IABP), despite an initial beneficial effect on mean arterial pressure (MAP) and arterial lactate, the two active percutaneous MCS strategies did not improve mortality in comparison to controls in patients with postAMI-CS (65). This meta-analysis confirmed a more than two-fold increase of bleeding in patients with MCS as compared with IABP control. Thus the benefits of active MCS on MAP and arterial lactate must be balanced against the potential complications associated with the implantation procedure.

Data on the timing of active MCS insertion in CS are limited. In the USpella registry (66), enrolling patients with AMI-CS, patients directly treated with Impella prior to PCI had an overall better survival at discharge compared with those treated with Impella after PCI, even when adjusting for potential confounding variables. This suggests that early hemodynamic support prior to PCI by active LV unloading and increased forward flow to the systemic circulation has the potential to improve outcomes by enabling stable hemodynamics during the intervention. This finding was confirmed in a retrospective analysis which included 15259 post-MI CS patients from 1010 US hospitals utilizing the Impella device, demonstrating early initiation of MCS before PCI, use of PAC monitoring, and greater institutional experience are associated with improved survival (67). Furthermore, a recent meta-analysis of trial and registry data (68) has suggested that in patients with postAMI-CS, a strategy of implanting the Impella prior to performing angioplasty is associated with

improved survival. These encouraging results suggested a standardized regimen of the early using of Impella in post AMI-CS patients(69).

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides cardiopulmonary support for patients in profound CS as a bridge to myocardial recovery, durable MCS, or heart transplant (HT), whereas veno-venous extracorporeal membrane oxygenation (VV-ECMO) is primarily used in patients with isolated pulmonary disease (70–72). VA-ECMO establishes a massive right-to-left shunt by draining venous blood from the right atrium and returning it after oxygenation to the ascending aorta (central cannulation) or to the iliac artery (peripheral cannulation). This flow support, which can reach 7 l/min with large cannulas and contemporary rotors, results in a significant increase in blood pressure and strongly improves end-organs perfusion. However, retrograde flow support by ECMO increases LV afterload. The retrograde ECMO output meets the antegrade LV output at different levels in aorta depending on the native output of the heart (73). Since the output of most ECMO devices is non-pulsatile, pulse pressure measured at the right radial artery serves as an estimate of LV output. Absent or low arterial pulsatility indicates that the LV is not ejecting, leading to blood stasis and thrombus formation, while higher pulsatility indicates possible myocardial recovery.

The proper understanding of the ECMO functionality has led to development of major technological advances (72). These improvements are related to ECMO technology, ECMO circuit configuration and additional procedures.

The improvement in the oxygenator membranes permitted low resistance and improved blood compatibility characteristics. The modern centrifugal pumps are less heat generating and less thrombogenic allowing extended duration of support (72).

The veno-arterio-venous (V-AV) configuration with triple cannulation avoids Harlequin Syndrome (upper body hypoxia) in which deoxygenated cerebral blood flow occurs during retrograde perfusion with peripheral cannulation (71). Venous blood returns to the oxygenator and is then reinfused via an arterial cannula to the femoral artery and a second venous cannula to the right heart at the level of the tricuspid valve, providing supra-oxygenated pulmonary blood flow(72).

In patients with extremely low systolic LV function, VA-ECMO support results in a functionally closed aortic valve without relevant trans-aortic blood flow. This potentially results in severe LV distension and pulmonary congestion. LV overload during VA-ECMO therapy represents a critical condition and urgent LV decompression is a fundamental component of VA-ECMO management to prevent lung injury related to elevated pulmonary venous pressures, avoid stasis within the LV, and promote myocardial recovery (71–72). Decompression strategies include additional procedures, such as septostomy, IABP, Impella and hybrid circuit configuration. Left heart decompression with balloon atrial septostomy (74) allows shunting of blood from the left atrium to the right atrium and the venous cannula and may positively influence the hemodynamic balance in the setting of V-A ECMO support associated with LV overloading in the presence of increased left-side pressure and pulmonary edema. In more severe cases, a percutaneous atrial trans-septal cannula can be

placed and connected to the inflow part of the ECMO circuit (75). Some studies showed that adding an IABP to peripheral VA-ECMO was associated with LV decompression, prevention of lung injury, improved LV function and increase survival (76,77). Combined support with VA-ECMO and Impella was associated with reduced hospital mortality and a higher rate of successful bridging to either recovery or the next therapy (LVAD implantation or heart transplantation) in one study including patients with refractory CS (78). These results may be explained by the effectiveness of Impella in relieving VA-ECMO-related LV overload. Also, a hybrid circuit configuration (71,72), along with variations of LV and other vents, allows selective decompression of either ventricle when myocardial recovery is the goal.

The hemodynamic improvement following MCS implant may be only a measure of technical success of MCS, and without limiting the progression of SIRS and MODS within the first few days, these hemodynamic improvements may be futile and may not translate into improved survival (79). Most of the studies suggest that improvement of tissue perfusion by MCS devices is a key factor responsible for improvement of outcome in patients with CS, and adequate tissue perfusion rather than maintenance of more normal arterial pressure is a crucial determinant of outcome(80).

Mechanical Ventilation

A proportion of 60–80% of the CS patients present with severe respiratory failure that require mechanical ventilation (MV), commonly via endotracheal intubation. In the SHOCK trial (11), 80% of the patients received MV, while in the Cardshock study(32), the percentage of patients mechanically ventilated was 75%, but 13% were just managed with noninvasive mechanical ventilation (NIMV). Although in non-CS patients, NIMV can improve dyspnea, hypoxemia, and metabolic acidosis (81), there are very few evidences to support NIMV in CS patients. To note, the altered mental status usually present in CS patients warrants endotracheal intubation.

In one study, patients who received NIMV showed a predominant pattern of congestion with significantly higher NT-proBNP and mild metabolic abnormalities, while those treated with invasive ventilation showed an hypoperfusion profile, with significantly higher metabolic acidosis and lactacidemia (82), suggesting that NIMV may be a safe strategy in the incipient stage of CS.

Regarding ventilation mode, there is insufficient evidence to recommend specific ventilation strategies in settings of CS. Although, in patients with reduced LV function, positive end-expiratory pressure can improve cardiac performance by decreasing LV afterload and preload, but higher pressures increase RV afterload and may deteriorate RV function (83).

Development of system of care for the management of CS

CS is a complex acute condition that requires a multidisciplinary treatment team to provide high quality medical care (9). To note, among hospitals treating CS patients, those performing the highest number of procedures, which defined 201Eclinical volume", had better survival compared to low volume hospitals (84).

High-volume hospitals include multidisciplinary teams, who more frequently implanted MCS(67) and took care for patients with MODS (85), and have therapeutic facilities to deliver care for any etiology of CS and for any phase of CS, from initial presentation to definitive therapy or palliation. The modern systems of care with CS centers used as hubs integrated with emergency medical systems and other referee hospitals has the potential to improve patient outcomes (84,85).

In addition, application of high-quality strategies to CS patients, requires medical personnel with adequate competencies (86–88) in acute cardiac care and an ongoing collaboration between cardiology and intensive care medicine.

Conclusions

CS is an ideal target for the development of new therapeutic interventions given its association with poor clinical outcomes. However, substantial investments in research and development have not yielded proof of efficacy and safety for any of the therapies tested. Additional research is required to prospectively validate risk-prediction models, triage algorithms, type and optimal level of MCS, including reestablishment of adequate perfusion of critical organs. Future randomized controlled trials of CS in the emergency setting are especially difficult to conduct, but data from such trials are needed to better inform guidelines and clinical care.

Abbreviations:

MAP	mean arterial pressure
MCS	mechanical circulatory support
MODS	multiple organ dysfunction syndrome
SIRS	systemic inflammatory response syndrome
SVR	systemic vascular resistance

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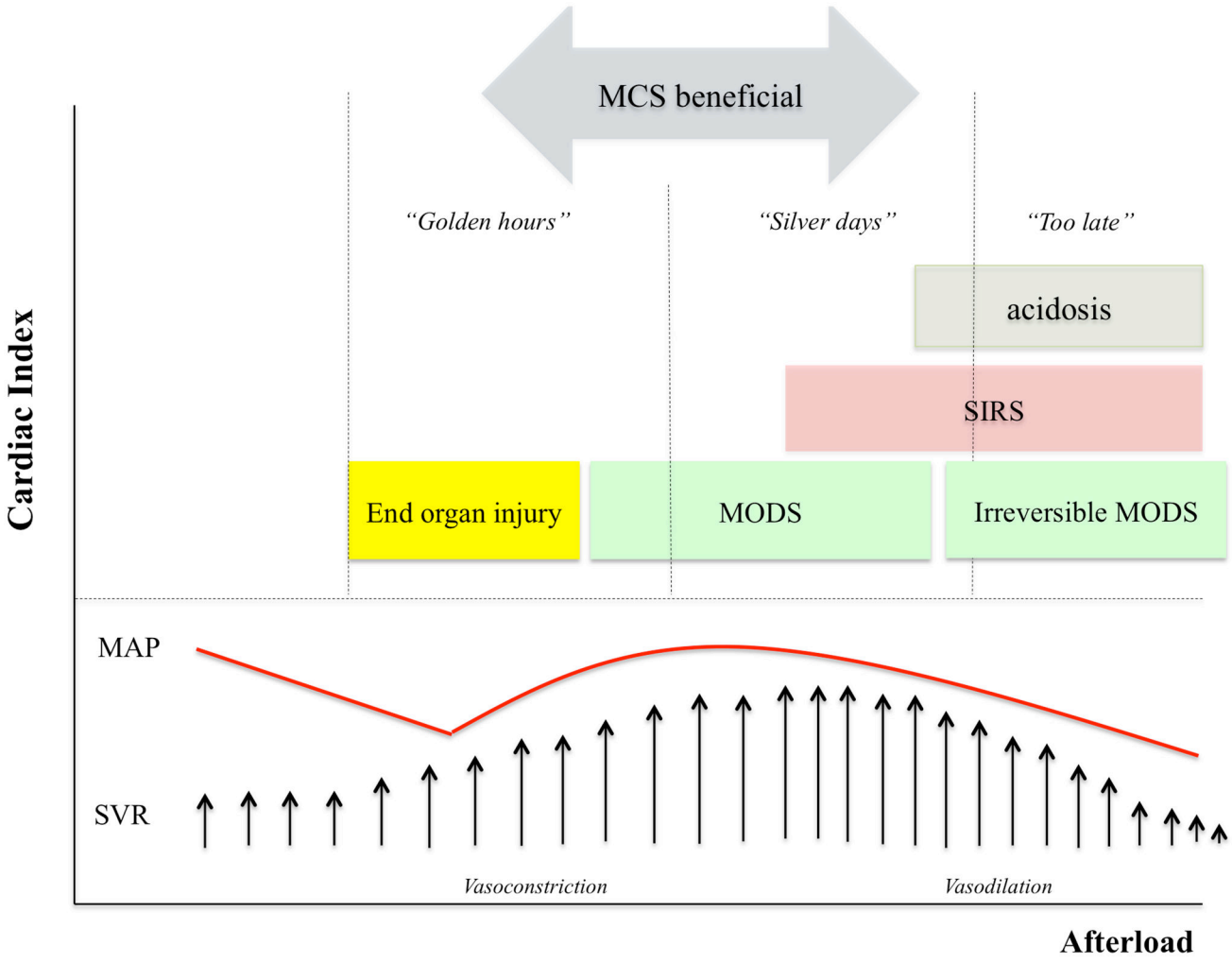

Figure 1.

Pathophysiology of CS. In initial stages, the main contributors are inadequate stroke volume and compensatory vasoconstriction, that may improve peripheral perfusion, but at the cost of increased afterload. The occurrence of the systemic inflammatory response syndrome (SIRS) results in pathological vasodilation and contributes to the further worsening of hypoperfusion and development of multi-organ injury or dysfunction (MODS), with limited reversibility. Thus, the hemodynamic improvement following MCS should be associated to prevention or reversing of SIRS and MODS.

Table 1.

Characteristics of patients with Cardiogenic Shock in European registries with different enrollment strategies. Study acronyms, methodology, time frame of enrollment and in-hospital ACM in overall cohorts are presented in the first row.

	FINN-AKVA[2] ***(2004)*** **N=620 14 sites 3 monts consecutive in-hospital ACM=7.1%**	**EHFS II[3]** ***(2004–2005)*** **N=3580 133 sites 20pts/site in-hospital ACM=6.7%**	**RO-AHFS[4]** ***(2008–2010)*** **N=3224 13 sites 1 year consecutive ACM=7.7%**	**ESC-HF pilot[5]** ***(2009–2010)*** **N=1892 137 sites periodic consecutive in-hospital ACM=3.8%**	**IN-HF[6]** ***(2007–2009)*** **N=1855 61 sites 1y-consecutive in-hospital ACM=6.2%**	**ESC-HF-LT[7]** ***(2011–2015)*** **N=6629 211 sites periodic consecutive in-hospital ACM=5.5%**
(%) pts CS	2.3	3.9	5	2.3	2.3	2.9
ACS settings(%)	79.3	71.9	59.1	-	-	68
In-hospital mortality (%)	28.6	40	62.4	23	23.8	36.1
One-year mortality (%)	35.7	56	-	-	38.1	54
IV therapies (%)						
Inotropes	71	88.2	94.2			81.0
Vasodilators	-	38.7	17.8			14.0
Diuretics	-	58.7	48.6			78.2
Interventions (%)						
Coronary angiography	88	-	19.1			37
PCI/CABG	66	46.9	10.4			26
PAC	-	-	1.2			3.1
IABP	22	30.9	3.5			14.9
MV	50	56.1	30.6			-

Abbreviations: ACS=acute coronary syndromes; CABG=coronary artery by pass graft; CS=cardiogenic shock; IABP=inta-aortic balloon pump; MV=mechanical ventilation; PAC=pulmonary artery catheter; PCI=percutaneous coronary interventions; FINN-AKVA= Finnish Acute Heart Failure Study; EHFS II = European Heart Failure Survey II; RO-AHFS =Romanian Acute Heart Failure Syndromes registry; ESC-HF pilot=Heart Failure pilot study; IN-HF = Italian Registry on Heart Failure Outcome; ESC-HF-LT =ESC Heart Failure Long Term Registry

Table 2.

Area of uncertainty in the management of Cardiogenic Shock

• Whether phenotyping patients with CS will improve decision-making algorithms
• The need for a pulmonary artery catheter (PAC) to guide clinical decision-making in certain patients
• Lack of adequate risk stratification models; lack of a large CS-specific derivation population, applicability to all CS types
• The type, timing and limitations of vasopressor/inotrope support
• The type and timing of MCS device therapy
• The timing of mechanical unloading relative to coronary reperfusion in AMI with CS
• The effectiveness of MCS by etiology of CS: AMI vs non AMI etiology
• The optimal level of MCS with reestablishment of adequate perfusion of critical organs
• Optimal approach to prevent and manage potential MCS-related complications
• Lack of studies evaluating the ideal mechanical ventilation mode, and ideal oxygenation targets

Table 3.

Scoring system, risk categories and relative risk for each categories.

A. CardShock Risk Score; C-statistics 0.85 (95%CI=0.79–0.90); in-hospital mortality in 219 CS patients of any any etiology

Variable	*Points*	*Risk category*	*Mortality*
Age >75 years	1	0–3 points: low	8.7%
Confusion	2	4–5 points: medium	36.0%
Previous MI or CABG	1	6–9 points: high	77.0%
ACS at presentation	1		
LVEF<40%	1		
Blood lactate			
<2mmol/l	0		
2–4mmol/l	1		
>4mmol/l	2		
eGFR $_{CKD-EPI}$			
>60ml/min/1.73	0		
30–60 ml/min/1.73	1		
<30ml/min/1.73	2		
Maximum	9		

B. **IABP-SHOCK II Risk Score**; C statistics= 0.74 (95%CI=0.69 to 0.78); 30-day mortality in 600 CS post AMI patients undergoing PCI

Variable	*Points*	*Risk category*	*Mortality*
Age >73 years	1	0–2 points: low	23.8%
History of stroke	2	3–4 points: medium	42.9%
Glucose >191 mg/dl	1	5–9 points: high	77.3%
Creatinine > 1.5 mg/dl	1		
Arterial lactate >5 mmol/l	2		
TIMI flow grade <3 after PCI	2		
Maximum	9		

C.**SAVE Risk Score**; C statistics= 0.68 (95% CI 0.66–0.69); in-hospital mortality in 3846 CS patients treated with ECMO

Variable	*Points*	*Risk category*	*Mortality*
Etiology of CS	−3–3		
Age	0–7	Class I>5	25%
Weight	0–2	Class II 1–5 points	42%
DBP>40mmHg	3	Class III −4–0 points	58%
PP<20mmHg	−2	Class IV −9–5 points	70%
Chronic renal failure	−6	Class V <−10 points	82%
Acute organ failure			
Liver	−3		
Renal	−3		
Neurologic	−3		
$HCO3^-$<15mmol/l	−3		
PIP<20mmHg	3		
Cardiac arrest	−2		

Maximum	−35–17		
D.ORBI Risk Score; C statistic=0.84(95% CI 0.76–0.91); risk of developing CS in 6838 patients with AMI			
Variable	*Points*	*Risk category*	*Risk CS*
Age >70 years	2	0–7 points: low	3.1%
History of stroke	2	8–10 points: medium	10.6%
Anterior STEMI	1	11–12 points: mid-high	18.1%
SBP<125mmHg	1	>13 points: high	34.1%
Killip class	0–6		
Heart Rate>90/min	3		
PP<45mmHg	1		
Glycemia>10mmol/L	3		
PCI delay>90 min	2		
Left Main coronary	5		
TIMI flow grade <3 after PCI	5		
Maximum	31		

Abbreviations: ACS=acute coronary syndromes; CABG=coronary artery by pass graft; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; LVEF=left ventricular ejection fraction; MI=myocardial infarction; PIP=peak inspiratory pressure; PCI=percutaneous coronary intervention; PP= Pulse pressure; STEMI=ST elevation myocardial infarction; TIMI= Thrombolysis In Myocardial Infarction