Epidemiology, pathophysiology and contemporary management of cardiogenic shock - a position statement from the Heart Failure Association of the European Society of Cardiology

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Epidemiology, Pathophysiology and Contemporary Management of Cardiogenic Shock - A Review by the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)

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Introduction

Cardiogenic shock (CS) is a syndrome variably defined (1-8), primarily due to cardiac dysfunction, and comprising a life-threatening state of tissue hypoperfusion associated with impairment in tissue oxygen metabolism and hyperlactatemia, which may result in multi-organ dysfunction/failure and death.

Although only a minority of acute heart failure (AHF) or acute coronary syndrome (ACS) patients present with shock, CS is seen frequently in intensive cardiac care units (ICCU) with a 30-day mortality of 40-50% depending on underlying etiology (1). Although recent European Society of Cardiology (ESC)-guidelines (2) describe a singular CS presentation as part of AHF Syndromes, several clinical trials (3-5) and registries (6, 7) and recent consensus document (8) have identified a wider spectrum of CS presentations. Phenotyping variability in CS results from the interaction between an acute cardiac insult and a patient's underlying cardiac and overall medical condition (9). Such phenotypes reflect the systemic effects of an initial acute reduction in CO, but then rapidly evolve into distinct clinical phenotypes through distinct molecular pathways.

Despite advanced management, including etiological treatment(10) and mechanical circulatory support (MCS)(4,5), clinical trials (4, 11) and a meta-analysis (12) have suggested that augmentation of CO or other hemodynamic parameters may not consistently improve mortality in patients with CS

The goal of this review is to summarize the current knowledge concerning the definition, epidemiology, underlying causes, pathophysiology and management based on important lessons from clinical trials and registries over the last several decades, with focus on improving in-hospital management.

Definition and Classifications

There are numerous definitions of CS (1, 4, 5), many of which include hypotension (systolic blood pressure [SBP] <90 mmHg for more than 30 min, or on catecholamines to maintain SBP >90 mmHg), although it is well-recognized that in shock, compensatory mechanisms may preserve blood pressure through vasoconstriction, while tissue perfusion and oxygenation may be significantly decreased. Thus, hypoperfusion is not always accompanied by hypotension and hypotension without hypoperfusion may portend a better prognosis (3, 6, 7). In SHOCK registry, clinical signs of hypoperfusion were associated with a substantial risk of in-hospital mortality even in normotensive patients, suggesting that early recognition of hypoperfusion signs, therefore identify high-risk regardless of hypotension (3). The Task Force of the European Society of Intensive Care Medicine defined shock (including its subtypes) as a 'life-threatening, generalized form of acute circulatory failure associated with inadequacy of tissue perfusion to provide enough oxygen to sustain basal metabolism at cellular level' (13). The presence of low SBP was not a prerequisite for defining CS considering that compensatory vasoconstriction may preserve blood pressure, albeit at the cost of impaired tissue perfusion..

CS registries (15) and consensus documents (8, 16-18) described a large phenotypic variability of CS, as result of the diverse etiologies and pathogenetic mechanisms , variability of hemodynamics and different stage of severity. The pathogenetic scenarios of CS range from advanced chronic HF decompensated by acute precipitants, to acute-onset de novo CS most often caused by ACS, but also by various etiologies other than ACS. Categorization according to the underlying aetiology is important, ACS- vs non-ACS-related, as it determines priorities for initial patient management and outcomes.

Subsequent classifications relate to clinical severity and response to interventions (16, 17). Based on clinical severity and response to treatment, the spectrum of CS can be divided into pre-CS, CS, and refractory CS (16) (**Figure 1**). Early identification of CS allows rapid initiation of appropriate interventions to reverse the underlying cause, introduction of supportive therapies. The presence of clinical signs of peripheral hypoperfusion even with preserved SBP, is referred as "pre-shock" (16) and precedes overt CS. Pre-shock may occur in severe AHF which can also be associated with clinical signs of tissue hypoperfusion but without compromising cellular basal metabolism and having normal lactate(3,8,16). This state should be differentiated from "Normotensive CS" which represents an entity of CS with all features of hypoperfusion and cellular alterations (including cellular dysoxia reflected by hyper-lactatemia) but without hypotension. At the other end of the spectrum, refractory CS has been defined as CS with ongoing evidence of tissue hypoperfusion despite administration of adequate doses of 2 vasoactive medications and treatment of the underlying etiology (16, 19).

The recently published Society for Cardiovascular Angiography and Interventions (SCAI) clinical consensus statement on the classification of CS (17) describes five evolutive stages, from A (at risk of CS) to E (extremis) (**Figure 1**) including a modifier for cardiac arrest (CA). This classification can be applied rapidly at the bedside upon patient presentation, across all clinical settings. The SCAI classification utilizes bedside clinical assessment of hypoperfusion, measurement of lactate level and invasive hemodynamic evaluation.

In the SHOCK trial, CS definition required hemodynamic parameters, such as reduced cardiac index (CI <2.2L/min/m^2) and elevated pulmonary capillary wedge pressure (PCWP >15mmHg). However, this definition reflects only "left-sided" CS, but while there are diverse hemodynamic phenotypes for CS (8) determined by the association of

the systemic inflammatory response syndrome (SIRS) (20, 21) and by the type of cardiac involvement (left vs right) (3,22) and . The common physiological characteristic is low CI, but PCWP, central venous pressure [CVP]) and systemic vascular resistance (SVR) may vary (8).

Epidemiology and Prognosis

The prevalence of CS varies according to the definition of CS, clinical settings care and era of data collection. CS accounts for 2-5% of AHF presentations, with a prevalence in ICU/ICCU datasets of 30% (10, 23). In-hospital mortality varied between 30 and 60% (24-28), with nearly half of in-hospital deaths occurring within the first 24 hours of presentation (6). One-year mortality in CS patients is approximately 50-60% (29), with 70-80% of deaths occurring in the first 30 to 60-days after onset of CS (6,29-31) suggesting that the risk of death is time-dependent and clustered in the early post-discharge period.

Severe LV failure secondary to ACS remains the most frequent cause of CS, with an incidence of 4-12%, with 30-40% occurring in the first hours after presentation (32, 33), and in-hospital mortality of 40-50% (32, 33)(34-37,38).

A decade ago, 81% of CS was due to underlying ACS (39), however, the contribution of ACS has declined over the past 2 decades (40), in parallel with an increase of CS of other etiologies (10). In a large US registry including 144,254 patients with CS, the proportion of CS complicating ACS has fallen between 2005 and 2014 from 65.3% to 45.6% (10). Also, in a contemporary ICCU dataset in the US and Canada, only a third of CS were related to ACS, while the remainder comprised ischemic cardiomyopathy

without ACS (18%), nonischemic cardiomyopathy (28%) and other causes (e.g., incessant ventricular tachycardia, severe valve disease) in 17% (23). Non-ACS CS patients are more resource-intensive and have a greater burden of disease (more severe pre-existent HF, pulmonary hypertension, arrhythmias), but in-hospital survival is significantly better than ACS-related CS (23, 39). In CardShock (39), ACS has been shown to be a predictor of worse outcomes in patients with shock (OR 7.4, 95% CI 1.9–29.8).

CS is a more common complication of ST-elevation myocardial infarction (STEMI) than non-STEMI (NSTEMI), with STEMI being more likely to present with CS on admission versus developing after hospitalization in NSTEMI (10, 41). Although, initial reports (41) suggested worse early mortality for NSTEMI vs STEMI, this has not been supported by later data (29).

Pathophysiology of CS

Although aetiologies vary widely (16, 19, 42) (**Table 1**), the pathophysiology of CS comprises several unique yet overlapping components to be considered : an initial cardiac insult that decreases CO, central hemodynamic alterations (including changes in the relation between pressure and volume with increase in LV and RV filling pressures), microcirculatory dysfunction, a systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction - as a terminal stage (**Figure 2).** Furthermore, precipitating factors (43-45), may cause an acute deterioration of cardiac compensation evolving to CS, and worse outcomes were described in the patients with non-cardiovascular precipitating factors, such as infection.

Although these mechanisms might be considered as temporal stages of CS, each may occur simultaneously, but the magnitude of the initial cardiac insult and/or early application of interventions may either mask or delay some of these mechanisms (46).

As a consequence of an acute decrease of LV contractility, CO, stroke volume (SV) are reduced leading to an acute reduction of blood pressure (BP), and corresponding elevation of LV end-diastolic pressure (16). As a reaction to the BP drop, compensatory vasoconstriction occurs (including venoconstriction which functionally shifts blood volume into the circulating compartment, causing elevations of central venous and pulmonary venous pressures), altering ventricular-arterial coupling (16(47) (48)). Low cardiac power output (CPO) (CO x BP), an indicator of significant LV dysfunction, has proven to be a strong hemodynamic predictor of poor outcome (49), while the calculated pulmonary artery pulsatility index (PAPi) <0.9 can identify significant RV failure (50).

Microcirculatory dysfunction is present early in CS patients and may precede central hemodynamic abnormalities (46). It is associated with the development of multi-organ failure and is a predictor of poor outcome in patients with AMI complicated by CS (51). As the microcirculatory network is flow dependent, the decrease in CO and elevated vascular tone probably reduces capillary responsiveness discordant to the cellular metabolic requirements resulting in cellular hypoxia (52). However, even in severe hypoxia, mitochondrial viability and function are preserved for several hours (53), and animal models suggest an initial up-regulation of mitochondrial function in order to match metabolic demand (54). In a sub-analysis of the CULPRIT-SHOCK trial, there was a significant and independent association between the microcirculatory perfusion parameters and the combined clinical endpoint of 30-day all-cause death and renal re-

placement therapy and in patients with loss of hemodynamic coherence between microcirculation and macrocirculation, microcirculatory parameters confer dominant prognostic value (55). Although targeting the microcirculation in CS is appealing (56), the response of the microcirculation to therapeutic interventions is often dissociated from systemic effects (57) and interventions aimed at normalization of the microcirculation in CS have proved inconclusive.

Clinically overt inflammation is seen in 20% of CS patients by day 2 post-CS onset, and may result in an initially low SVR (21). Increased levels of cytokines (interleukin (IL)-1β, -6, -7, -8, and -10) have been detected shortly after CS onset, with levels correlating with early mortality (58). Local factors, such as NO-mediated pathological vasodilatation and tissue hypoxia (59), metabolic factors, dysglycemia and acute increase of advanced glycation end-products further induce vasodilation, and are associated with increased mortality (60). The gut appears to be among the first organs involved in shock, and microcirculatory injury in the intestinal barrier leads to increased bacterial translocation (61, 62). Lipopolysaccharide or endotoxins produced by gram negative bacteria enter the circulatory system and contribute to cytokine generation and inflammation (62). In addition, infection complicates approximately 40% of CS cases (63). Risks for bloodstream infection include vascular access as well as hypoperfusion-related damage to the gastrointestinal mucosal barrier and resulting bacterial translocation.

The occurrence of organ dysfunction is the result of both macro-hemodynamic alterations (64), and microcirculatory dysfunction (65) and portends a poor prognosis. In a recent retrospective analysis, including 443.253 patients with post-MI-CS (66), there was a gradual relationship between the number of dysfunctional organs and in-hospital mortality, a lower probability of home discharge and higher in-hospital cost.

Proteonomic research may further assist the understanding of pathophysiology, improves risk-stratification and provides an opportunity for treatment (67). A recent proteonomic research study identified a complex of 4 proteins (CS4P) associated to multiorgan dysfunction, systemic inflammation and immune activation (67). During the early hours of CS, changes in the expression of CS4P may precede overt multiorgan failure and identify patients at a higher mortality risk (67).

Further, intraplasmic Dipeptidyl-peptidase-3 (DPP-3) was associated to worsening hemodynamics, evolution to refractory CS and 90-day mortality (68, 69). DPP-3 is a cytosolic enzyme associated with alteration in inflammation pathway, inducing strong negative inotropic and vasodilation effect (69) which can be reversed in animal models (67, 68).

Iatrogenic factors, such as administration of countershocks, cardiodepressant sedatives (such as propofol), antiarrhythmics, beta-blockers, excessive use of diuretics, excessive volume loading in RV shock, could further contribute to the cardiovascular dysfunction in CS (42, 70).

In-hospital monitoring and investigations

Immediate assessment of hypoperfusion signs and vitals and continuous monitoring of SBP, rhythm, respiratory rate and saturation are recommended (I/C) (2, 71). A SBP ≥90 mmHg or mean arterial pressure (MAP) in the range of 60–65 mmHg is generally recommended, but this target BP has not been validated in RCTs (2).

A *12 lead ECG* should be immediately performed (I/B) followed by continuous ECG monitoring.

Echocardiography should be used to determine the underlying diagnosis, guide interventions and monitor response to therapies (**Figure 3**), and should be performed urgently, ideally with an immediate, comprehensive study undertaken by an expert (72), Where not available, FoCUS (73) can provide useful information, and should be followed by echocardiography as soon as possible (74). In ED, lung ultrasound (LUS) provides point-of-care evaluation of pulmonary congestion, lung consolidation, pleural effusion, and pneumothorax (73).

The non-invasive methods of hemodynamic monitoring (75) have certain advantages though none have been adequately validated in the context of CS.

Chest X-ray remains of paramount importance for the evaluation of congestion and to monitor the catheter and cardiac device position.

Invasive monitoring using *an arterial line* is recommended in all CS patients (I/C recommendation) (2).

We recommend insertion of a *central venous catheter* in all patients with CS (6, 7), allowing transduction of central venous pressure, and measurement of $ScVO^2$, and access for vasoactive drug administration (76).

The routine use of a pulmonary artery catheter (PAC) remains contentious. The ESCAPE trial (77) and several studies (78-82) suggested no overall benefit in terms of mortality or readmissions from routine invasive assessment of hemodynamics compared to rigorous clinical assessment and a high rate of catheter-related complications. Although, the majority of PAC studies, including ESCAPE, did not enroll CS patients, the use of PAC has decreased significantly over the past decade and is specially reserved for the care of critically ill patients in tertiary hospitals (83) with high level of user competence. Based on expert opinion, PAC is currently recommended in selected

patients who failed to respond to initial therapeutic interventions (persistence of hypotension and hypoperfusion) (IIb/C) (2, 71), or in case of diagnostic/therapeutic uncertainty (cases of mixed shock or patients with advanced right HF) (13).

Biomarker use can provide information for the recognition, prognostication and management of CS. Elevated lactate reflects inadequate tissue oxygenation/metabolism, and the diagnosis of shock includes serum lactate >2 mmol/ (2), which also have a strong prognostic role (13, 84). Although lactate clearance is a signal of response to interventions, improved organ function and survival (85, 86), due to the long-time delay between the intervention and drop in lactate, lactate targeted management has not been shown to be of benefit (13). Natriuretic peptides (NPs) are markers of disease severity and indicative of increased filling pressures. While a retrospective analysis suggested elevated NP were predictive for development of CS (87), this has not been prospectively validated.

Current guidelines recommend at least daily monitoring of complete blood count, serum electrolytes, serum creatinine, liver function tests, coagulation, lactate, arterial blood gas analysis and mixed venous oxygen saturation (when PAC available) (8, 71).

Risk stratification and prognostic models

Current CS risk scores developed in the post-PCI era (*Supplementary Table 1)* relate to identification of patients at risk for developing CS (ORBI) (88), prediction of short-term mortality (CardShock, IABP-SHOCK-II) (39, 89) and prediction of survival after the use of MCS (ENCOURAGE, SAVE-ECMO) (90-92). The CardShock score predicts mortality in CS with a large spectrum of etiologies, while the rest address only post-MI-CS patients. The only scores with external validation are CardShock (39),

IABP-SHOCK II (89), and ORBI (88). Recently, CS4P risk score model improved risk prediction within 24 h of CS admission beyond the IABP-SHOCK-II and CARD-SHOCK clinical risk scores (67).

6. Management

Systems of Care

CS management should start as early as possible. In the pre-hospital setting, physicians should stabilize patients' vital signs (oxygenation and circulation) and treat the underlying etiology while monitoring pulse-oximetry, blood pressure, respiratory rate, and cardiac rhythm(14, 93). All patients with CS should be rapidly transferred to a tertiary care center which has a 24/7 service of cardiac catheterization, and a dedicated ICU/CCU with availability of short-term MCS. A model, analogous to primary PCI pathways, has been proposed by the AHA, to facilitate optimal care coordination and to minimize time-delay (8) (**Figure 4**). This model consists by a network between several satellite-centers (type II and III) and a central "CS-center"(type I) (8). CS-centers should be high volume centers (>107 cases/year) (94) with highly experienced multidisciplinary team (MDT), and availability of on-site operating rooms, short and long-term MCSs, other end-organ supports and provision of safe transfer by a mobile MCS team (95-97), as these are associated with improved outcomes (94) **(Figure 4)**. A nurse to patient ratio of 1:1 is recommended (8, 98) and full integration into the post-ICU pathways.

Management of underlying cause

Early revascularization strategy represents the cornerstone in the management of patients presenting with CS complicating ACS (93). In the SHOCK trial, an early invasive strategy (<12 hours post-CS onset) compared to initial stabilization conferred significantly lower all-cause mortality at 6, 12 and 60 months (99). The benefit was strongly consistent across several subgroups (age, sex, ethnicity, type of ACS, presence of diabetes) (32, 93, 100-102), leading to a current class I/B recommendation in current guidelines (32, 93, 100-102).

In the CULPRIT-SHOCK trial (5), "culprit-lesion only strategy" compared to immediate multi-vessel PCI, results in a significant reduction in 30-day mortality or renal replacement therapy (45.9% culprit-lesion-only PCI versus 55.4% immediate multivessel PCI, relative risk, 0.83; 95% confidence interval, 0.71–0.96; *P*=0.01). This was mainly driven by an absolute 8.2% reduction in 30-day mortality (43.3% versus 51.5%), a consistent finding across all predefined subgroups. Thus, "culprit lesion only PCI" with possible staged revascularization has recently been implemented in the ESC-2018 revascularization guidelines (103). The lack of benefit of immediate multi-vessel PCI has been attributed to the higher doses of contrast media and prolonged procedures and is consistent at 1-year follow-up (104, 105).

Radial access, when feasible (106), is currently recommended by the guidelines (103). The groin area often needs to be preserved for insertion of MCSs. However, the radial access may be challenging in hypotensive patients with CS, and radial access cannot be used to place temporary MCS. The implantation of DES over BMS irrespective of the clinical presentation is recommended (class IA) (103).

Periprocedural antithrombotic management

In CS enteral antiplatelet administration may be inconsistent because of poor splanchnic perfusion and absorption, and to decreased hepatic bioactivation of thienopyridines

(clopidogrel). Concerning the comparison of orally administered clopidogrel, prasugrel and ticagrelor, no difference was observed in terms of efficacy or safety in a secondary analysis of the IABP-SHOCK-II trial (107). However, in the absence of definitive evidence, more potent oral P2Y12 inhibitors with rapid onset of action are recommended in CS. Cangrelor IV infusion provides rapid onset of action and potential rapid reversibility because its bioavailability does not depend on hepatic and gastrointestinal perfusion. Cangrelor has shown its safety with similar bleeding risk and efficacy with better TIMI-flow compared with orally administered antiplatelets in a retrospective analysis of the IABP-SHOCK II trial (108). A RCT comparing cangrelor vs ticagrelor is currently running (ClinicalTrials.gov: NCT03551964).

In patients with CS following resuscitated cardiac arrest (CA), therapeutic hypothermia induces acquired platelet dysfunction and diminishes the bioavailability of orally administered drugs due to additional gastrointestinal dysmotility (109).

One small randomized trial has tested the use of glycoprotein IIb/IIIa inhibitor abciximab in CS patients and failed to prove superiority vs standard treatment, while a prospective but non-randomized trial has showed abciximab more effective than standard treatment in patients <75 years (110, 111). Use of IV anticoagulants is similar to patients with ACS without CS, and IV unfractionated heparin is the primary choice because of the rapid reversal and the acute renal impairment that often coexists in this setting.

Fibrinolysis

The use of fibrinolysis is according to current revascularization guidelines, however its use may increase the risk of bleeding in the context of subsequent MCS.

Surgical revascularization

Although there are no direct randomized comparisons between PCI and coronary artery bypass grafting (CABG) in postMI CS patients, a sub-analysis from the SHOCK-trial (112) suggested similar 1-year mortality between PCI and CABG (48% vs 53%) and a similar finding was found in a subsequent meta-analysis (113). The benefit of PCI is related to its early performance, but usually limited to the "culprit-lesion", while CABG achieves a complete revascularization, outweighed by the increased peri-operative morbidity. Between 2003 to 2010, the rate of early PCI in CS rose from 26% to 54%, whereas CABG rates remained relatively stable at 5% to 6% (14), which might represent current clinical practice (37).

Surgery for mechanical complications

The incidence of ventricular septum rupture (VSR) post STEMI has decreased from 1-3% in the pre-reperfusion era, to 0.2% (114). Surgical closure represents the definitive treatment for post-infarction VSR, although mortality remains high (87% in SHOCK-trial) (115, 116). One study reported a sharp decrease in mortality if surgery was performed late (54.1% within 7 days from MI versus 18.4% after 7 days from MI) which is however mainly attributed to a selection bias and survival of the fittest effect (114). Survival rates following transcatheter septal closure are equally disappointing (117). While delaying of surgery is in most cases not possible because of the hemodynamic compromise secondary to the VSR, early use of MCS may allow to bridge patients to a decision of delayed repair, transplantation, or palliative options, after discussion in MDT.

Papillary muscle rupture occurs in 0.25% of patients following AMI, representing up to 7% of patients with CS (118). Peri-procedural mortality (lower than in VSR because necrotic myocardium is not involved in suture lines) may depend on the extent

of infarction and multi-organ dysfunction (14). Mitral valve replacement is preferred, as repair may be highly challenging.

Free wall rupture presents as sudden onset cardiac tamponade or cardiac arrest, with contained rupture presenting subacutely. In both cases, surgery aims pericardial drainage and closure of the ventricular wall defect (119).

Current guidelines recommend that mechanical complications should treated as early as possible after Heart Team discussion (93) (**Figure 5),** and that IABP may be considered (IIa/C) as interim support (93).

Medical Treatment

Almost one third of patients presenting with CS are "euvolemic", but respond to fluid administration by increasing stroke volume (120). Volume responsiveness assessment is guided by Echocardiography (**Figure 3**). A fluid challenge with infusion of normal saline or Ringer's lactate 250ml over 15-30 min is therefore recommended as first line treatment, if there are no signs of congestion (I/ C) (2).

Inotropes/ Vasopressors

More than 80-90% of patients with CS receive inotropes and/or vasopressors (6) (*Supplementary Table 2*). Although vasoactive medications may restore hemodynamics, it is at the cost of increasing myocardial oxygen consumption and arrhythmogenic burden. Therefore, the general recommendation on their use is to avoid when tissue perfusion is restored and limit the dose and the duration of infusion to the lowest possible (14).

In the SOAP-II trial, the predefined subgroup analysis of CS patients showed that dopamine was associated with higher 28-day mortality and increased arrhythmia burden,

compared with norepinephrine (121). However, this is only hypothesis-generating since the overall trial was neutral. A recent meta-analysis suggested similar unfavorable findings when dopamine was compared to norepinephrine (122), and in a propensity-matching-score analysis from the ESC-HF–LT-registry, dopamine was associated with worse short and long-term outcomes compared with other inotropes/vasopressors (123).

Epinephrine was associated to a significantly higher rate of "refractory CS" compared to norepinephrine in a RCT including post-MI-CS patients (124) and in recent meta-analysis, epinephrine use for hemodynamic management of CS was associated with a threefold increase of risk of death (125). Additionally, epinephrine during resuscitation for CA failed to improve survival with good neurologic outcome when compared to placebo(126).

All these data suggest norepinephrine should be the first line vasopressor recommended by guidelines (IIb/B) to sustain perfusion pressure (2), while we do not recommend routine use of dopamine or epinephrine in CS.

The addition of an inotrope in order to increase cardiac contractility (dobutamine) is recommended with a class IIb/C recommendation, reflecting the paucity of data in this setting (2). The inodilator, levosimendan, (129) may be used in particular CS patients already on chronic beta-blocker therapy (14, 18), as well as in patients with CS and acute RV failure or pulmonary hypertension (PHT), owing to its favourable effects on pulmonary vascular resistance (127, 128)

Milrinone had similar effectiveness and safety profiles as compared to dobutamine (130), but safety concerns over its use in ischemic etiology warrant caution owing to the results of the early OPTIME-CHF trial in decompensated HF patients (131).

Mechanical Circulatory Support

Temporary mechanical circulatory support (MCS) (**Table 2)** has an emerging role and treatment target of MCS is to bridge either to recovery, re-evaluation, transplantation or a permanent implanted left ventricular assist device (LVAD) (132). However, MCSs are associated with significant complications, require specialist multidisciplinary expertise for implantation and management, and high-quality evidence regarding outcomes is largely absent. 2016-HF-Guidelines recommend the early use of MCS in patients with CS refractory to fluid load and inotropes/vasopressors (IIb/ C) (2).

IABP produces no relevant augmentation of CO and may have even less benefit in younger patients with preserved elasticity of the aorta. For IABP, RCTs were performed only in post-MI-CS patients. In the IABP-SHOCK II trial (4) IABP failed to demonstrate benefit on mortality or any of the secondary endpoints. A meta-analysis including 12 RCTs and 15 registries, showed no survival benefit after IABP in post-MI-CS, and has further called into question the utility of IABP therapy (133). Recently, the 6-year follow-up of IABP-SHOCK II has been published confirming the negative results in post MI-CS patients (134). Therefore, 2017-ESC-STEMI guidelines gave III/B recommendation for the routine use of the IABP in CS but still consider IABP only in patients with mechanical complications (IIa/C) or to stabilise for transfer for higher-levels of MCS (93).

Impella is a microaxial pump giving only left-sided support, that unloads the LV by expelling blood flow from the LV into aorta and may provide up to >5L/min of blood-flow depending on the device used and depending on afterload (132, 135, 136). Impella 2.5 and Impella CP can rapidly be implanted percutaneously in the catheterization la-

boratory while Impella 5.0 requires surgical cannulation (137). Unlike IABP, the Impella does not require EKG or arterial waveform triggering, facilitating stability even in the setting of tachyarrhythmias or electromechanical dissociation. In one small randomized trial (138) Impella 2.5 was superior to IABP with respect to hemodynamics whereas in another small randomized trial no hemodynamic benefit of Impella CP over IABP was observed(11). In both trials the Impella device did not show a signal of mortality benefit in CS (11, 139). In addition, a propensity-matched study showed no survival benefit with Impella use and significantly more complications (140). More recent large-scale registry trials using matching showed even higher mortality with Impella use which was also accompanied by more bleeding and access site complications (141, 142). Taken together, the broad use of the Impella MCS in unselected cases should be avoided and larger RCTs addressing survival benefit, timing of implementation (pre/post- revascularisation) and mechanism of benefit are needed. The DanGer Shock study (143) will be the first adequately powered RCT to address whether Impella-CP will improve survival in postMI-CS.

High quality evidence regarding use in other causes of CS(144) is also lacking, however in the RECOVER-I study, including patients with CS-postcardiotomy, the Impella 5.0 was associated with 94%, 81%, and 75% survival at 30-days, 6-months, and 1-year, respectively (145).

The Tandem-Heart provides a continuous flow (4L/min) via a centrifugal pump. The venous cannula is inserted through the femoral vein and is advanced via transseptal puncture into the left atrium (LA), and arterial cannula provides oxygenated flow into the abdominal aorta or iliac arteries. In two randomized studies, including post-MI-CS patients, Tandem-Heart significantly improved hemodynamic indexes as compared to IABP, but 30-day mortality did not differ between the two groups (146, 147)

VA-ECMO provides cardiopulmonary support 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). VA-ECMO provides high levels of biventricular cardiac (V-A) and respiratory support (V-V), up to and including for malignant arrhythmia and cardiac arrest. Some studies indicated an improvement in microcirculatory flow as measured by side-stream dark field imaging (148, 149). Typical ECMO complications are hemolysis, thromboembolic complications, renal failure, limb ischemia/amputation and bleeding. The improvement in the oxygenator membranes permitted low resistance and improved blood compatibility characteristics (18, 150). The modern centrifugal pumps generate less heat and are less thrombogenic, allowing extended duration of support (150). Recent developments with miniaturized systems and percutaneous cannula insertion may confer an advantage for VA-ECMO compared to other MCSs, and have led to a wider adoption by interventional cardiologists (14, 18).

In the event of very poor LV function, peripheral VA-ECMO can be associated with progressive LV distension and pulmonary congestion, potentially resulting in impaired myocardial recovery (150, 151). Decompression strategies for LV venting include additional procedures, such as, IABP, Impella, septostomy and hybrid circuit configuration (150, 152, 153).

When cardiac recovery precedes pulmonary recovery , ejection of deoxygenated blood flow into the ascending aorta results in upper body hypoxia -“Harlequin syndrome” (154), requiring reducing cardiac ejection or reconfiguration (VVA or VAV) until the lungs recover.

In a recent meta-analysis including CS and CA patients, VA-ECMO was associated with significantly improved 30-day survival in both groups compared with IABP, but no difference when compared with Tandem-Heart or Impella (155), making difficult selection of the individual type of MCS and argumenting against the unselected use of active MCS in CS (156). However, the results of a large recent registry with a 9-year observational period suggests 30-day in-hospital mortality remained unchanged over time (59.0% in 2007–2012 versus 61.4% in 2013–2015) (157).

Ongoing randomized clinical trials in post MI-CS, will test whether VA-ECMO on top of revascularization and standard therapy will lead to a reduction in mortality (ECLS-SHOCK [NCT02544594] and EURO-SHOCK [NCT 03813134]).

Isolated RV support

Right-sided support with eiither Impella-RP or Protek Duo (with additional oxygenation capability) has been described in numerous case reports and case series. RV support with Impella-RP in patients with refractory RV failure, was feasible and associated with early hemodynamic benefit, in a small non-randomized study, RECOVER-RIGHT((144). Future RCTs will test whether RV support for either RV pressure unloading (Impella RP 4L/min) or RV volume unloading (TandemHeart RA-PA) will improve clinical endpoints (137).

Temporary MCSs represent a therapeutic modality that is available as a bridge to recovery or as a bridge to decision in refractory cases (158). However, despite of initial beneficial effect on MAP and arterial lactate (156), the unselected use of active MCS in patients with CS is not supported since data on patients' selection are still scare, the results of most trials or meta-analyses were at best neutral on survival and the costs (in terms of patient morbidity/mortality, as well as healthcare economics) are

high and unproven. Although, risk scores such as SAVE and ENCOURAGE have been used to predict survival after the insertion of VA-ECMO (90)(91), MCS are associated with severe complications that may counterbalance beneficial hemodynamic effects, and further research is needed to establish a better risk/benefit ratio. This is of utmost importance in particular groups of patients such as elderly, patients with long duration of CS, or patients with multiple comorbidities. The neutral results of the existing RCTs have multiple explanations related to inclusion of heterogeneous population, large variability in timing of intervention, different learning curves of institutions, lack of data regarding level of anticoagulation, and poorly defined endpoints. The observed improvement of macrocirculation will not automatically translate to improved microcirculation, and macrocirculatory improvements should be considered as a measure of technical success rather than an endpoint. Clinic relevant endpoints, such as 30-day and 180-day mortality should be considered in future RCTs. In addition, future studies should address the choice of an individual type of MCS as well as the markers of monitoring during MCS (hemodynamic markers, echocardiography markers, inflammatory response or organ damage markers) that can guide weaning and final decisions (159). For the time being, the monitoring is primarily based on Echocardiography, PAC hemodynamics, lactate and organ function tests. In clinical practice, if the patient is stable, weaning starts from vasopressors followed by a reduction of levels of support. If the patient remains stable on low-level of support and without requiring higher doses of vasopressors/inotropes, the MCS can be explanted (158). When the patient is hemodynamically unstable on initial MCS, a combined support may be considered. Especially in patients with biventricular failure and severe hypo-oxygenation, combined VA-ECMO and Impella may be considered. Duration of support is often unpredictable, and

weaning should incorporate evaluation of bridging strategies Patients who cannot recover on temporary MCSs, but without irreversible end-organ damage should be directed to a permanent modality (durable LVAD or heart transplantation) (120).

Organ Dysfunction and specific non-cardiac interventions

Mechanical Ventilatory Support

Acute respiratory failure is present in almost all patients presenting with CS, either from intrapulmonary shunting generated by pulmonary congestion, and the reduction in lung space with increasing the ventilation–perfusion mismatch, and/or cerebral hypoperfusion. Further lactic acidosis results in increased respiratory drive with hyperventilation, thereby augmenting total body oxygen requirements (160).

Hypoxemia is addressed with conventional oxygen therapy in various inflow rates, with one third of the patients (usually with less severe hemodynamic impairment) successfully managed via this approach (161). 60 to 80% of the patients develop progression of respiratory failure requiring mechanical ventilatory support (MVS) and these patients have worse prognosis. In the SHOCK-trial, nearly 80% of the patients received MVS, while in the CardShock study, the percentage of patients mechanically ventilated was nearly 75% (39). However, it should be noted that the incidence of acute respiratory failure and, consequently, the use of both non-invasive and invasive mechanical ventilation has decreased over time (162). Decision to initiate MVS is multifactorial, including arterial blood gas levels, cerebration and required interventions.

Even if noninvasive ventilation (NIV) is basically contraindicated in post-MI CS, the Cardshock study showed that a minority of patients (13%) who were more congested

than hypoperfused, may be successfully treated with this technique, avoiding intubation.

No specific ventilation modality has demonstrated superiority over the others (163), however high levels of PEEP are poorly tolerated, in particular in patients with RV dysfunction. If invasive ventilation is required, lung-protective ventilation (6 mL/kg/ body weight tidal volume) should be undertaken to prevent pulmonary injury (18, 160, 164).

In cases of CS secondary to RV dysfunction, permissive hypercarbia/hypoxaemia should be avoided due to the associated pulmonary vasoconstriction. Also, positive intrathoracic pressure should be generally avoided because worsens RV failure, but final decision will depend beside of hemodynamics, on degree of hypoxemia and presence of atelectasis (164).

Liver injury

Liver injury frequently complicates CS, and >50% of patients present with elevated liver enzymes (165). Ischemic hepatitis is diffuse hepatic injury from a sudden drop in cardiac output. Here the aminotransferases peak ≈1 to 3 days after the hemodynamic insult, and return to normal 7-10 days in the absence of any further insult. Transaminases are associated with worse in-hospital mortality(166) and can be used as biomarkers of hemodynamic reserve (167). Congestive hepatopathy is commonly seen in patients with RV dysfunction, with the combination of low CO and elevated venous pressure being particulary injurious. No specific therapies are recommended per se, although discussion with specialist liver intensive care is recommended, and particular attention must be paid to RV function, including reduction in pulmonary vascular resistance and right atrial pressure.

Renal Dysfunction

About one third of patients with CS develop acute kidney injury (AKI), but many CS survivors do experience gradual renal recovery. The process may be slow (5-20 days) and depends on severity of AKI (168). Systemic hypoperfusion, backward congestion, nephrotoxic drugs and MCS may contribute to AKI in CS. If acute tubular necrosis develops renal replacement therapy (RRT) will be required and prognosis worsens.

Continuous veno-venous hemodiafiltration (CVVHDF) is recommended in severe AKI (creatinine ≥2× baseline and urine output <0.5 mL/kg/h for ≥12 hours) or when life‐threatening changes in fluid, electrolyte, and acid‐base balance mandate (169). Intermittent hemodialysis should not be used as it is poorly tolerated (170).

Temperature Management

Following cardiac arrest, targeted temperature management reduces overall metabolic rate and myocardial oxygen consumption contributing to better neurological protection (171, 172), but the data is limited in CS following CA. In the SHOCK-COOL trial, mild therapeutic hypothermia failed to show a substantial beneficial effect on cardiac power index at 24 hours in patients with CS after AMI (173). The HYPO-ECMO trial (NCT02754193) is currently recruiting CS patients on VA-ECMO and will address whether moderate hypothermia is associated with improved organ function.

VI. Stabilization phase - Discharge

Patients discharged home without having fully recovered from critical illness carry a very high rate of early re-hospitalization and death (174, 175). A MDT approach before

discharge is mandatory, in order to address psychosocial aspects, educate in terms of symptoms, diet, exercise, manage comorbidities) (176) **(***Supplementary Table 3***).** In patients with HF with reduced ejection fraction, disease-modifying therapies should be re/initiated at lowest doses when patients are clinically stable, euvolemic and at least 24 hours after IV catecholamines stopped. When the patient cannot be discharged home, a rehabilitation program or a palliative care center should support the transition phase (8).

7. CS in various clinical settings

In patients presenting with CS, non-ACS causes, should always be considered, as they represent different clinical settings with particular pathophysiological characteristics and specific management (**Table 1**).

RV failure

Rapid identification of the presence and aetiology of RV dysfunction, correction of hypervolemia/hypopvolemia, appropriate management of ventilation and assessment of associated PHT are pivotal to successful management. (**Table 1**). Echocardiography and PAC-tailored management to optimize hemodynamics and volume status of the patient are recommended. When patients fail to respond to inotropes/vasopressors, VA-ECMO or Impella-RP may be considered (157).Acute RV failure post LVAD implantation has an incidence of 20-25% and may be clinically recognized (176) and diagnosed using the modified EUROMACS score (including clinical, laboratory, echocardiographic and hemodynamic variables) (177). It should be managed with standard supportive therapies, up to and including the use of right-sided MCS.

Fulminant myocarditis

The combination of flu-like symptoms in association with evidence of myocardial injury should raise the suspicion of acute myocarditis. The diagnostic approach In the critically ill patient with rapidly progressive HF despite standard therapy includes RV endomyocardial biopsy to exclude giant cell myocarditis, where treatment with immunosuppressant agents (178, 179) should not be delayed. In a prospective study, combination therapy (cyclosporine plus prednisolone) was associated with more favorable outcome (177).The contemporary transplant-free survival of otherwise lethal giant-cell myocarditis treated with combined immunosuppressive drugs is 65% at one year and 42% at five years (179).

In patients with fulminant myocarditis, irrespective of the underlying aetiology, early MCS should be considered, and is associated with acceptable mid-term survival rates (180). Due to the diffuse myocardial involvement, percutaneous univentricular MCS are often insufficient to restore peripheral tissue oxygenation, and biventricular support (e.g. peripherally VA-ECMO in combination with Impella for unloading the LV) is frequently required. Where myocardial function does not sufficiently recover, longer-term MCS may be required, potentially followed by transplantation.

Takotsubo Syndrome

Takotsubo syndrome is characterized by severe myocardial failure often accompanied by LV outflow-tract obstruction (LVOTO), CS and cardiac arrest. The incidence of CS in the Takotsubo population varies from 2.8 to 12.4%, while a recently published 28-day mortality was 28.6%, implying the natural reversibility of the disease if the patient is initially stabilized (181). Catecholamine administration should be avoided, as already

have a causative relationship with the syndrome. Alternative inotropes, such as milrinone or levosimendan seem a rational approach (182). Early MCS may diminish the need for catecholamines and provide the reasonable time frame for LV recovery (158).

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy occurring in the last month of pregnancy or in the puerperium, with unpredictable outcome. In the majority of cases myocardial function recovers within months, while in about one third it stabilizes or worsens (183). Some PPCM patients may have thrombus in the LV that may lead to stroke. The pathophysiologic trigger is the formation of 16 kD prolactine that promotes oxidative stress. In CS complicating PPCM, catecholamine therapy is detrimental. Although, the evidence is provided only by case reports, the combination of high dose bromocryptine (inhibitor of prolactin production), inodilators and early MCS seems to be a rational strategy (184).

Cancer

Although data regarding the incidence of CS in patients with a malignancy are scarce, history of cancer is an independent risk factor of mortality in CS (185). CS can develop due to cancer itself, the co-existing cardiovascular disease, thromboembolic events, or the type of treatment (surgery, chemotherapy and radiotherapy) (186).

Valvular Disease

A variety of mechanisms may contribute to CS in the setting of decompensated valvular disease and initial stabilization is recommended before evaluation for corrective sur-

gery. For patients with aortic or mitral valve endocarditis with severe acute regurgitation, obstruction or fistula causing refractory CS, surgery must be performed on an emergency basis, irrespective of the status of infection (187). MCSs should be individualized based on pathophysiology of the valvular disease (157) (**Table 1**).

Out of hospital cardiac arrest (OHCA)

OHCA patients represent a special category, with increasing prevalence in the ICCUs. In the IABP-SHOCK-II and the CULPRIT-SHOCK trials 40-50% of patients were resuscitated before randomization (4, 5). Immediate mortality is high, reaching more than 85% in some registries (188). Pathophysiology of CS secondary to CA is determined by pump failure (as result of the initial cardiac insult responsible by CS and prolonged myocardial stunning due to cardiac arrest) and systemic vasodilation secondary to regional and global ischemia-reperfusion injury (189, 190). For patients with CA refractory to CPR, E-CPR (ECMO support during CPR) may be considered. The goal of E-CPR is to support patients in refractory CA of potentially reversible etiology (e.g. AMI, pulmonary embolism, cardiac injury) while reversible causes are being identified and treated (191-193). In comparison with conventional CPR, E-CPR is associated with a 13% absolute increase in the 30-day survival rate based on registry studies (155).

These patients have a higher burden of in-hospital complications with more frequent use of resources (194) and 30% are discharged with functional impairment, requiring a skilled nursing facility (195).

Post-cardiotomy cardiogenic shock (PCCS)

The incidence of PCCS varies between 2% and 5%(196-198) and it is associated to poor outcomes. In a study including 1764 PCCS patients, 30-day and 3-months mortality were 49 and 65%, respectively, with only 29% alive at 1 year (199). Numerous

factors may contribute to PCCS, including pre-operative morbidity, type of surgery, insufficient cardio-protection and prolonged cardiopulmonary bypass. Inability to wean from cardiopulmonary bypass and/or poor postoperative hemodynamics may be indications for MCS.

Two readily remediable conditions must be rapidly excluded/addressed including localized pericardial tamponade and dynamic left-ventricular outflow tract obstruction. The localized tamponade in the first week post cardiotomy has been reported at 0.2-2% of patients with CABG and 8.4% in heart transplant patients, and precipitating factors included administration of anticoagulants, coagulation disorders, excessive mediastinal bleeding, the removal of epicardial pacing wires (200).

Dynamic LVOTO leading to CS in the first days post-surgery has an incidence of 0.3% and associated conditions are hypovolemia, cardiac hypertrophy, aortic valve replacement, and high doses of catecholamines (200).

Refractory RV failure occurs in 0.1% of patients following cardiotomy and in-hospital mortality is as high as 70-75% (201).

Gaps in Evidence - Future directions

CS is a complex, multifactorial clinical syndrome with extremely high mortality. Despite advances in revascularization, valve interventions, immunomodulation and MCSs, CS remains the most common cause of in hospital death after AMI and a major cause of death in young patients with other potentially reversible underlying cardiac pathology. Gaps in evidence are extensive **Table 3**; the pathophysiology is not well elucidated, the definition and clinical/hemodynamic profiles are not well studied, and

randomized data are scarce, with only approximately 2000 patients being randomized in trials of CS. Evidence from RCTs is limited, mostly because small numbers of patient are recruited, blinding is often not possible and the primary endpoint often differs from one study to another. Designing outcome trials in CS remains particularly challenging in this critical, rare and very costly scenario in cardiology.

Summary/Conclusion

CS is a complex multifactorial clinical syndrome with extremely high mortality, developing as a continuum, resulting from the initial insult (underlying cause) to the subsequent occurrence of organ failure and death. Substantial investments in research and development have not yielded proof of efficacy and safety for most of the therapies tested, and outcome in this condition remains poor. Future studies should consider delivering pathophysiologically appropriate therapies in a timely and targeted manner, in appropriately selected population, whilst avoiding iatrogenic harm. High quality translational research should facilitate incorporation of more targeted interventions in clinical research protocols, aimed to improve individual patient outcomes.

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