



Cardiogenic Shock Complicating Myocardial Infarction: An Updated Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author AE designed the Review and authors AE, AS, MM and HA wrote the first draft of the manuscript. Authors AS, MM and AE managed the literature searches. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

The current review aimed to highlight the update management in patients with ischemic Cardiogenic shock (CS) and its impact on mortality. We reviewed the literature using search engine as MIDLINE, SCOPUS, and EMBASE from January 1982 to October 2012. We used key words: "Cardiogenic Shock". This traditional narrative review did not expand to explore the mechanical complications or other causes of CS. There were 7193 articles assessed by 3 reviewers. We excluded 4173 irrelevant articles, 1660 non-English articles and 93 case-reports. The current review evaluated 888 articles (880 studies and 8 meta-analyses) that were tackling ischemic CS from different points of view before and after the era of SHOCK trial. Ischemic CS remains the most serious complication of acute MI, being associated with high mortality rate both in the acute and long-term setting, despite the advances in its pathophysiology and management. Further randomized trials and guidelines are needed to save resources and lives in patients sustained ischemic CS.

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1. HISTORICAL OVERVIEW

Cardiogenic shock (CS) is a serious complication of acute myocardial infarction [MI] [1]. The mortality rate is approximately 50% even with rapid revascularization, optimal medical care, and use of mechanical support [2-3]. Clinical features of cardiogenic shock are first described 100 years ago by James Herrick [4]. It took several decades before the first large series of patients with CS have described [5,6]. Following the introduction of CCUs for the care of patients with ACS, substantial steps have been taken in explaining the pathophysiology as well as improving the management of these patients [7,8]. Table 1 summarizes the history of CS until the SHOCK trial [1912-1999].

Table 1. Summary of the management of ischemic CS before the era of the SHOCK trial

1912	James Herrick described the clinical features of coronary thrombosis and cardiogenic shock and suggested that efforts should be made to diagnose cardiogenic shock (CS)
1935-1940	Harrison (1935) and Blalock (1940) were the first to propose an etiological classification for shock into: cardiogenic, oligemic, vasogenic and neurogenic
1942	Stead and Ebert described the manifestations of shock caused by failure of the heart as a disease with multiple systemic effects
1954	Griffith and colleagues described the first large series of patients with CS admitted with acute MI. They evaluated the use of norepinephrine, methoxamine, and isoproterenol in CS.
1955	A standard definition of CS related to acute MI was suggested by Binder and colleagues. Shock state did not improve with cortisone or the use of intravenous infusions. There was mortality benefit with norepinephrine, while Isoproterenol was beneficial in patients who had heart block accompanying shock.
1960s	Coronary care units (CCUs) were introduced as a specialized area to care for patients who had AMI. CCUs were shown to improve in-hospital mortality from acute MI, however, mortality in those who had CS was not improved and was reported at 81% to 85%.
1962	Moulopoulos et al described a device that was inserted into the descending aorta and pumped blood during diastole. When tested in dogs, hemodynamic benefits were achieved.
1964	Cohn and Luria showed that bedside hemodynamic monitoring helped to differentiate patients who would respond to volume expansion from those who need vasopressors.
1967	Killip and Kimball, using bedside evaluation of 250 patients with acute MI, described a classification system for risk stratification based on clinical evidence of left ventricular dysfunction. class IV was defined as CS
1968	Kantrowitz and colleagues used intra-aortic balloon pumping (IABP) in CS patients. The device was placed in the descending aorta via femoral arteriotomy and helium was used to fill the balloon. In all five patients, hemodynamics improved and stabilized after 1 to 15 hours of balloon pumping.

- 1970 Swan and colleagues described balloon-tipped catheter for catheterization of the heart in man. In the same year, some reports showed that vasopressors could improve hemodynamics but not mortality.
- 1971 Page and colleagues showed that patients dying from CS had larger areas of infarction than patients dying suddenly of AMI without shock. Extensive 3-vessel disease was often present at autopsy. This observation, along with the failure of IABP support alone to improve mortality, lead to efforts to treat patients with surgical revascularization.
- 1972 The first report of use of emergency CABG for complicated MI including CSk. Dunkman and colleagues reported that shock was reversed by IABP in 31 of 40 patients and emergency CABG in this setting could result in a favorable outcome.
- 1972 Swan and colleagues suggested that revascularization would improve left ventricular function by restoring contractile muscle mass and by improving diastolic compliance.
- 1973 Scheidt and colleagues showed the results of using IABP in 87 patients who had CS. Although significant improvement in cardiac output, only 40% of patients could be weaned from balloon support and only 17% survived to hospital discharge. Leinbach and colleagues noted that Urgent coronary angiography was feasible with IABP support.
- 1976 Forrester and colleagues postulated the advantage of hemodynamic monitoring in patients who have AMI, using the previously described balloon-tipped catheter that was advanced from a peripheral vein to the pulmonary artery at bedside, without the use of fluoroscopy. Mortality of patients who had pulmonary congestion and systemic hypoperfusion was 51%
- 1977 Johnson and colleagues recommended revascularization within 12 hours of the onset of MI for appropriate patients who had CS, with postoperative use of IABP.
- 1978 Mueller and colleagues described the use of dopamine in patients who had CS and AMI and found that peripheral perfusion improved at the expense of increased myocardial oxygen consumption. They recommended cautious use of dopamine in these patients
- 1980 DeWood and colleagues compared treatment with IABP alone and IABP combined with revascularization surgery. Although hospital mortality was similar, long-term mortality was improved in the revascularization group. This improvement in mortality was more significant if revascularization was done within 16 hours of onset of symptoms.
- 1985 O,Neill et al published the first report of percutaneous transluminal coronary angioplasty in the treatment of cardiogenic shock
- 1999 The landmark SHOCK trial was the first prospective, randomized study in CS. (see text)
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In the last decades, new insights into the pathophysiology of CS have been appreciated. In addition, there have been progresses in the management of CS including hemodynamic stabilization as well as revascularization strategies. We reviewed the literature using search engine as MIDLINE, SCOPUS, and EMBASE from January 1982 to October 2012. We used key words: "Cardiogenic Shock". This traditional narrative review did not expand to explore the detailed mechanical complications or other causes of CS. There were around 7193 articles assessed by 3 reviewers. We excluded 4173 irrelevant articles, 1660 non-English articles and 93 case-reports. The current review evaluated 888 articles (880 studies and 8 meta-analyses) that were tackling ischemic CS from different points of view. This review

aims to summarize the management of CS complicating MI [ischemic CS] before and after the era of the SHOCK trial.

2. DEFINITION

CS is a clinical condition of inadequate tissue (end-organ) perfusion due to cardiac dysfunction. The definition includes clinical signs in addition to the hemodynamic parameters. Clinical criteria include hypotension [a SBP<90mmHg for at least 30 min or the need for supportive measures to maintain SBP≥90mmHg] and end-organ hypoperfusion (cool extremities or a urine output<30 ml/h). The hemodynamic criteria are a cardiac index (CI) at least 2.2 l/min/m² and a pulmonary capillary wedge pressure (PCWP) at least 15 mmHg [27, 28]. CS is a systemic clinical syndrome that needs hemodynamics assessment to support the diagnosis and guide the management [29].

3. MYOGENIC, MECHANICAL AND ARRHYTHMOGENIC CAUSES OF CS

Acute MI with left ventricular failure is the most common etiology of CS. Other myogenic reasons include cardiomyopathy, myocarditis, cytotoxic agents and others. In addition to the mechanical complications of acute MI (e.g. papillary muscle dysfunction, ventricular septal rupture, or ventricular free wall rupture), other mechanical reasons of CS involve: valvular heart diseases, hypertrophic cardiomyopathy, pericardial tamponade, outflow tract obstruction and traumatic cardiac injury. Lastly, arrhythmogenic reasons include tachyarrhythmias or bradyarrhythmias [29, 30].

4. Pathophysiology of ischemic CS

In classic ischemic CS, significant hypotension results from an acute drop in stroke volume, following acute myocardial ischemia and necrosis. The fall in blood pressure may be initially compensated by a marked elevation in systemic vascular resistance, mediated by endogenous vasopressors such as norepinephrine and angiotensin II. However, such response occurs at the expense of marked reduction in tissue perfusion. A vicious cycle can develop, with decreased coronary perfusion pressure, more myocardial ischemia and dysfunction, resulting in a downward spiral with progressive end-organ hypoperfusion and finally death [31].

The pathophysiological concept of combined low cardiac output and high systemic vascular resistance has been recently challenged by the fact that post-MI shock may be associated with relative vasodilation rather than vasoconstriction. The most likely explanation for that is the presence of a systemic inflammatory state similar to that seen with sepsis [32]. Despite intensive management, patients with CS often progress into systemic inflammatory response syndrome [SIRS] followed by multiorgan dysfunction syndrome and death [33]. This acute inflammatory response has associated with elevated serum cytokine concentrations especially interleukin-6 [33-36]. Cytokine activation leads to induction of nitric oxide [NO] synthase and elevated levels of NO, which can induce inappropriate vasodilation with reduced systemic and coronary perfusion pressures [37]. Lim et al found that several patients with CS died despite normalization of cardiac index, suggesting a maldistribution effect with low systemic vascular resistance [38]. Recent data suggest that enhanced expression of monocyte receptor for advanced glycation end products and decreased plasma soluble receptor for advanced glycation end products levels interplay a central role in patients with CS and are associated with high short-term mortality [39]. This study could be a

step for further confirmative studies addressing the role of new biomarkers in the diagnosis and management of CS patients [40].

5. Incidence and Outcome of ischemic CS

The incidence of CS was nearly constant for decades and complicated approximately 5–9 % of acute ST elevation MI (STEMI) [41-42]. However, data from large registries have shown a decline of 5 % in the last decade although the rates of CS present on hospital admission have not changed [43-44]. This may be the result of increased frequency of revascularization for acute coronary syndrome (ACS) as shown in the AMIS PLUS registry [45]. In this registry, the overall incidence of CS fell from 13% to 5.5% while the use of primary percutaneous coronary intervention (PCI) during the same period in patients with CS increased from 8% to 66% with lower hospital mortality [45]. Despite advances in the management of CS, the rates of mortality, although improved to an extent in the recent decades, remain significantly high [46]. The results of three nationwide French registries have shown changing trends in the management and outcomes of patients with CS complicating AMI. The overall rate of CS after AMI was 6.5%. The prevalence of CS tended to decrease from 1995 to 2005 (7% in 1995; declined to 6% in 2005) [47].

Although, the majority of patients who develop CS have STEMI, CS may occur in patients with NSTEMI as well [41, 48]. Cardiogenic shock can develop either acutely or within the first few days of hospital admission. In the SHOCK trial and registry, one quarter of patients had shock on admission [49]. CS on admission has associated with rapid and profound hemodynamic deterioration that was more severe than who developed CS later. The median time to the onset of shock was 5.6 hours after infarction [27]. However, CS develops faster if the left coronary artery is the infarction-related artery [30] and among those with STEMI compared to patients with NSTEMI [48, 50]. In the TRACE trial, patients who develop CS after 48 hours of infarction had significantly higher mortality than those who develop it in the first two days of MI [51].

6. Risk Factors for ischemic CS

Several studies and registries have shown multiple risk factors for development and outcome of CS in patients with acute MI. There are numerous predictors of CS in patients with AMI such as old age, anterior MI, hypertension, diabetes mellitus, renal failure, multivessel coronary artery disease, prior stroke, prior peripheral arterial disease, prior MI, heart failure, left bundle branch block, initial systolic blood pressure, heart rate, and Killip class [41, 47, 52-53]. Moreover, creatinine clearance and number of vasopressors used were significant predictors of mortality [53-54].

The Acute Physiology and Chronic Health Evaluation (APACHE) II scores are used as predictors of mortality among the patients presenting with AMI and CS. The initial score as well as the progress over 4 days in response to treatment was closely related to prognosis in these patients [33, 40]. Sleeper et al. [55] proposed a severity scoring system for CS to assess the potential benefit of early revascularization in different risk strata using data from the SHOCK Trial and Registry. This two-staged system included clinical variables (stage 1) and hemodynamic parameters (stage 2). The clinical risk variables included age, shock on admission, clinical evidence of end-organ hypoperfusion, systolic blood pressure, prior coronary artery bypass grafting (CABG), non-inferior MI, and serum creatinine.

In stage 1, mortality ranged from 22% to 88% by score category and the revascularization benefit was greatest in moderate- to high-risk patients. However, in stage 2, the effect of early revascularization did not vary by risk stratum. Numerous studies [38-39, 56-57] suggested that PCI improves short-term survival in patients with CS. However, the French registries in 2012 demonstrated that although early mortality has decreased with the broader use of PCI and recommended medications at the acute stage, 1-year survival has remained unchanged [47].

7. Hemodynamic Measurement

The hemodynamic criteria for CS can be confirmed by insertion of a balloon-tipped PAC and an intraarterial blood pressure monitoring catheter [58-59]. The role of PAC in the management of CS patients remains controversial. Although retrospective data have raised the possibility of increased mortality associated with this procedure [60], data from GUSTO-I trial [52] and SHOCK registry [61] reported that it is not harmful, and could be beneficial, in terms of prognosis. PAC insertion is recommended for the management of STEMI patients with CS in both the current ACC/AHA guidelines (class IIa) and the European Society of Cardiology guidelines (class IIb) [58,62].

8. TREATMENT OF CS

8.1 Initial Stabilization

The aim of Initial resuscitation is to stabilize oxygenation and perfusion while revascularization is contemplated [63-64]. Advanced CS requires full intensive care management including ventilation to ensure oxygenation, hemodialysis, and sedation [63-64]. The previously recommended intravenous insulin infusion for aggressive blood sugar control has been challenged after the results of NICE-SUGAR study and The ACC/AHA guideline which showed unfavourable effects of such strategy [65-66]. Further measures under investigation include therapeutic hypothermia [2,67,68] and Continuous lateral rotation [kinetic therapy] [69]. The latter measure is a continuous turning of a patient slowly to >40% onto each side along the longitudinal axis. It was initially used for pressure ulcer prevention and was found to reduce pulmonary complications in trauma patients, critically ill patients, and recently in ventilator-dependent CS patients [69].

8.2 Inotropes and Vasopressors

Inotropic and vasopressor drugs are considered the principal initial interventions for reversing hypotension and improving vital organ perfusion. However, those drugs should be used at the lowest possible doses as higher doses have been associated with poorer survival [70]; this corresponds to both more severe underlying hemodynamic derangement and direct toxic effects [41].

The beneficial short-term hemodynamic improvement occurs at the cost of increased oxygen demand when the heart is critically failing and supply is already limited. However, use of inotropic and vasopressor agents is always needed to maintain coronary and systemic perfusion until other measures of management become available [41].

Large-scale controlled studies have not been performed to compare different combinations of inotropes in patients who have CS. The efficacy of inotropes can be affected by the local

tissue perfusion and metabolism that are progressively impaired in CS. The most commonly used agents in CS include dopamine, dobutamine, epinephrine and norepinephrine (Table 2) [29, 71-72]. The SOAP II study included 1679 patients with shock of various etiologies. Although there was no significant difference in mortality between patients with treated with dopamine as the first-line vasopressor and those treated with norepinephrine, however, the use of dopamine was associated with a greater number of adverse events. Furthermore, the CS subgroup of the study showed that norepinephrine treatment led to a significantly better survival rate than the dopamine treatment [73].

The ACC/AHA guidelines recommend dopamine as the agent of choice in low output states and norepinephrine for more severe hypotension because of its high potency. Although both dopamine and norepinephrine have inotropic properties, dobutamine is often needed once arterial pressure is brought to 90 mmHg at least [58]. Similarly, in the German-Austrian guidelines, norepinephrine is considered the vasopressor of choice in patients with mean arterial pressure [MAP] values < 65 mmHg and dobutamine is recommended as the inotrope of choice rather than dopamine [63]. However, the recently published ESC STEMI guidelines ranked dopamine and dobutamine class IIa recommendation [level of evidence C] and norepinephrine as class IIb (B). However, norepinephrine is preferred to dopamine in case of persistent hypotension [62].

Newer classes of inotropes and vasopressors have been introduced; some of them are being used in clinical practice and others are still under investigations (i.e., Amrinone, milrinone, Levosimendan, Vasopressin, Nitric Oxide (NO) inhibitors, Complement blocking agents, and Sodium/hydrogen-exchange inhibitors):

8.2.1 Amrinone and milrinone

Amrinone and milrinone are phosphodiesterase-3 inhibitors that lead to accumulation of intracellular cAMP, affecting a chain of events in vascular and cardiac tissues resulting in vasodilation and a positive inotropic response. These drugs lead to a short-term improvement in hemodynamic performance in patients with refractory heart failure; however they are largely limited in shock states because of their vasodilatory properties [74]. Unfortunately, studies have largely failed to translate their hemodynamic benefits into long-term mortality benefits [75-76].

Table 2. Receptor activities and hemodynamic/clinical effects of the commonly used inotropes/vasopressors in cardiogenic shock

Drug	Main receptor activity					Dose ($\mu\text{g}/\text{kg}/\text{min}$)	Clinical/hemodynamic effects						
	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	DA		CO	Dp/dt	HR	SVR	PVR	PCWP	MVO2
dobutamine	0(+)	0(+)	++++	+++	0	2-20	↑↑↑	↑	↑↑	↓	↓	↓ or ↔	↑
Dopamine						2-20							
- 0-3	0	(+)	+	+	++		↑	↑	↑	↓	↓	↑	↑
-3-8	+	(+)	++	+	++		↑↑	↑	↑	↓	↓	↑	↑
-> 8	+(++)	(+)	++(++)	+(+)	++		↑↑	↑	↑(↓)	↑	↔(↑)	↑(↔)	↑↑
epinephrine	++++	+++(+)	+++	0(+)	0	0.05 – 0.5	↑↑	↑	↑↑	↑(↓)	(↑)	↑ or ↔	↑↑
norepinephrine	++++	+++	+++	0(+)	0	0.02-1	↑	↑	↔(↑↓)	↑↑	↔	↔	↑

Abbreviations: CO=cardiac output; HR=heart rate; dp/dt=myocardial contractility; SVR=systemic vascular resistance; PVR=pulmonary vascular resistance, PCWP=pulmonary capillary wedge pressure; MVO2= myocardial oxygen consumption; α = alpha adrenergic receptor; β = beta adrenergic receptor; DA= dopaminergic receptor; 0=no effect; +=minimal receptor stimulation; ++ mild receptor stimulation; +++ moderate receptor stimulation; ++++ strong receptor stimulation; () variable effects; ↑ = mild increase; ↑↑ = moderate increase; ↑↑↑ = marked increase; ↓ = decrease; ↔ = equivocal effect.

[Modified from (29, 71-72)].

8.2.2 Levosimendan

Levosimendan represents a new calcium sensitizer with positive inotropic properties [77]. It causes conformational changes in cardiac troponin C during systole, leading to sensitization of the contractile apparatus to calcium ions without increasing intracellular calcium [in contrast to other positive inotropic drugs] [78-80]. This counteracts the undesired side effects of increased intracellular calcium such as increased oxygen consumption and increased risk for fatal arrhythmia [29]. In addition to its positive inotropic action, levosimendan exerts vasodilating properties that reduce cardiac preload and afterload, enhances coronary blood flow, and increases myocardial oxygen supply [81-82]. The combined use of levosimendan with other vasoactive drugs may be considered on an individual basis more than milrinone [83]. Levosimendan has been used as the sole inotrope in post-MI CS patients in isolated case reports [84]. It seems to be effective, compared to dobutamine, in increasing both cardiac index and contractility in patients with post-MI CS in the short term outcome [85]. It also has been shown to improve the Doppler echocardiographic parameters of LV diastolic function in patients with CS post-STEMI who were revascularized by primary PCI [77,86]. Despite these favorable hemodynamic short term effects, Levosimendan showed controversial results regarding its effect on survival in short and long term follow up compared to dobutamine or placebo [87-88]. Thus, larger controlled randomized studies are needed to support such findings.

8.2.3 Vasopressin

Jolly and colleagues [89] identified the patients who had refractory CS and were treated with vasopressin or norepinephrine under hemodynamic monitoring. Intravenous vasopressin therapy was associated with increased MAP with no adverse effect on other hemodynamic parameters [89]. An experimental study showed that combined dobutamine-norepinephrine had an efficient hemodynamic profile in CS, while vasopressin which acts as pure afterload-increasing substance aggravated the shock state by causing a ventriculoarterial mismatch [90]. Randomized prospective trials are required to confirm the benefit and safety of vasopressin in the setting of CS after MI.

8.2.4 Nitric oxide (NO) inhibitors

Although low levels of NO are cardioprotective, excess levels of NO have further detrimental effects on the myocardium and vascular tone [29]. N-Monomethyl-L-Arginine (L-NMMA), a NO inhibitor, was tested in 11 patients who had refractory CS after maximal treatment with catecholamines, IABP, mechanical ventilation, and percutaneous revascularization. Urine output and blood pressure increased markedly, with a 72% 30-day survival rate [91]. The same investigators randomized 30 CS patients after revascularization to supportive treatment or supportive treatment and L-NAME [[N-Nitro L-arginine methylester]] (L-NMMA prototype). One-month survival in the L-NAME group was 73% versus 33% in the supportive treatment alone, with a significant increase of mean arterial pressure and urinary output in the L-NAME group [92]. The SHould we inhibit nitric Oxide synthase in Cardiogenic shock 2 (SHOCK-2) assessed preliminary efficacy and safety of four doses of L-NMMA in patients with AMI complicated by CS despite an open infarct-related artery [93]. Although the potent haemodynamic effects of NO inhibition in patients with CS suggested by prior studies have not been confirmed by SHOCK-2, this study has demonstrated the feasibility of a multicentre, randomized trial of an investigational agent in CS complicating AMI [93].

Based on the results of SHOCK-II, the Food and Drug Administration approved a prototype drug, tilarginine acetate (L-NMMA) injection, for the treatment of CS. However, the TRIUMPH Study, a Phase III international multicenter, randomized, double-blind study, is recently terminated because of a lack of efficacy [94]. It was suggested that all these studies evaluated compounds with little selectivity for iNOS and their failure may have been due to the inhibition of the other NOS isoforms [94].

8.2.5 Complement blocking agents

Pexelizumab is a unique antibody fragment that blocks activation of complement C5, which is involved in inflammation, vasoconstriction, leukocyte activation, and apoptosis [95]. In the COMMA trial, the administration of pexelizumab in patients who had an acute STEMI, managed with primary PCI, was associated with a considerable reduction in mortality and CS compared with placebo [96]. However, APEX-AMI, a large phase III mortality trial with pexelizumab was stopped after disappointing results of two major trials of this drug in CABG patients [97]. Analysis of the enrolled patients showed that pexelizumab infusion given with PCI did not reduce mortality or the risk of reinfarction, or shock in patients with acute STEMI compared with PCI alone [97].

8.2.6 Sodium/hydrogen-exchange inhibitors

During ischemia, acidosis activates anaerobic metabolism and sodium/hydrogen exchange, thus leading to intracellular sodium accumulation, resulting in increased intracellular calcium and eventually cell death [98]. Two large trials; the GUARDIAN trial of 11,590 patients who had ACS and the ESCAMI trial studied the effects of sodium/hydrogen-exchange inhibitors and demonstrated no benefit in terms of reduction in infarct size or adverse outcomes [98,99].

8.3 Reperfusion Strategies

Immediate restoration of blood flow at both the epicardial and microvascular levels is crucial in the management of CS [8]. The survival benefit of early revascularization in CS has been clearly reported in the randomized SHOCK trial, where there was a 13% absolute increase in 1-year survival in patients assigned to early revascularization compared to those in medical stabilization arm [27, 100]. The benefit was similar in the incomplete, randomized Swiss Multicenter Study of Angioplasty for Shock [101]. Furthermore, numerous studies have confirmed the survival advantage of early revascularization, whether percutaneous or surgical, in the young and possibly the elderly. Thrombolytic therapy is less effective than revascularization procedures but is indicated when PCI is impossible or delayed due to transport difficulties and when MI and CS onset were within 3 hours [41].

8.3.1 The thrombolytic therapy

Treatment of MI with thrombolytic therapy has been proven to save lives, reduce infarct size, preserve left ventricular function and reduces risk of the occurrence CS [58,102-103]. Comparative trials of thrombolytic agents have shown variable results [64]. Interestingly, the trials that compared streptokinase with alteplase showed mortality benefit for shock patients randomized to streptokinase [104-105]. This may be due to facts that it is less fibrin specific, has better thrombus penetration, and has prolonged lytic state which may reduce the risk of reocclusion [64].

However, the use of thrombolytic therapy for patients presenting in manifest CS is associated with relatively low reperfusion rates and unclear treatment benefit [106-107]. CS is a state of intense thrombolytic resistance, which occurs due to a hostile biochemical environment and failure of the lytic agent to penetrate to the thrombus due to decreased blood pressure and passive collapse of the infarct related artery [8, 108]. In addition, acidosis that accompanies tissue hypoxia and shock can inhibit the conversion of plasminogen to plasmin, antagonizing the action of thrombolytics [8]. Animal studies demonstrated that restoration of blood pressure to normal ranges with norepinephrine infusion improved reperfusion rates of thrombolytics, suggesting that coronary perfusion pressure, not cardiac output, is the main determinant of thrombolytic efficacy [109].

The SHOCK registry showed an evidence-based support for the relative ineffectiveness of thrombolysis in shock, where patients receiving thrombolysis had a similar mortality compared to thrombolytic-eligible patients who did not receive thrombolysis [110]. Because of the limitations of thrombolytic therapy for CS, it is recommended to be the second option in treatment when revascularization therapy with PCI or CABG is not rapidly available [58, 62]. Most patients will require transfer to revascularization-capable hospital as soon as possible so that the potential benefits of further revascularization therapy might still be obtained [64].

8.3.2 Percutaneous coronary intervention

Multiple observational studies reported survival improvement for patients with ischemic CS treated with PCI. PCI is the most efficient and easily available therapy to restore coronary blood flow in the Infarct-related artery (IRA) [111]. The prospective Polish Registry of Acute Coronary Syndromes reported that the In-hospital and long-term mortality of patients treated by PCI were significantly correlated to the IRA, being highest for Left main (LMCA) disease and lowest for RCA. Furthermore, Final TIMI 3 flow in the IRA after angioplasty was the most powerful independent predictor of lower mortality [112]. In another study, the presence of chronic total occlusion in non IRA was an independent predictor of one year mortality in patients with CS treated with primary PCI [113].

8.3.2.1 Timing of PCI

Similar to MI without shock, earlier revascularization is better in patients presented with MI and CS. Presentation with 6 hours after symptom onset was associated with the lowest mortality among CS patients undergoing primary PCI in the ALKK registry [114]. In the SHOCK trial, long term mortality appeared to be rising as time to revascularization increased from 0 to 8 hours. However, the survival benefit was present as long as 48 hours after MI and 18 hours after shock onset [100].

8.3.2.2 Stenting and glycoprotein IIb/IIIa inhibition

Stenting and glycoprotein (GP) IIb/IIIa inhibitors were independently associated with improved outcomes in patients undergoing PCI for CS in multiple registries, including the large ACC-National Cardiovascular Data Registry [115]. Some observational studies in CS suggest lower mortality rates with stents than PTCA [116-118] while others show no benefit [119] or even higher mortality rates [120]. In clinical practice, most patients undergoing primary PCI for CS receive stents which improve the immediate angiographic result and decrease subsequent restenosis rate and target vessel revascularization [58, 64]. Data comparing bare metal stenting (BMS) versus drug-eluting stenting (DES) in CS are scarce.

However, BMS are often used because compliance with long-term dual antiplatelet therapy is often unclear in the emergency setting [64].

The use of platelet GP IIb/IIIa inhibitors has been demonstrated to improve outcome of patients with acute MI undergoing primary PCI [121]. Observational studies suggest a benefit of abciximab in primary PCI for CS [117-118, 120, 122]. The recent large ALKK registry, which evaluated the outcome of 1333 patients undergoing PCI for CS, recommended that all efforts should be made to bring younger patients with CS as early as possible in the catheter laboratory and to restore patency and normal flow of the IRA [114].

8.3.2.3 Thrombus aspiration during PCI

Distal embolization has emerged as a causative factor of impaired myocardial perfusion after primary PCI. Thus increasing the rate of optimal myocardial perfusion could represent an effective strategy in order to achieve better clinical outcomes in patients with CS undergoing primary PCI. Anti-embolic devices, in general, do not decrease early mortality but are associated with a higher rate of myocardial perfusion [123-125] and are considered as class IIa in the recent AHA/ACC and ESC guidelines for PCI [126-127].

Data on the anti-embolic devices in the setting of primary PCI for CS are scarce. Rigattieri et al [128] assessed the impact of thrombus aspiration performed during primary PCI in 44 high risk patients with STEMI complicated by CS. They concluded that in-hospital mortality was significantly lower in patients treated by thrombus aspiration as compared to patients undergoing standard PCI, with a trend toward greater ST segment resolution in the former group. In addition, thrombus aspiration was the only variable independently associated with survival.

8.3.3 Surgical revascularization

Data has shown that emergency CABG for CS patients is associated with survival benefit and improvement of functional class, but not commonly performed [129]. The SHOCK trial documented that revascularization improved outcomes when compared with medical therapy [130]. Patients chosen for surgical revascularization were more likely to have LMCA disease, three-vessel disease and diabetes mellitus than those treated with PCI. Despite that, the 30-day mortality for patients undergoing PCI was equivalent to surgical mortality (45% versus 42%). Patients presenting with mechanical complications required surgical intervention for survival carry a poorer prognosis than patients requiring revascularization only. Various surgical strategies designed to optimize outcomes for patients in CS have been addressed such as the use of warm blood cardioplegia enriched with glutamate and aspartate, beating heart techniques, and grafting of large areas of viable myocardium first followed by treatment of the infarct artery [64].

8.3.4 Revascularization approach debates

8.3.4.1 Multivessel disease

Although multivessel disease is common in patients presented with MI and CS, the optimal revascularization strategy for such patients is not clear [111, 131]. No randomized clinical trial has compared PCI with CABG in patients with CS, and only few observational data are available in the literature. There is an ongoing debate on whether non-culprit PCI is useful at the time of primary PCI of the IRA [132]. As in the SHOCK trial, multivessel PCI is performed

in approximately one fourth of patients with CS undergoing PCI [130]. The SHOCK trial recommended emergency CABG within 6 hours of randomization for those with severe 3-vessel or LMCA disease. For moderate 3-vessel disease, the SHOCK trial investigators recommended proceeding with PCI of the IRA, followed by delayed CABG for those who are stabilized [32].

Data from SHOCK and NRMI registries showed evidence of better survival for patients with 2- and 3-vessel CAD who developed CS and were treated with CABG compared with PCI [42, 133]. However, these registries have notable limitations such as the selection bias in choosing PCI or CABG, the small number of patients with CS, and the use of adjunctive medications to PCI [134]. Large randomized trials are to evaluate the use of newer antithrombotic agents and stents as adjunctive therapies in this patient population [134].

8.3.4.2 LMCA

LMCA occlusion is infrequently found in angiographic studies in patients with acute MI [135]. However, its presence has been associated with worse prognosis in most cases, where most patients die from CS or lethal arrhythmias; unless adequate collateral circulation is present or prompt revascularization is done [135]. Definitive guidelines for managing patients with LMCA-related AMI are lacking. Although CABG has a good outcome in nonemergency cases, the role of PCI in critically ill patients with CS should be considered in acute situations because prompt restoration of coronary flow is crucial for patients with AMI and CS. Hata et al. [136] demonstrated an operative mortality of 20% for emergency CABG in patients presenting with AMI and LMCA disease. In the surgical arm of the SHOCK Trial, patients with LMCA disease treated with CABG presented a 1-year mortality of 53% [130], while the few patients who underwent PCI had a 27% one year survival [133]. DES have shown to be a safe therapeutic choice for LMCA stenosis in high risk patients with a high likelihood of stent thrombosis (one third of these patients were in CS). However, it has the advantage of less restenosis without increasing the risk of early or late stent thrombosis [137]. Kim et al. showed that in-hospital mortality for patients with unprotected LMCA-related AMI with initial shock presentation was 48% compared with 9% for those without shock. However, clinical outcomes after survival of the in-hospital period were not different between the two groups [138]. These results were similar to other reports that had shown rather beneficial outcome in the follow up in those who survived to hospital discharge [139-141]. The ACC/AHA guidelines recommended LMCA PCI as class I indication "for patients with acute MI who develop CS and are suitable candidates "(Level of Evidence: B) [125]. In summary, PCI of the unprotected LMCA should be considered as a feasible option to CABG for selected patients with high risk MI or CS [142]. Fig. 1 summarizes the management of ischemic cardiogenic shock.

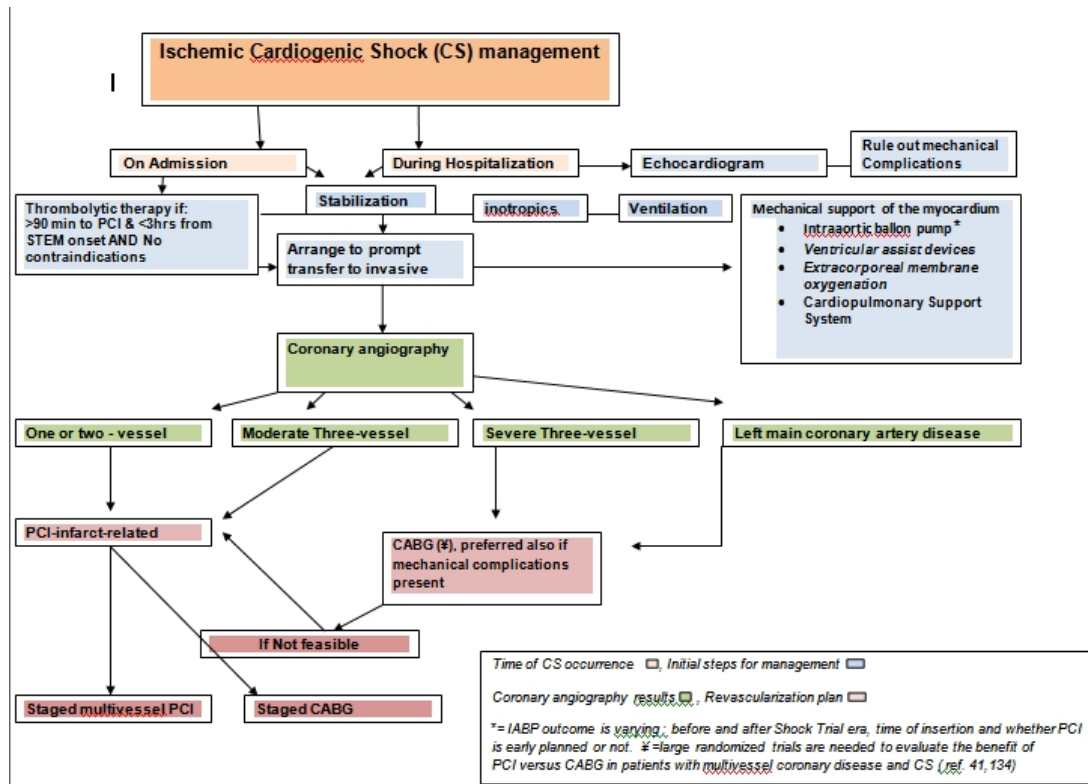


Fig. 1. Algorithm for the management of ischemic cardiogenic shock

8.3.5 Summary of SHOCK trial

The SHOCK trial [27, 100,143] randomized 302 patients to emergent revascularization or immediate medical stabilization. Simultaneously, 1190 patients presenting with CS who were not randomized were followed up in a registry [56]. In the revascularization arm, about two thirds underwent PCI and one third had CABG. Although there was no statistically significant difference in 30-day mortality between the two arms, a significant survival benefit had emerged for patients randomized to revascularization by the 6-month endpoint that was maintained at one year and 6 years. Similar early survival advantage was noted in the SHOCK registry population after exclusion of those patients presenting with mechanical complications. Of multiple pre-specified subgroup analyses performed in the SHOCK trial, only age above 75 years showed significantly better survival in the medical stabilization arm than in the revascularization arm. The results of the SHOCK trial and registry have confirmed that patients with CS complicating AMI should be referred for coronary angiography and emergent revascularization unless contraindicated [64]. Based on SHOCK trial, the ACC/AHA advised a class I recommendation for "the use of early revascularization, either PCI or CABG, for patients less than 75 years old with ST elevation or LBBB who develop shock within 36 hours and who are suitable for revascularization that can be performed within 18 hours of shock unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care" (Level of Evidence: A) [58]. Analysis of the elderly patients in the SHOCK Trial registry [144] showed that they were more likely to be females and to have a prior history of MI, congestive heart failure, and renal

insufficiency. Moreover, they were less likely to have therapeutic interventions such as PAC, IABP, angiography and revascularization. Overall, in-hospital mortality in the elderly versus younger age group was 76% versus 55%. The elderly patients selected for early revascularization, however, showed a significantly lower mortality rate than those who did not undergo revascularization [48% versus 81%]. Subsequent reports supported the benefit of early revascularization in elderly patients [145-147].

Based on the SHOCK trial and other registry, the ACC/AHA STEMI guideline recommended a class IIa for "early revascularization, either PCI or CABG, for selected patients 75 years or older with ST elevation or LBBB who develop shock within 36 hours of MI and who are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status and agree to undergo invasive care may be selected for such an invasive strategy" (Level of Evidence: B) [58].

Recent ESC guidelines recommended early revascularization for patients with STEMI and CS with no specific advice regarding age or time limit between the onset of symptoms and revascularization [62]. SHOCK trial and registry nearly closed loop of the debate over emergent revascularization options in CS patients [i.e., Single vessel vs mechanical complications]; however, others (i.e., Multivessel disease) remain unresolved and further prospective studies are needed to minimize the long-term mortality rate.

9. MECHANICAL SUPPORT IN PATIENTS WITH CS

Although early reperfusion of the coronary system is the corner-stone of management of CS, this will not always provide full resolution for such a grave situation. Additional time may be needed after restoration of blood flow for the injured myocardium to recover from stunning or hibernation [148]. This time delay is critical because persistent hypoperfusion may worsen cardiac function and cause multiple organ failure. Thus, methods for mechanical support of the myocardium that maintain normal systemic perfusion may improve the outcome of patients with CS complicated acute MI [148].

Surgically Implanted ventricular assist devices (VADs) were initially designed to support patients in hemodynamic collapse, but are now used for several clinical situations, e.g. Prophylactic insertion for invasive procedures, CS and cardiopulmonary arrest [149]. Despite advances in surgically implanted external VAD technology, the currently available LVADs still have significant drawbacks; they require extensive surgery with the need for general anesthesia, systemic inflammation associated with an open surgical procedure, and the emergency need to apply in cases of CS. To overcome such drawbacks, percutaneous VADs were developed [149].

9.1 Intraaortic Balloon Pump Counterpulsation (IABP)

IABP can be considered as a short term VAD. It is the first device introduced and remained the most commonly used support device in CS [33, 150]. It is effective in stabilization of patients, decreasing afterload and increasing coronary perfusion pressure through the principle of diastolic inflation and systolic deflation. It can augment cardiac output by 0.5 l/min but does not provide full cardiac support as it depends on intrinsic cardiac function and need a stable rhythm [150-151]. Despite the theoretical and hemodynamic benefit, the current evidence on the use of IABP in patients with CS is mixed and appears to be different in the pre-fibrinolytic, fibrinolytic and primary PCI eras [33,152,153].

In a recent metaanalysis, Sijauw and colleagues evaluated the use of IABP in patients with acute MI and CS and showed conflicting results for the three eras, where IABP use was associated with mortality benefit in pre thrombolytic era and with thrombolytic use [29% and 18% mortality reduction respectively], however they found 6 % higher mortality when primary PCI was performed [152]. On the other hand, Bahekar et al found a significant reduction in mortality using IABP in patients with AMI with CS but with an increase of the risk of major bleeding [154].

The TACTICS (Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy) trial [155], a prospective, randomized trial, evaluated the use of IABP in patients treated with thrombolytic therapy in the presence of severe hypotension. It showed no difference in mortality in the overall population, however, patients with Killip III and IV showed significant survival benefit for the use of IABP. A similar benefit from IABP combined with thrombolytic therapy was noted in the SHOCK trial registry, NRM-2 registry and GUSTO-1 trial [156-158].

In the IABP SHOCK trial, which assessed 40 patients with CS, who were undergoing primary PCI, IABP use did not result in a significant improvement in serial APACHE II scoring. Moreover, IABP use had no significant effect on the cardiac index and interleukin-6 levels, although BNP levels were significantly lower in IABP-treated patients. These effects of BNP reduction may be related to the reduction of the afterload through IABP [33].

Moreover, IABP-SHOCK II study showed that, in randomly assigned 600 patients with CS complicating AMI to IABP vs no IABP group, the use of IABP did not significantly reduce 30-day mortality in patients with planned early PCI. However, the study showed some limitations. Blinding was not possible and there was greater number of patients with mild or moderately severe CS, a factor that could preclude generalization of the results to include the most severe forms of CS [159].

It should be noted that controversies exist in other issues related to IABP insertion in patients with CS especially for those planned for PCI; For example, the optimal timing of placement is unknown as some studies detected a decrease in hospital mortality if IABP inserted before PCI, compared to insertion after PCI [160], while analysis from SHOCK trial did not find such advantage [156]. Furthermore, CS patients who were thrombolized seem to benefit from insertion of IABP for subsequent transfer to mechanical revascularization, but with increased risk of bleeding [161].

The ESC guidelines for the management of STEMI in 2012 have changed the level of recommendation for IABP use in CS from class I in the previous recommendation [162] to class IIb (level of evidence B) [62]. Moreover, the German-Austrian guidelines give weak recommendation for IABP in case of systemic fibrinolysis but not for patients treated with primary PCI [63]. Further trials should examine the therapeutic and prognostic effect of IABP support according to the pathophysiologic status of CS [163].

9.2 Percutaneous Ventricular Assist Devices [pVADs]

pVADs, in contrast to IABP, can compensate for the loss of myocardial pump function, normalizing cardiac output and thus allowing physiologic perfusion of vital organs. These effects interfere with the severe inflammatory reaction associated with refractory CS and eventually improve end-organ perfusion [164]. Moreover, the use of pVADs reduces ventricular strain and negative remodeling and may lead to better long-term prognosis [151].

In cases of CS, pVADs are mainly used as a "bridge to recovery" or "bridge to LVAD" in addition to prophylactic use in certain invasive coronary procedures [150].

The use of pVADs in the setting of CS generally requires a stepwise approach, involving the use of inotropes, vasopressors, and IABP before considering implantation of a pVAD, unless patients are considered too sick to benefit from the initial stabilizing procedures [149, 151]. The choice between different types of mechanical support depends on several factors, including initial hemodynamics, end-organ function, presence of right/left ventricular dysfunction, respiratory failure, degree of emergency need, and underlying co-morbidities as well as the anticipated amount and duration of mechanical support needed [149, 151].

The two main currently available pVADs are TandemHeart [Cardiac Assist Inc., Pittsburgh, PA, USA] and the Impella Recover LP 2.5 (AbioMed, Europe, Aachen, Germany) in addition to the recent application of extracorporeal life support and percutaneous cardiopulmonary bypass devices in CS.

Possible complications that may occur in both pVADs types include thrombocytopenia, thromboembolic risk, infections and insertion-related complications. Relative contraindications to both pVADs are severe aortic regurgitation, prosthetic aortic valve, aortic aneurysm or dissection, severe peripheral vascular disease, left ventricular and/or atrial thrombi, severe coagulation disorders, and uncontrolled sepsis [150].

The Reitan Catheter Pump (RCP) is a novel, fully percutaneous circulatory support system, delivered via the femoral artery and positioned in the proximal descending aorta, distal to the left subclavian artery. It may offer more effective cardiac support than the IABP, while being less invasive compared to Impella 2.5 and the TandemHeart [165].

9.2.1 Tandem heart percutaneous ventricular assist device

The Tandem heart is a percutaneous left atrial-to-femoral arterial ventricular assist device. This device is placed via the femoral vein and then crosses the interatrial septum. Blood from the left atrium will be directed to an extracorporeal pump and then redirected to the abdominal aorta to provide temporary circulatory support up to 4.5 l/min of cardiac output while performing high-risk PCI or waiting ventricular recovery. Its use can extend from hours to 15 days [149-150].

The initial trials comparing Tandem-Heart with IABP for CS showed a favorable hemodynamic response, however, complications as severe bleeding and limb ischemia were more common with Tandem Heart [166-167]. A recent study on a single center experience of Tandem-Heart pVAD in an extremely sick cohort of 117 patients with refractory CS showed marked improvement in hemodynamics and end-organ perfusion [168]. Similar hemodynamic benefit was shown in a cohort of 20 patients, as a "bridge to decision" allowing more time for complete evaluation of neurological status and end organ damage [169]. The TandemHeart pVAD has been also used for high-risk PCI and for right ventricular support in CS patients [170,171].

9.2.2 Impella recover system

The impella recover is a percutaneous transvalvular LVAD (axial flow pump), which is placed via the femoral artery, retrograde across the aortic valve into the left ventricle, and is able to augment the cardiac output by 2.5 l/min [149]. Despite the weaker support, shorter duration

of use and the more risk of hemolysis and insertion-induced ventricular arrhythmias compared to TandemHeart, it has the advantages of single arterial puncture, faster insertion, and the absence of transeptal puncture [150]. Impella 5.0 is a more powerful version, which can provide up to 5.0 l/min of support, but requires a surgical cut-down for its implantation [151,172]. A new 4L/min Impella CP (Cardiac Power) (Abiomed) has been recently approved for use in both European and North American markets, being more powerful than Impella 2.5 and percutaneously implanted via a 9 French catheter into the left ventricle [173].

Several trials have shown the feasibility of impella recover system mainly in comparison to IABP [174-175]. The randomized trial (ISAR-SHOCK) [175] compared the efficacy of the Impella 2.5 system vs. IABP for STEMI with CS in 26 patients and showed that Impella device produced greater increase of mean arterial pressure and cardiac index and a more rapid decrease in serum lactate levels. Notably, severe aortic regurgitation is a contraindication against IABP, while prosthetic valve is a contraindication against Impella.

9.3 pVADs Versus IABP

A recent meta-analysis [176] compared pVADs [both TandemHeart and Impella] with IABP in 100 patients with acute MI complicated by CS. Although patients on pVADs had higher CI and MAP and lower PCWP as compared with patients on IABP, however, there was no difference in 30-day mortality between the two groups. Furthermore, patients on TandemHeart had a higher incidence of bleeding complications, while those on Impella had a higher incidence of hemolysis.

Similarly, Shah et al. [177] compared IABP with pVADs in 74 patients either undergoing high-risk PCI or presented with CS. They found that both groups had similar in-hospital clinical outcome in both the high-risk PCI and CS cohorts. However, there were significantly different baseline patient, clinical, procedural, and angiographic characteristics.

9.4 Percutaneous Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) support is well-established technology that provides temporary circulatory support in patients who present with severe hemodynamic instability associated with multiorgan failure [178].

ECMO is now considered an important tool in the management of patients suffering from refractory CS [179-180]. ECMO has several advantages; simple and easy insertion via femoral vessels even during CPR, as well as providing both cardiac and respiratory support without the need of sternotomy, and it provides time to assess potential transplant candidates [181]. It can be even used with additional IABP in selected patients and can be used as "bridge to bridge" followed by insertion of long-term VADs or as "bridge to a decision" to allow to restore adequate systemic perfusion, allowing further time to evaluate myocardial recovery or candidacy for VAD or heart transplantation [181-183]. Despite these advantages, ECMO support has several limitations precluding its use as long-term support; including hemolysis, bleeding, stroke, infection, patient immobilization, and inadequate LV decompression. It is also found to increase left ventricular afterload and wall stress [179, 181].

Both extracorporeal life support and axial flow pumps (impella 5) provided adequate support in patients with various etiologies of CS. Axial-flow pump may be an optimal type of support

for patients with univentricular failure, whereas extracorporeal life support could be reserved for patients with biventricular failure or combined respiratory and circulatory failure [184].

ECMO support could improve survival in recent retrospective reviews of patients who suffer AMI associated with CS and early ECMO initiation yielded better outcomes [148, 185-186]. Newer, minimized extracorporeal life support (ECLS) systems such as the ELS-System and Cardiohelp (both from MAQUET Cardiopulmonary AG, Germany) have been developed allowing rapid insertion and facilitated interhospital transport [186-187].

9.5 Percutaneous Cardiopulmonary Support System

Percutaneous cardiopulmonary support systems are compact, battery-powered, portable heart-lung machines that can be implemented rapidly via the femoral vessels. The systems provide temporary circulatory/oxygenation support but with a limited support time [usually <6 h] [188]. If the need for circulatory support extends beyond 6 h, conversion to a ventricular assist device or conventional long-term extracorporeal membrane oxygenation is recommended [189].

9.6 Summary of VAD use in Cardiogenic Shock

In 2007, Garatti and colleagues revised 17 major studies of LVAD support [surgical and percutaneous] for CS complicating acute MI reported in the literature. They found a mean weaning and survival rate of 58.5% and 40%, respectively. Despite the different patient groups in these studies, VAD support did not show survival improvement in patients with CS complicating acute MI, compared with early reperfusion alone or in combination with IABP [190]. This is in contrast to recent data from the Society of Thoracic Surgeons' National Cardiac Database, which suggest that these devices could save approximately 60% of patients with persistent shock after CABG, and their use should be considered in appropriate patients [191].

Recently, ESC guidelines recommended LVADs as class IIb (level of evidence C) for use in patients with STEMI and CS not responding to standard treatment including IABP and as a bridge to transplantation despite limited experience [62].

10. CONCLUSION

Despite the fast advances in the pathophysiology understanding and management technology, ischemic CS remains the most serious complication of acute MI. ischemic CS is associated with high mortality rate both in the acute and long-term setting. Further randomized trials and guidelines are needed to save resources and lives.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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