Cardiogenic Shock Complicating Myocardial Infarction:

An Updated Review

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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 the 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,” “Management ““Myocardial infarction” and “mortality”. All non-English articles were excluded. The review did not expand to explore the mechanical complications or other causes of CS. There were around six thousands articles tackling the CS from different points of view. Despite the fast advances in the pathophysiology understanding and management technology, ischemic CS remains the most serious complication of acute MI, being 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.
Introduction

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). We reviewed the literature using search engine as MIDLINE, SCOPUS, and EMBASE from January 1982 to October 2012. We used key words: “Cardiogenic Shock,” “Management” “Myocardial infarction” and “mortality”. There were around six thousands articles tackling the CS from different points of view. All non-English articles were excluded. The review did not expand to explore the mechanical complications or other causes of CS. This review aims to summarize the management of CS complicating MI (ischemic CS).

Definition: CS is a clinical condition of inadequate tissue (end-organ) perfusion due to cardiac dysfunction. The definition includes clinical signs in addition to 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 (4-5). CS is a systemic clinical syndrome that needs hemodynamics assessment to support the diagnosis and guide the management (6). It represents a wide spectrum, ranging from preshock (patients at risk of developing CS), mild shock (responding to low-dose inotropes/vasopressors), profound shock [responding to intraaortic balloon pump (IABP) implantation along with high-dose inotropes/vasopressors] to severe refractory CS.
Aetiology: Acute MI with left ventricular failure is the most common etiology of CS, but it can also be caused by mechanical complications, e.g. acute mitral regurgitation, ventricular septal rupture, or ventricular free wall rupture. However, any cause of acute, severe left or right ventricular dysfunction may lead to CS (4).

Pathophysiology: 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 [9].

The pathophysiological concept of combined low cardiac output and high systemic vascular resistance has been recently challenged by the fact that in some patients, post-MI shock is 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 [10]. Furthermore, this acute inflammatory response is associated with elevated serum cytokine concentrations [11-13]. 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 [14]. Several patients with CS could be died despite normalization of cardiac index, suggesting a maldistributive effect with low systemic vascular resistance [15]. Recent data suggest that enhanced expression of monocytic 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 an enhanced short-term mortality-rate (16).

**Incidence & Outcome:** The incidence of CS was nearly constant for decades and complicated approximately 5 to 9 percent of acute ST elevation MI [17-18]. 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 [19-20]. This may be the result of increased frequency of revascularization for acute coronary syndrome (ACS) as shown in the AMIS PLUS registry (21). 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% and was associated with lower hospital mortality. Despite advances in the management of CS, the rates of mortality, although improved to an extent in the recent decades, remain significantly high (21). 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) (22).
Although, the majority of patients who develop CS have an ST elevation MI (STEMI), CS may occur in patients with a non-ST elevation MI (NSTEMI) [17, 23]. Also, as most patients develop CS after hospital admission [24-25], CS has been reported to occur significantly later among patients with NSTEMI compared to those with STEMI (median 76 to 94 hours versus 9.6 hours) (23, 26).

**Risk factors:** Predictors of CS in patients with acute MI include old age, anterior MI, hypertension, diabetes mellitus, multivessel coronary artery disease, prior MI or diagnosis of heart failure, STEMI, and left bundle branch block on the electrocardiogram [17].

In the French registries, patients who developed CS were significantly older and were more likely to be women, or to have a history of diabetes mellitus, heart failure, MI, stroke, peripheral arterial disease, or renal failure. They were also more likely to have a STEMI and clinical concurrent complications at admission compared with patients who did not develop CS. However, patients with CS were significantly less often smokers and had less often known hyperlipidemia (22). In the GUSTO-I and GUSTO-III trials of thrombolytic therapy in acute STEMI, four clinical variables (age, systolic blood pressure, heart rate, and Killip class) were proved to be major predictors of CS [27]. In the GRACE study, the degree of troponin elevation was predictive of post-MI shock, cardiac arrest, and heart failure in NSTEMI patients (28). In a recent subanalysis of the same study, patients with CS were more likely to be older, have history of diabetes or atrial fibrillation and present with higher pulse rate or cardiac arrest. Furthermore, advanced age, DM, angina and stroke were associated with increased risk of death in patients with CS (29).
Sutton et al [30] reported that old age, previous infarction, shock complicating failed thrombolysis treatment, and multivessel disease were associated with adverse outcomes in patients undergoing primary PCI. In an analysis of TRUIMPH trial, about half of patients with refractory CS, despite patent infarct related artery (IRA), died at 30 days. Systolic blood pressure, creatinine clearance and number of vasopressors used were also significant predictors of mortality (31).

Sleeper et al [32] 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). They identified 8 clinical risk factors that predict the 30-day in-hospital mortality risk. These factors included age, shock on admission, clinical evidence of end-organ hypoperfusion, anoxic brain damage, systolic blood pressure, prior coronary artery bypass grafting (CABG), non-inferior MI, and creatinine ≥1.9 mg/dL. Mortality ranged from 22% to 88% by score category and revascularization benefit was greatest in moderate- to high-risk patients. The Stage 2 model based on patients with pulmonary artery catheterization included age, end-organ hypoperfusion, anoxic brain damage, stroke work, and left ventricular ejection fraction ≤28% but the effect of early revascularization did not vary by risk stratum. (32).

Numerous studies (15-16, 33-34) suggested that PCI improves short-term survival in patients with CS, where survival was concordant with the ability to establish adequate coronary reperfusion. It is to be noted that the improvement
in early mortality may also have been related to the use of other recommended measures and to the global management (22).

On the other hand, mortality in the French registries analysis from 1 month to 1 year remained high and did not improve over time, in spite of the higher use of recommended medications at hospital discharge over the study period. Such evidence may require further studies in the future (22).

**Hemodynamic Measurement**

The hemodynamic criteria for CS can be confirmed by insertion of a balloon-tipped pulmonary artery catheter [PAC] and an intraarterial blood pressure monitoring catheter [35-36]. 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 [37], the data from GUSTO-I trial [27] and SHOCK registry [38] suggest that it is not harmful, and possibly 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) [35] and the European guidelines (class IIb) [39].

**Treatment of CS**

**1) Initial stabilization:** Initial resuscitation is aimed at stabilizing oxygenation and perfusion while revascularization is contemplated (40-41). Further measures under investigation include therapeutic hypothermia (2) and Continuous lateral rotation (kinetic therapy) (42-43).
(2) **Inotropes and vasopressors:** Inotropic and vasopressor drugs are considered the major 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 (44); this corresponds to both more severe underlying hemodynamic derangement and direct toxic effects (17).

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 (17).

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 1) [6, 45-46]. 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 (35). Similarly, in the German-Austrian guidelines, norepinephrine is considered the vasopressor of choice in patients with mean arterial pressure (MAP) values below 65 mm Hg. Furthermore, dobutamine is the inotrope of choice rather than dopamine, based mainly on the results of a
multicenter cohort observation study that showed that administration of dopamine was an independent risk factor for mortality, while application of dobutamine or norpinephrine was not. (41).

Recently 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, Nitrergic Oxide (NO) inhibitors, Complement blocking agents, and Sodium/hydrogen-exchange inhibitors).

- **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 [47]. Unfortunately, studies have largely failed to translate their hemodynamic benefits into long-term mortality benefits [48-49].

- **Levosimendan** represents a new calcium sensitizer with positive inotropic properties (50). 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) [51-53]. This counteracts the undesired side effects of increased intracellular calcium such as increased oxygen consumption and increased risk for fatal arrhythmia (6). In addition to its positive inotropic action, levosimendan exerts vasodilating properties that reduces cardiac preload and
afterload, enhances coronary blood flow, and increases myocardial oxygen supply [54-55]. The combined use of levosimendan with other vasoactive drugs may be considered on an individual basis more than milrinone (56). Levosimendan has been used as the sole inotrope in post-MI CS patients in isolated case reports [57]. 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 (58). 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 (50, 59). 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 (60-61). Larger controlled randomized studies are needed to confirm such findings.

- **Vasopressin:** Based on the favorable effects of vasopressin in septic shock, Jolly and colleagues (62) identified the patients who had refractory CS who 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 has been shown [62]. However, in a recent experimental study, 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 (63). However, randomized prospective trials are required to confirm the benefit and safety of vasopressin in the setting of CS after MI.
- **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 (6). 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 [64]. 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 supportive treatment alone, with significant increase of mean arterial pressure and urinary output in the L-NAME group [65]. 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, prospective, randomized, double-blind study, was recently terminated because of a lack of efficacy (66). 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 (66).

- **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 [67]. 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 [68]. 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 [69]. Analysis of the enrolled patients showed that pexelizumab infusion given with PCI didn’t reduce mortality or the risk of reinfarction, or shock in patients with acute STEMI compared with PCI alone (69).

- **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 [70]. Two large trials the GUARDIAN trial of 11,590 patients who had ACS [70] and the ESCAMI trial [71] studied the effects of sodium/hydrogen-exchange inhibitors and demonstrated no benefit in terms of reduction in infarct size or adverse outcomes.

(3) **Reperfusion strategies:**

Immediate restoration of blood flow at both the epicardial and microvascular levels is crucial in the management of CS (72). 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 (5, 73). The benefit was similar in the incomplete, randomized Swiss Multicenter Study of Angioplasty for Shock (74). 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 (17).

**Summary of the SHOCK trial:** The SHOCK trial [5, 73, 75] 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 [33]. 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 acute MI should be referred for coronary angiography and emergent revascularization unless contraindicated (40). Based on these findings from 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 of MI 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)
Analysis of the elderly patients in the SHOCK Trial registry [76] showed that they were more likely to be women and to have prior history of MI, congestive heart failure, renal insufficiency, and other co-morbidities. Moreover, they were less likely to have therapeutic interventions such as PAC, IABP, angiography and revascularization. Overall, in-hospital mortality in the elderly versus the 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 data supported the benefit of early revascularization in elderly patients (77-79).

On the basis of SHOCK trial and registry analysis and other registry findings, the 2004 ACC/AHA STEMI guideline update 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 who agree to invasive care may be selected for such an invasive strategy" (Level of Evidence: B) (35).

The ESC guidelines recommended early revascularization for patients with STEMI and CS with no special advice regarding age or time limit between onset of symptoms and revascularization (39).

Although SHOCK trial ended the debate over emergent revascularization versus initial medical stabilization for CS, many issues regarding the optimal revascularization strategy in this setting remain unresolved.

**Thrombolytic therapy:** Treatment of MI with thrombolytic therapy has been
proven to save lives, reduce infarct size, and preserve left ventricular function [35]. It also reduces the risk of subsequent CS in patients who initially present without shock [80-81]. Comparative trials of thrombolytic agents have shown variable results (40). Interestingly, the trials that compared streptokinase with alteplase showed mortality benefit for shock patients randomized to streptokinase [82-83]. This may be due to the fact that it is less fibrin specific, thus may penetrate the thrombus better. It also causes a prolonged lytic state in the setting of low coronary blood flow (which may reduce the risk of reocclusion) (40).

However, the use of thrombolytic therapy for patients presenting in manifest CS is associated with relatively low reperfusion rates and unclear treatment benefit [84-85]. 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 [72,86]. In addition, acidosis that accompanies tissue hypoxia and shock can inhibit the conversion of plasminogen to plasmin, antagonizing the action of thrombolytics (72). 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 major determinant of thrombolytic efficacy [87].

The SHOCK registry showed an evidence-based support for the relative ineffectiveness of thrombolysis in shock [88], where patients receiving thrombolysis had a similar mortality compared to thrombolytic-eligible patients who did not receive thrombolysis.
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 and there is contraindication to fibrinolysis (35, 39). 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 (40).

**Percutaneous coronary intervention:** Multiple observational studies reported survival improvement for patients with ischemic CS treated with PCI. 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 Infarct-related artery (IRA), being highest for Left main disease and lowest for RCA. Furthermore, Final TIMI 3 flow in the IRA after angioplasty was the most powerful independent predictor of lower mortality (89). 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 (90).

**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 (91). In the SHOCK trial, the 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 (73).

**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 (92).

Some observational studies in CS suggest lower mortality rates with stents than PTCA [93-95] while others show no benefit [96] or even higher mortality rates [97]. 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 (35, 40). Although data comparing bare metal stenting (BMS) versus drug-eluting stenting (DES) in CS are scarce, BMS are often used because compliance with long-term dual antiplatelet therapy is often unclear in the emergency setting (40).

The use of platelet GP IIb/IIIa inhibitors has been demonstrated to improve outcome of patients with acute MI undergoing primary PCI [98]. Observational studies suggest a benefit of abciximab in primary PCI for CS [94-95, 97, 99]. The recent large ALKK registry, which evaluated the outcome of 1333 patients undergoing PCI for CS [91], 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.

**Thrombus aspiration during PPCI**: 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 (100-102) and are considered as class IIa in the recent AHA/ACC and ESC guidelines.
for STEMI (103-104).

Data on the anti-embolic devices in the setting of primary PCI for CS are scarce. Rigattieri et al (105) 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.

**Surgical revascularization**

Data has shown that emergency CABG for patients in CS is associated with survival benefit and improvement of functional class, but not commonly performed [106]. The SHOCK trial documented that revascularization improved outcomes when compared with medical therapy [107]. Patients chosen for surgical revascularization were more likely to have left main 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 (40).
Revascularization Approach Debates

(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 (108). 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 nonculprit PCI is useful at the time of primary PCI of the IRA (109). As in the SHOCK trial, multivessel PCI is performed in approximately one fourth of patients with CS undergoing PCI (107). The SHOCK trial recommended emergency CABG within 6 hours of randomization for those with severe 3-vessel or left main coronary artery disease (LIMA). For moderate 3-vessel disease, the SHOCK trial recommended proceeding with PCI of the IRA, followed by delayed CABG for those who stabilized (10).

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 (18, 110). However, these registries have important 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 (111). Large randomized trials are needed to evaluate the relative merits of currently available revascularization strategies using newer antithrombotic agents and stents as adjunctive therapies in this patient population (111).

(2) LMCA: LMCA occlusion is infrequently found in angiographic studies in patients with acute MI (112). 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 (112).

There is currently no definitive guideline for patients with LMCA-related AMI. 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 [113] demonstrated an operative mortality of 20% for emergency CABG in patients presenting with acute MI 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% [107], while the few patients who underwent PCI had a 27% one year survival (110).

DES have been shown to be a safe therapeutic choice for LMCA stenosis in very high risk patients with a high likelihood of stent thrombosis (one third of these patients were in CS), with the advantage of less restenosis without increasing the risk of early or late stent thrombosis (114).

Kim et al showed that in-hospital mortality for patients with LMCA-related AMI with initial shock presentation was 48% compared with 9% for those without shock. However, patients who survive to discharge after PCI of the LMCA have a favorable prognosis (115). These results were similar to other reports that show rather beneficial outcome in follow up of those who survive to hospital discharge (116-118).

The ACC/AHA guidelines recommended left main artery PCI as class I indication "for patients with acute MI who develop CS and are suitable candidates (Level of Evidence: B)" (103).
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 (119).

**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 grave situation. Additional time may be needed after restoration of blood flow for the injured myocardium to recover from stunning or hibernation (120). 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 (120).

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 (7). Despite advances in surgically implanted external VAD technology, the currently available LVADs still have important 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 (7).

**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 (121). 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 (8, 121).

The TACTICS trial (122), a prospective, randomized trial, evaluated the use of IABP in patients treated with systemic fibrinolysis due to hypotension and suspected CS. It showed no difference in mortality in the overall population, however, the subgroup of patients with Killip III and IV showed a statistically significant survival benefit for the use of IABP. A similar benefit from IABP combined with thrombolytic therapy was noted in the SHOCK trial registry, in the NRMI-2 registry and the GUSTO-1 trial [123-125].

With the use of IABP in cases of CS undergoing PCI, the improvement of outcome has not been demonstrated in individual trials (IABP-SHOCK trial) (126) and registries like NRMI-2 (124) although some benefit was found in hospitals with a higher rate of IABP use [127]. Two recent metaanalyses ended with conflicting results regarding the use of IABP [128-129]. However, these analyses used registry data, secondary analysis and nonrandomized studies for IABP implantation [129]. Thus, the current evidence on the use of IABP in patients with CS is confusing, and further trials and analyses are needed to clarify the indications for IABP in this setting.

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 lower in hospital mortality if IABP inserted before PCI, compared to insertion after PCI [130], while analysis from SHOCK trial did not find such advantage [123].
Furthermore, CS patients who were thrombolyzed seem to benefit from insertion of IABP for subsequent transfer to mechanical revascularization (131), but with increased risk of bleeding.

Despite the lack of mortality benefit from randomized trials and equivocal results in meta-analyses, IABP is currently being used as a standard of care in patients with CS and is currently a class I indication for the management of acute MI not rapidly reversed by pharmacological therapy in both the ACC/AHA and the ESC guidelines [35,39].

However, in the recently published IABP-SHOCK II study, which was a randomized, prospective, open-label, multicenter trial, the investigators randomly assigned 600 patients with CS complicating acute MI to (IABP vs no IABP group). All patients were expected to undergo early revascularization. The use of IABP did not significantly reduce 30-day mortality in patients with CS complicating acute MI for whom an early revascularization strategy was planned (132).

**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 [133]. Additionally, the use of pVADs reduces ventricular strain and negative remodeling and may lead to better long-term prognosis (8). 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 (121, 134).
The use of pVADs in the setting of CS generally requires the use of 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 (7-8). 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 (7-8).

The two main currently available pVADs are: the 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. (121).

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. (135).
**TandemHeart 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 across the interatrial septum, thus blood is collected from the left atrium, 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 awaiting ventricular recovery. Its use can extend from hours to 15 days (7, 121). 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 (136,137). 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 [138]. 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. [139]. The TandemHeart pVAD has been also used for high-risk PCI, including patients in CS (140). It was also used in CS due to refractory ventricular tachycardia/ventricular fibrillation [141] and for right ventricular support [142].

**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 (7). 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 transseptal puncture (121). 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 (8, 143).

Several trials have shown feasibility of impella recover system mainly in comparison to IABP [144-145]. The randomized trial (ISAR-SHOCK) (145) 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.

**pVADs versus IABP:** A recent meta-analysis [146] 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 (147) 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 the CS cohorts. However there were significantly different baseline patient, clinical, procedural, and angiographic characteristics.

**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 (148).

ECMO is now considered an important tool in the management of patients suffering from refractory CS [149-150]. ECMO has several advantages; simple and easy insertion via femoral vessels even during CPR, as well as providing both cardiac and respiratory support without need of sternotomy, and it provides time to assess potential transplant candidates [151]. 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 decision" to allow to restore adequate systemic perfusion, allowing further time to evaluate myocardial recovery or candidacy for VAD or heart transplantation(151-153). 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 (149, 151).

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 (154).

ECMO support could improve survival in recent retrospective reviews of patients who suffer AMI associated with CS and early ECMO initiation yielded better outcomes (120,155-156).

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 [156-157].

**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) (158). 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 (159).

**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 (160). 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 (161).

In the ESC guidelines, LVADs are given class IIa for use in patients with STEMI and CS not responding to standard treatment including IABP and as a bridge to transplantation despite limited experience (39).
**Conclusion:** Despite the fast advances in the pathophysiology understanding and management technology, ischemic CS remains the most serious complication of acute MI, being 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.

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**References**


Stenosis and Acute Myocardial Infarction, for the Korea Acute Myocardial Infarction Registry Investigators Am J Cardiol 2012;110:36–39


(122) Ohman EM, Nanas J, Stomel RJ, et al. Thrombolysis and counterpulsation to improve survival in myocardial infarction complicated by hypotension and


(128) Bahekar A, Singh M, Singh S, et al. Cardiovascular outcomes using intra-aortic balloon pump in high-risk acute myocardial infarction with or without


(136) Burkhoff D, Cohen H, Brunckhorst C, & O’Neill WW. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with


(143) Engstrom AE, Cocchieri R, Driessen AH, et al. The Impella 2.5 and 5.0 devices for ST-elevation myocardial infarction patients presenting with severe


(157) Philipp A, Arlt M, Amann M, et al., “First experience with the ultra compact mobile extracorporeal membrane oxygenation system cardiohelp in


Table 1: Receptor activities and hemodynamic/clinical effects of the commonly used inotropes/vasopressors in cardiogenic shock [modified from ref. 6, 45, 46]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main receptor activity</th>
<th>Dose (µg/kg/m in)</th>
<th>Clinical/hemodynamic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α 1</td>
<td>α2</td>
<td>β1</td>
</tr>
<tr>
<td>dobutamine</td>
<td>0(+)+</td>
<td>0+(+)</td>
<td>+++</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0-3-8</td>
<td>(+)</td>
<td>++</td>
</tr>
<tr>
<td>epinephrine</td>
<td>++++(++)</td>
<td>+++</td>
<td>0(+)</td>
</tr>
<tr>
<td>norepinephrine</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

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.