REVIEW ARTICLE

Devices for mechanical circulatory support and strategies for their management in cardiogenic shock

Federico Marin, Michele Pighi, Gabriele Pesarini, Anna Piccoli, Flavio Ribichini

Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy

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ABSTRACT

Cardiogenic shock (CS) is a low cardiac output state resulting in end-organ hypoperfusion and hypoxia, which, if untreated, leads to an irreversible multiorgan failure. Acute coronary syndrome is the most common cause of CS, with a high prevalence of patients with multivessel disease. Cardiogenic shock management remains a challenge, since mortality rates are still high and have not declined over the last 20 years. The treatment strategy of CS in patients with acute coronary syndrome needs to take into account both the presence of myocardial ischemia and tissue hypoperfusion. The first part of this review focuses on the characteristics, hemodynamic profile, and available evidence of the mechanical circulatory support devices for an optimal patient–device matching. The second part focuses on the management strategy of CS in terms of myocardial revascularization and hemodynamic support in light of the most recent available evidence.

Introduction Shock is a clinical condition characterized by a severe mismatch between the supply and demand for oxygen. Shock is classified based on the causative agent, and cardiogenic shock (CS) is a subtype in which circulatory impairment is determined primarily by the cardiac dysfunction.

Cardiogenic shock is characterized by a reduction of cardiac index (<1.8 l/min/m^2 without support or <2 to 2.2 l/min/m^2 with support), associated with: 1) systolic blood pressure above 90 mm Hg for over 30 minutes despite adequate fluid resuscitation or need for vasopressor therapy to maintain systolic blood pressure of 90 mm Hg or above; 2) clinical signs of hypoperfusion (altered mental status, cold extremities or oliguria); or 3) increased blood lactate levels.[1]

Irrespective of the cause, CS is characterized by a low cardiac output state resulting in life-threatening end-organ hypoperfusion and hypoxia, determining activation of the inflammatory cascade that amplifies and perpetuates the vicious circle leading to an irreversible condition.[2]

It is important to note that CS represents a continuum of disorders, depending on the severity of the reduction of cardiac output, and ranges from a state of pre-CS, classic CS, to refractory CS. The first stages of CS are characterized by a reversible hemodynamic status; however, it may evolve to a more complex "hemometabolic" condition that may not respond to treatment of the underlying cause or to hemodynamic support alone.[3] Pre-CS is an initial form of shock in which hypotension is not yet present. As described by Menon et al,[4] compared with patients with CS, patients with pre-CS had similar hemodynamics parameters in terms of cardiac index, left ventricular (LV) ejection fraction, and pulmonary capillary wedge pressure, but higher systemic vascular resistance. Absence of hypotension makes diagnosis very difficult, which could be the reason for the high rates of in-hospital mortality (up to 43%).[4] Once hypotension has been established, classic CS becomes manifest. Refractory CS is a form unresponsive to medical or mechanical support, in which hemodynamic impairment has led to the activation

Correspondence to: Prof. Flavio L. Ribichini, Professor of Cardiovascular Medicine, Division of Cardiology, Department of Medicine, University of Verona, AOUI Verona, Verona Piazzale Aristide Stefani 1 37128, Verona, Italy, phone: +39 045 812 2320, email: flavio.ribichini@univr.it

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of inflammation that frequently determines multiorgan failure and can lead to death.

From an epidemiologic standpoint, the most common cause of CS is acute coronary syndrome (ACS), which accounts for about 80% of the cases.[5] The remaining 20% of the CS cases are caused by mechanical complications, acute myocarditis, cardiac tamponade, arrhythmias, cardiomyopathies, pulmonary embolism, and decompensation of chronic congestive heart failure or chronic valvular heart disease. In regard to ACS, despite conflicting reports, CS complicates approximately 5% to 10% of ST-segment elevation myocardial infarction (STEMI) cases and 2% to 3% of non-STEMI ones.[6]

Mortality rates of CS remain high, ranging between 35% and 50%, depending on the etiology.[5] Patients with concomitant ACS and CS have poor prognosis. After the introduction of early revascularization, mortality rates in patients with ACS and CS declined over the last 20 years and reached a plateau. Indeed, the 30-day mortality reported in the revascularization arm of the SHOCK trial (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock),[7] a landmark study on CS published in 1999, is almost identical to that of CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock),[8] a recently published study on revascularization strategy in patients with ACS and CS (SHOCK, 46.7%; CULPRIT-SHOCK, 43.4% in culprit-lesion-only percutaneous coronary intervention [PCI] group and 51.6% in the multivessel-PCI group).

TABLE 1 **Comparison of the main characteristics and hemodynamic performance of mechanical circulatory support devices**

Parameter	IABP	Impella	VA-ECMO
Mechanism	Intra-aortic	From LV to aorta	From RV to aorta
Flow support, l/min	<0.5	1–5[a]	2–7
Flow pattern	Pulsatile	Continuous	Continuous
Maximum implant days	4–5 weeks	7 days	Weeks
LV preload	–	↓↓	↓
LV afterload	↓	↓	↑↑↑
LV stroke volume	↑	↑↑	–
LV end-diastolic pressure	↓	↓↓	↑
Coronary perfusion	↑	↑↑	–
RV support	–	↑↑ (Impella RP)	↑↑
Blood oxygenation	–	–	↑↑↑
Mean arterial pressure	↑	↑↑	↑↑

a Impella 2.5 delivers forward blood flow up to 2.5 l/min, Impella CP up to 4 l/min, and Impella 5 up to 5 l.

↑ – increase; ↓ – decrease

Abbreviations: IABP, intra-aortic balloon pump; LV, left ventricle; MCS, mechanical circulatory support; RV, right ventricle; VA-ECMO, venoarterial extracorporeal membrane oxygenation

Mechanical circulatory support devices It is well known that the escalating use of vasopressors and inotropes increases oxygen consumption, leading to worse myocardial ischemia. Use of mechanical circulatory support (MCS) devices may interrupt the vicious circle of hypoperfusion, preventing the onset of refractory CS. Different MCS devices are available, each with different characteristics that are briefly described in TABLE 1.

Intra-aortic balloon pump Historically, intra-aortic balloon pump (IABP) was the first percutaneous MCS device available, and today is the most commonly used one. It is composed of a balloon catheter and a pump console. The balloon is placed in the descending thoracic aorta and is inflated and deflated in synchrony with the cardiac cycle. The balloon is inflated with helium because of its low viscosity that allows it to travel quickly through tubes and because it is also absorbed rapidly in blood in the case of balloon rupture. The console synchronizes the inflation and the deflation of the balloon with echocardiography (ECG). It permits the balloon to inflate with the onset of diastole at the middle of the T wave on the surface ECG and to deflate at the onset of LV systole at the peak of the R wave on the surface ECG.

In terms of the hemodynamic effects, IABP elevates diastolic pressure and decreases afterload. In the presence of ischemia, coronary autoregulation is exhausted and myocardial blood flow is directly and proportionally dependent on perfusion pressure. Elevation of systemic diastolic pressure favors coronary perfusion by augmenting the aorto-coronary perfusion gradient (diastolic augmentation).[9,10] Reduction of afterload permits a decrease of both the peak LV systolic and diastolic pressures and a modest increase of LV stroke volume (systolic unloading). The net effect is a reduced slope of arterial elastance, as shown in FIGURE 1A. The efficacy of IABP is influenced by numerous variables related to the patient and to the device. The correct timing of the inflation and deflation of the balloon plays a key role in terms of efficacy: poor ECG quality as well as cardiac arrhythmias may reduce the benefits of the device, impeding LV ejection and increasing afterload.[11] Other factors that influence the efficacy of the device are the correct position of the balloon in the aorta and its dimension in relation to the aortic diameter, which affects the amount of blood displaced.[12,13] The main limitation of IABP is its total dependence on the LV efficacy; indeed, it has neither a pump capability nor a gas exchange function. The use of IABP is contraindicated in the presence of moderate to severe aortic regurgitation. It is important to pay attention in patient with peripheral artery disease because of an increased risk of vascular complications.[14]

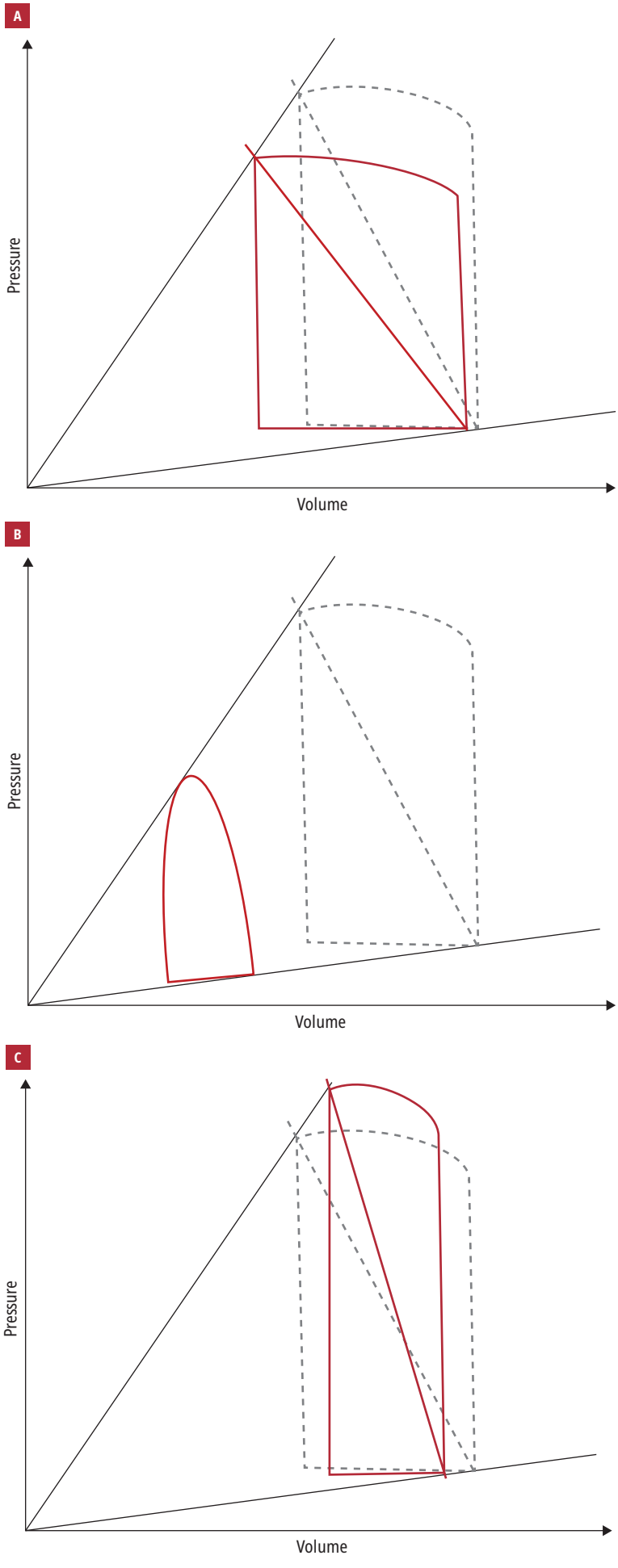

FIGURE 1 Schematic representation of hemodynamic modifications induced by different mechanical circulatory support devices on left ventricle pressure-volume loops shown in continuous line. **A** – intra-aortic balloon pump reduces systolic afterload, in turn decreasing the slope of the of arterial elastance; however, it only slightly reduces left ventricular end--diastolic volume. **B** – Impella device reduces both the volume and the filling pressure, unloading the ventricle; pressure--volume loop has a typical triangular shape. **C** – VA-ECMO, despite its positive impact on the tissue perfusion and the reduction of the preload, increases left ventricular afterload and myocardial workload.

For many years, IABP has been strongly recommended to treat CS complicating acute myocardial infaction (AMI), despite lack of robust randomized data. The IABP-SHOCK-II trial (Intraaortic Balloon Pump in Cardiogenic Shock II) was a multicenter, open-label, prospective trial that randomized 600 patients with CS complicating MI either to receive IABP therapy or not to receive IABP therapy to test its clinical value. The trial failed to meet its primary endpoint, with both the 30-day[15] and 1-year[16] follow-up showing no overall difference in all-cause mortality between groups. There was also no benefit with respect to secondary outcomes such as hemodynamic parameters, lactate levels, catecholamine doses, or renal function.

The role of IABP has been redefined also in other settings. The CRISP-AMI trial (Counterpulsation Reduces Infarct Size Pre-PCI for AMI), an open, multicenter, randomized controlled trial that included 337 patients with anterior STEMI in the absence of CS, showed no benefit in reducing infarct size measured by cardiac magnetic resonance with the routine use of IABP in anterior MI without shock.[17] Also, in a high-risk elective PCI cohort of patients with severe LV dysfunction and extensive coronary disease, elective IABP insertion did not reduce the incidence of major adverse cardiac and cardiovascular events following PCI.[18] After considering the neutral results of all the above trials, the international guidelines downgraded the indication of routine use of IABP in STEMI complicated with CS to class IIa, level of evidence B in the American Heart Association guidelines[19] and to class III, level of evidence B in the European counterpart.[20] The use of IABP in patients with ACS and CS may be considered for hemodynamic support in selected patients who do not respond to standard pharmacological therapy or with mechanical complications, that is, severe mitral insufficiency or ventricular septal defect.[21]

Impella The Impella device (Abiomed, Danvers, Massachusetts, United States) has been approved by the United States Food and Drug Administration in 2008. It is an intravascular microaxial blood pump that temporary supports

the patient's circulatory system, allowing heart recovery and early assessment of residual myocardial function. The catheter is inserted percutaneously through the femoral artery into the LV. The catheter passed retrogradely across the aortic valve and its inlet area is positioned into the LV. The outlet opening is placed in the ascending aorta. This is an active pump, which can deliver up to a maximum of 3.5 liters of blood per minute from the LV into the ascending aorta, resulting in continuous flow augmentation. Different models are available for the left heart: Impella 2.5, Impella CP, Impella 5.0, and Impella 5.5, with different maximum flow capacity, numbers of days for which they could remain in site, and sheath dimensions. Recently, the Impella RP, an intravascular microaxial blood pump specifically designed to support the patient's pulmonary circulation in the setting of acute right ventricular failure, has been approved. The cannula is placed through the right femoral artery, and the inlet area of the cannula pumps the blood from the inferior vena cava to the pulmonary artery. The Impella device is contraindicated in the presence of ventricular thrombus, mechanical aortic valve, severe aortic valve stenosis or calcification, severe aortic insufficiency, and severe peripheral artery disease.

The Impella device directly unloads the ventricle, increasing cardiac output, mean arterial pressure and peak coronary flow.[22] The unloading of the LV decreases end-diastolic volume and pressure,[23] reducing myocardial oxygen consumption and decreasing pulmonary capillary wedge pressure. The pumping of the blood is continuous and independent of the ventricular contraction, determining uncoupling between aortic and peak LV pressure generation.[24] The loss of normal isovolumic periods modifies the form of the pressure-volume loop into a triangular shape, as shown in FIGURE 1B.

The ISAR-SHOCK trial (Efficacy Study of LV Assist Device to Treat Patients With Cardiogenic Shock) was one of the first studies that tested the safety and effectiveness of the Impella 2.5 device as compared with IABP in a population of patients with ACS and CS. In this prospective, 2-center, randomized, open-label study, the Impella 2.5 device demonstrated a superior hemodynamic performance as compared with the standard therapy.[25] However, no impact of the hemodynamic improvement on the mortality rate was observed. In 2016, the randomized, prospective, multicenter IMPRESS trial (Initial Management of Patients Receiving a Single Shock) failed to demonstrate a reduction in 30-day mortality as compared with IABP in a very small population of patients with CS (n = 48).[26] A recent meta-analysis of the 3 major randomized controlled trials comparing Impella with IABP confirmed no difference in 30-day and 6-month all-cause mortality rates.[27] Data were confirmed by a recent retrospective analysis involving patients with AMI and CS, in whom the routine use of Impella did not reduce all-cause mortality at 30 days compared with a matched cohort from the IABP-SHOCK II trial.[28] Even though there is still no evidence of benefit in terms of mortality and clinical outcomes, Impella was shown to provide more hemodynamic support than IABP.

Extracorporeal membrane oxygenation Extracorporeal membrane oxygenation (ECMO) is an evolution in the heart–lung machines used in cardiac surgery. There are 2 types of EMCO, venovenous and venoarterial (VA), which refer to the source and target of blood flow between the 2 large-bore catheters and the pump. The first guarantees respiratory support, and the second is used in the management of antegrade circulatory failure, as in the presence of CS. Venoarterial ECMO (VA-ECMO) refers to a system that draws out venous blood from the patient via a long venous cannula placed in large central veins, removes carbon dioxide and oxygenates the blood using an oxygenator (replacing lung function), and pumps back the blood into the arterial system using a centrifugal pump (replacing heart function) via a short arterial cannula placed in an artery.

Extracorporeal membrane oxygenation provides full biventricular cardiac support by replacing the native heart function, guaranteeing a blood flow of up to 7 l/min. The goal of ECMO is to "buy time" while sustaining an adequate tissue perfusion, providing a bridging therapy either for the healing of the natural organs or for long-term support devices or transplantation.[29] The diffusion of ECMO has increased in the last decades thanks to advances in technology.[30] Centrifugal pumps cause less blood damage, membrane oxygenators have better gas exchange capability, and the biocompatibility of the components cause less hematologic alterations. Extracorporeal membrane oxygenation is implanted percutaneously at the bedside or in the prehospital setting.[29] The 2 main configurations of VA-ECMO are the peripheral ECMO, which is the most common, and the central ECMO. In peripheral ECMO, cannulas are inserted both into the right femoral artery and the right common femoral vein, while in central ECMO, usually an arterial cannula is placed into the ascending aorta and a venous cannula into the right atrium.

The extracorporeal pump works in parallel with the patient's heart. The total flow is the sum of the well-oxygenated blood coming from the extracorporeal circuit and the blood passing through the native heart and lungs. Beyond improving blood oxygenation, the main hemodynamic effects are the reduction of the preload, loss of pulsatile blood flow, and increase

of the LV afterload,[24] as shown in FIGURE 1C. Part of the venous return trough the venous cannula is diverted into the extracorporeal circuit, reducing the total venous return to the right side of the heart, which is a beneficial effect in right ventricular dysfunction. Since the centrifugal pumps provide continuous flow, the reduction of the LV ejection determines loss of arterial pressure pulsatility at the increase of ECMO blood flow.

The effect of continuous versus pulsatile flow on organ perfusion has been extensively investigated, and no definitive conclusion has been drawn to date on its potential negative effects.[31] A recent study demonstrated that pulsatile ECMO produces significantly higher hemodynamic energy and improves systemic microcirculation, as compared with nonpulsatile ECMO in patients with CS.[32] Aortic counterpulsation during VA-ECMO could guarantee the preservation of a pulsatile flow waveform. After oxygenation, blood returns via the arterial cannula into the arterial systemic circulation increasing LV afterload, and this is of particular concern in peripheral VA-ECMO.[33] The inadequate drainage of the LV increases the ventricular diastolic pressure, which raises LV wall stress and myocardial oxygen demand, perpetuating a vicious circle. To avoid an increase of pulmonary congestion, left side venting should be considered. That may be obtained by: 1) increasing natural ejection with inotropes; 2) decreasing systemic vascular resistances with vasodilators; 3) aortic counterpulsation; or 4) with percutaneous or surgical venting.

Small studies demonstrated better outcomes in concomitant treatment with VA-ECMO and Impella or with VA-ECMO and IABP, as compared with VA-ECMO alone.[34,35] A prospective, randomized trial is ongoing to evaluate whether the addition of early ventricular unloading using Impella improves cardiac recovery (REVERSE). Looking at the coronary perfusion, central VA--ECMO, in which the outflow cannula is positioned in the ascending aorta or in the right subclavian artery, guarantees a better coronary flow in comparison with the peripheral VA-ECMO, but as discussed, it deteriorates the afterload.

The 2 main characteristics that differentiate ECMO from the other MCS devices are its usefulness in case of refractory hypoxemia due to pulmonary failure, which improves tissue perfusion, and the simultaneous support of the right ventricle. Negative aspects are the rise of the LV afterload and possible secondary complications such as major bleedings and limb ischemia.

The role of ECMO has been validated mainly in single-center registries. No data from randomized, multicenter trials are available. In the European guidelines, the use of ECMO in the setting of refractory CS is reported in class II, level of evidence B, based on expert opinion. The survival rates of patients undergoing VA-ECMO remain low: 30-day mortality is about 50% and survival at 1 year is 38%.[36] The outcomes of ECMO have improved despite increasing comorbidity[36] owing to the continuous improvement of the technique, patient selection, and ancillary therapeutics. Survival rates are strongly dependent on the etiology of CS. Patients with potentially reversible causes of myocardial injury, such as fulminant myocarditis, coronary occlusion, or primary graft failure, have better survival rates than those with CS after bypass surgery or MI.[37,38] A wide body of evidence shows that ECMO support improves prognosis in patients with STEMI complicated by severe CS who undergo primary PCI. Patients with STEMI and profound CS undergoing primary PCI treated with combined ECMO support and IABP have lower mortality rates compared with those on IABP alone.[39] To improve the selection of candidates to ECMO therapy, numerous prognostic predictors have been investigated. Schmidt et al[40] developed the Survival After Venoarterial ECMO (SAVE) score to predict survival after VA-ECMO in patients with refractory CS, using 12 pre-ECMO parameters.

To clarify the role of ECMO in patients with CS, there are 2 ongoing multicenter, prospective, randomized trials. EUROSHOCK (Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock), a Pan-European study including more than 400 patients, and ECMO-CS (Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock) are testing the role of the early use of ECMO in improving outcomes.[41]

Door-to-balloon time The urgent treatment of the culprit lesion is imperative in patients presenting with ACS complicated by CS, as shown in the landmark SHOCK Trial. So far, no other intervention with a device or pharmacologic agent showed a significant mortality benefit.[7]

The prevalence of multivessel disease in patients with AMI complicated by CS reaches 80%.[42] The revascularization strategy in multivessel disease presenting with CS remains debatable. There is no doubt as to whether an urgent PCI of the infarct-related artery should be performed, but whether PCI should be performed immediately for stenosis in nonculprit arteries is controversial. On the one hand, multivessel PCI may reduce the burden of global myocardial ischemia and improve myocardial function, but on the other hand, it may cause harm due to increased procedural time, contrast volume, and possible ischemia in different territories. In patients with multivessel disease and MI without CS, the previous trials: DANAMI-3-PRIMULTI (Primary PCI in Patients With ST-elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization),[43] PRAMI (Randomized Trial

of Preventative Angioplasty in Myocardial Infarction),[44] and CvLPRIT (Complete Versus Lesion-Only Primary PCI Trial)[45] have suggested potential benefits of complete revascularization. Data from each trial were confirmed by a meta-analysis demonstrating lower rates of composite major adverse cardiac events with complete revascularization. The last European guidelines on STEMI, published in 2017, stated that complete revascularization during the index procedure should be considered in patients presenting with CS, based on expert opinion (class II, level of evidence A).[20]

In the same year, a few months later, the results of the randomized, multicenter, large-scale CULPRIT-SHOCK trial (n = 706) showed that among patients who had multivessel coronary artery disease and AMI with CS, the risk of a composite of death or renal-replacement therapy at 30-day follow-up was lower in those who initially underwent PCI of the culprit lesion only, as compared with those who underwent multivessel PCI.[46] This outcome was mainly driven by the lower mortality rate in patients who underwent culprit-lesion-only PCI. However, this randomized trial received some criticism. First, the presence of patients who were switched from culprit-lesion-only PCI to multivessel PCI, for reasons such as lack of hemodynamic improvement, may lead to bias towards including more complex patients in the multivessel PCI group. Second, 24% of patients in the multivessel CAD arm had a chronic total occlusion for which revascularization was attempted (successful in 81%) and revascularization of these lesions has failed to show a beneficial effect also in patients without CS and STEMI. Third, an MCS device was used only in 28% of patients. The results of the trial were included in the European Society of Cardiology guidelines on myocardial revascularization published in 2018, which recommended against revascularization of non–infarct-related artery lesions in patients with CS (class III, level of evidence B).[47] The results of the CULPRIT-SHOCK should be included in the discussion on revascularization in patients with AMI, because they confirmed that CS represents a complex setting in which ischemia coexists with hemodynamic instability. Treatment of ischemia (irrespective of the strategy) may not be sufficient to avoid the development of refractory CS, a condition that may be prevented by the use of appropriate MCS devices.

Door-to-support time A cornerstone of the emergent revascularization strategy in cardiology is the "time is muscle" principle, and the door-to-needle and door-to-balloon times are considered gold standards for AMI therapy. This concept should be applied also to patients with AMI complicated by CS. There is a growing body of evidence that the lack of benefits in terms of mortality rates in patients with MCS devices may be due to their late implantation when irreversible shock is already established. Within this framework, the time between the onset of CS and initiation of MCS should be included in the door-to-support time. The early identification of CS and prompt application of mechanical support may improve clinical outcomes. Mechanical circulatory support implantation early after the onset of shock, before initiation of inotropes or vasopressors and before PCI, is independently associated with improved survival rates in patients presenting with ACS and CS.[48] Basir MB et al[49] designed the Detroit Cardiogenic Shock Initiative, a single-arm, multicenter study, to assess the feasibility of early MCS in patients who present with AMI complicated by CS who undergo PCI.[49] The principles of the initiative are: 1) rapid door-to-support times (<90 minutes); 2) MCS initiation prior to PCI; 3) achievement of normal coronary blood flow (Thrombolysis In Myocardial Infarction grade flow III) and attempting to provide complete revascularization of all coronary lesions other than chronic total occlusion; and 4) hemodynamic monitoring to assess the need for MCS escalation and to safely and rapidly wean inotropes. The preliminary findings from this strategy provide the first supportive data showing that early application of MCS immediately before reperfusion in patients with hemodynamic (not hemo-metabolic) ACS and CS can improve clinical outcomes.

Conclusion Mortality rates in patients with CS remain high and have not declined over the last 20 years. Urgent revascularization is the only treatment that was shown to improve mortality, but it seems not enough. Early initiation of MCS, guided by invasive hemodynamic monitoring, may play a fundamental role in improving survival, avoiding the onset of irreversible hemo-metabolic shock. Different MCS are available, each with specific hemodynamic properties. A proficient knowledge of these principles guarantees an optimal patient–device matching. Currently, the management of CS is undergoing major changes, but further studies are still needed to establish the best treatment strategy in terms of hemodynamic support and extension of the revascularization.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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