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REVIEW

A Long-Forgotten Tale: The Management of Cardiogenic Shock in Acute Myocardial Infarction

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ABSTRACT

Patients with acute myocardial infarction (AMI) complicated with cardiogenic shock (CS) present one of the highest mortality rates recorded in critical care. Mortality rate in this setting is reported around 45–50% even in the most experienced and well-equipped medical centers. The continuous development of ST-segment elevation acute myocardial infarction (STEMI) networks has led not only to a dramatic decrease in STEMI-related mortality, but also to an increase in the frequency of severely complicated cases who survive to be transferred to tertiary centers for life-saving treatments. The reduced effectiveness of vasoactive drugs on a severely altered hemodynamic status led to the development of new devices dedicated to advanced cardiac support. What's more, efforts are being made to reduce time from first medical contact to initiation of mechanical support in this particular clinical context. This review aims to summarize the most recent advances in mechanical support devices, in the setting of CS-complicated AMI. At the same time, the review presents several modern concepts in the organization of complex CS centers. These specialized hubs could improve survival in this critical condition.

Keywords: cardiogenic shock, mechanical support devices, acute heart failure, acute myocardial infarction

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INTRODUCTION

The tale of cardiogenic shock (CS) in the setting of acute myocardial infarction (AMI) has long been forgotten. Many years have passed since anything notable happened with regard to mortality in CS, except for its continuously increased occurrence. Neither the mechanism, nor the treatment of this critical illness have been elucidated. At the same time, inflammation, the defendant of all elusive diseases, has come more and more into the spotlight.

This review aims to summarize the most recent advances in mechanical support devices in the setting of CS-complicated AMI. At the same time, the review presents several modern concepts in the organization of complex CS centers. These specialized hubs could improve survival in this critical condition.

INFLAMMATORY RESPONSE AND AMI-RELATED CS

Local intramyocardial inflammation represents an important issue in the development of left ventricular remodeling after an AMI.[1] This aspect gains a special meaning

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in CS, as some patients surviving the acute event recover most of their left ventricular function. Eighty-seven percent of one-year survivors in the SHOCK trial were in NYHA functional class I or II.[2]

The development of systemic inflammation with impaired microcirculation is also an important factor in the vicious spiral of CS pathophysiology. Blood transfusion or the use of mechanical support (MS) devices contributes to inflammatory derangements. However, through unloading of the left ventricle, some MS devices (e.g., Impella), demonstrated that the inflammatory response was significantly reduced during their functioning time. Early revascularization, as shown in the SHOCK trial, is the most important treatment strategy in CS complicating AMI.[3]

The warm and wet patient phenotype in CS is linked to this overexpressed inflammatory status and, what's more, to increased mortality. At the same time, several inflammatory reactions, such as the cytokine cascade, the chemokine response, and the inducible nitric oxide (NO) synthase expression, are associated with coronary plaque rupture, the index event in AMI and the link between inflammation and acute coronary syndromes.[4]

CARDIOGENIC SHOCK IN ACUTE MYOCARDIAL INFARCTION – A VERY HIGH-RISK CONDITION

Patients with CS complicating AMI present one of the highest mortality rates recorded in critical care. Mortality rate in this setting is reported around 45–50% even in the most experienced and well-equipped centers.[5] Moreover, a significant number of patients who survive to discharge are readmitted in the first 30 days after the acute event, for advanced deterioration of their cardiac status.[6] In the last years, an increasing prevalence of CS has been reported in the STEMI population. It is currently estimated that 7% to 12% of STEMI patients >75 years of age develop CS.[7–9] The continuous development of STEMI networks has led not only to a dramatic decrease in STEMI-related mortality, but also to an increase in the frequency of severely complicated cases who survive to be transferred to a tertiary center for advanced life-saving treatments.[10] As a result of effective STEMI networks, more and more patients with complex multivessel disease, high-risk coronary lesions or delayed presentation arrive in the catheterization laboratory. This leads to a significant increase in the complexity of the cases treated in the acute cardiac care units and in the incidence of CS.

CS is usually diagnosed at the moment of the first medical contact.[11] The diagnosis of CS is established based on clinical and laboratory criteria: systolic blood pressure <90 mmHg, heart rate >100 per minute, signs or symptoms of poor organ perfusion and oxygen saturation <90%, increased lactate level, and altered arterial blood gas values.

TREATMENT STRATEGIES IN CS COMPLICATING AMI

Commonly used therapies in CS include administration of inotropes (dobutamine, dopamine, levosimendan) and vasopressors (norepinephrine). Vasopressors are usually recommended to increase blood pressure and vital organ perfusion, especially in cases who do not adequately respond to inotropes.[12] However, despite the continuous development of modern drugs for the immediate correction of hemodynamic status, these substances remain associated with high long-term mortality and are only recommended for short-term administration.

The reduced effectiveness of vasoactive drugs led to the development of new devices in the field of critical care cardiology. These devices are dedicated to advanced cardiac support and to the correction of hemodynamic instability.[13] Their use represents one of the main recent directions of development in patients with CS following an AMI.

At any level of first medical contact (FMC), the therapeutic approach might include, if necessary, endotracheal intubation and surface cooling for therapeutic hypothermia.

THE ROLE OF CARDIAC CATHETERIZATION LABORATORY IN CS COMPLICATING AMI

The role of the catheterization laboratory in the treatment of CS is constantly increasing. The "cath lab" is the place of revascularization and, more recently, the scene of initial placement and escalation of MS.

In this study, the group of patients undergoing early revascularization had a significantly reduced mortality at the 6- and 12-month follow-up (50% vs. 37%, p = 0.027 at 6 months and 47% vs. 34%, p = 0.025 at 12 months).[14]

Revascularization retains a Class I indication in both the European and American practice guidelines.[4,15] The concept of early initiation of MS in the setting of AMI-associated CS, even before percutaneous coronary intervention (PCI) or vasoactive therapy, emerged recently, and the time from FMC to initiation of MS was defined as a measure of treatment effectiveness. One of the most interesting questions aroused recently regards the importance of FMC-to-balloon (FMC-B) vs. FMC-to-support

(FMC-S) time. It has been demonstrated that vasoactive support as a bridge to MS, although important for blood pressure maintenance, is associated with an increase in both myocardial oxygen consumption and mortality, in accordance with the number of inotropes and their dose.[4] Therefore, the question remains whether FMC-S time should be lower than FMC-B time. Short time to reperfusion has been demonstrated as a powerful predictor of a good outcome in AMI patients. However, total ischemic time could explain the magnitude of left ventricular remodeling and the difference in mortality only when associated to microvascular obstruction and an old coronary thrombus.[16,17] In recent guidelines, revascularization has gained a Class I indication, while MS only a Class IIa.[4,15] The 3% increase in mortality recorded between 2005 and 2014 in patients with CS following AMI in the NCDR Cath/PCI registry is difficult to understand.[18] The incorrect use of MS, the timing of its initiation, and the difference in expertise of the catheterization laboratories involved could explain this increase in mortality. Expertise is generally a key to success, and the volume of activity stands at its base. "Good judgment comes from experience; experience comes from bad judgment" is an aphorism attributed to Dr. Kerr L. White.[19] CS is a severe condition which does not allow bad judgments. A multidisciplinary approach could bring an end to the truth in the quotation above.

REPERFUSION IN CS

It needs to be underlined that reperfusion in CS remains the same important therapeutic step, even if a little delayed by the early insertion of MS.[20] The most frequent anatomic scenario in patients with CS and AMI is represented by a culprit lesion either on the left main or on the left anterior descending coronary artery. Primary PCI, preferably performed through radial access, is the first therapeutic option after MS insertion.

The results of the CULPRIT-SHOCK trial (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) have shown lower 30-day mortality in patients with coexisting multivessel disease who underwent revascularization of the culprit lesion only compared to those who underwent complete revascularization.[21] The strategy of culprit-only revascularization was associated with a significant reduction in the composite endpoint represented by all-cause mortality or severe renal failure and a significant reduction in 30-day all-cause mortality (43.3% vs. 51.6%, HR = 0.84, p = 0.03).[21] Therefore, the recent European and American guidelines recommend only culprit lesion PCI in patients with CS, while the non-culprit lesions remain subject to staged revascularization.[4,15] Primary PCI in CS respects all the technical rules of reperfusion from AMI.[22,23]

MECHANICAL DEVICES FOR CS

The insertion of mechanical devices improves the performance of the left ventricle. Recovery of left ventricular function is one of the main therapeutic goals in patients with AMI. Since the extent of viable myocardium has been proved to be directly associated with survival, the timely initiation of adequate measures to restore the severely altered myocardial performance in CS can be lifesaving.[24-26]

For this purpose, new devices have been developed with the aim of providing increased mechanical circulatory support and improved survival in case of refractory CS.[27-30] The most frequently used devices in clinical settings are the intra-aortic balloon pump (IABP), veno-arterial extracorporeal membrane oxygenation (ECMO), and left ventricular assist devices (LVAD). IABP, a device inserted in the aorta during an interventional procedure, consists in an intra-aortic balloon which inflates during diastole and deflates during systole, being able to decrease ventricular workload and to increase cardiac output.[31] However, the use of IABP in patients with CS complicating AMI failed to demonstrate a significant reduction in 30-day mortality in the IABP-II Shock trial.[32]

The recently introduced ECMO devices are also inserted percutaneously, being able to increase coronary, cerebral, and peripheral perfusion and demonstrating a 33% higher survival at 30 days compared with IABP.[33] The third type of percutaneously inserted devices is represented by left ventricular assist devices, the most commonly used types being represented by Impella (implanted using the transaortic route) and TandemHeart (implanted using the transapical route). As to what mechanical device should be used first, a recent meta-analysis suggested that early initiation of Impella in AMI-related CS led to a 48% decrease in 30-day mortality compared to late initiation.[34] Early initiation of Impella provides effective left ventricular unloading and maintains adequate systemic and coronary perfusion.[35,36] Flaherty *et al*. also stated that Impella's role in reducing endothelin levels prevented the downward spiral of systemic inflammatory response, hypoperfusion, and multiorgan failure.[34]

Escalation of device therapy from a primarily left ventricular to a biventricular support (e.g., Bipella: Impella CP for left ventricular support and Impella RP for right ventricular support, or ECPELLA: Impella and ECMO, simul-

taneously) is determined by the persistence of left ventricular failure.

THE LEVEL OF CS CENTERS AND MORTALITY

A recent meta-analysis that included 22 PCI and CABG studies demonstrated a significantly lower AMI-related mortality in hospitals with large PCI or CABG volume (>600 cases/year).[14] Similarly, in an intensive cardiac care unit, mortality is directly associated not only to the available facilities, but also to the experience of the involved medical staff.[37,38]

Several recent studies demonstrated the impact of a properly organized intensive care unit on cardiac-related mortality in patients with advanced heart failure. In a study by Na *et al.*, the transition from a model in which a general intensivist provided assistance for critical cardiac patients, to a model in which assistance was provided by dedicated personnel resulted in a significant reduction in mortality from 18% to 12%.[39] In another report, the implementation of high-intensity management in the cardiac critical care unit led by a specialized intensivist, resulted in a decrease in cardiovascular mortality from 6% to 3%.[40] The case volume of the cardiac critical care unit is also important. A comparative study between centers with a low volume versus a high volume of annually treated AMI cases reported significantly lower mortality rates when patients were referred to a high-volume center (11% vs. 4%, p <0.0001 for in-hospital mortality and 7% vs. 3%, p <0.0001 for intensive care unit mortality).[41]

These observations are also valid in the case of CS, the most critical condition recorded in a cardiac critical care unit. A statistically significant decrease in overall adjusted mortality was seen in hospitals with high numbers of CS cases. Mortality was 42.0% in centers with less than 27 patients/year compared to 37.0% in centers with more than 107 cases/year.[42] These facts advocate for the establishment of CS care centers with different levels of competence and mandatory multidisciplinary approach. At the base of this concept stands the metrics of FMC-S time. The aim is to achieve a FMC-S time of less than 90 min in the pre-PCI model of MS insertion.[43]

The modern systems of care for CS include a high-volume center acting as a hub, several spoke centers, and an integrated emergency medical system with clearly defined protocols for early diagnosis of CS, prompt initiation of the first therapeutic measures, and immediate transfer to the hub center.

NETWORKS FOR CS COMPLICATING AMI

The FITT-STEMI (Feed-back Intervention and Treatment Times in ST-Elevation Myocardial Infarction) trial demonstrated a 3.3% increase in mortality for every 10-minute delay from symptom onset to revascularization in patients with CS, underlining the need for a well-functioning network.[44] A significant development in the field of CS management was ensured through the implementation of dedicated networks for acute cardiac care. These result from the extension of STEMI networks and are based on the same concept of reducing time from symptom onset to targeted intervention.[45-55] The main advantages of a STEMI network consist in well-established transfer protocols and standardized procedures between centers, which can

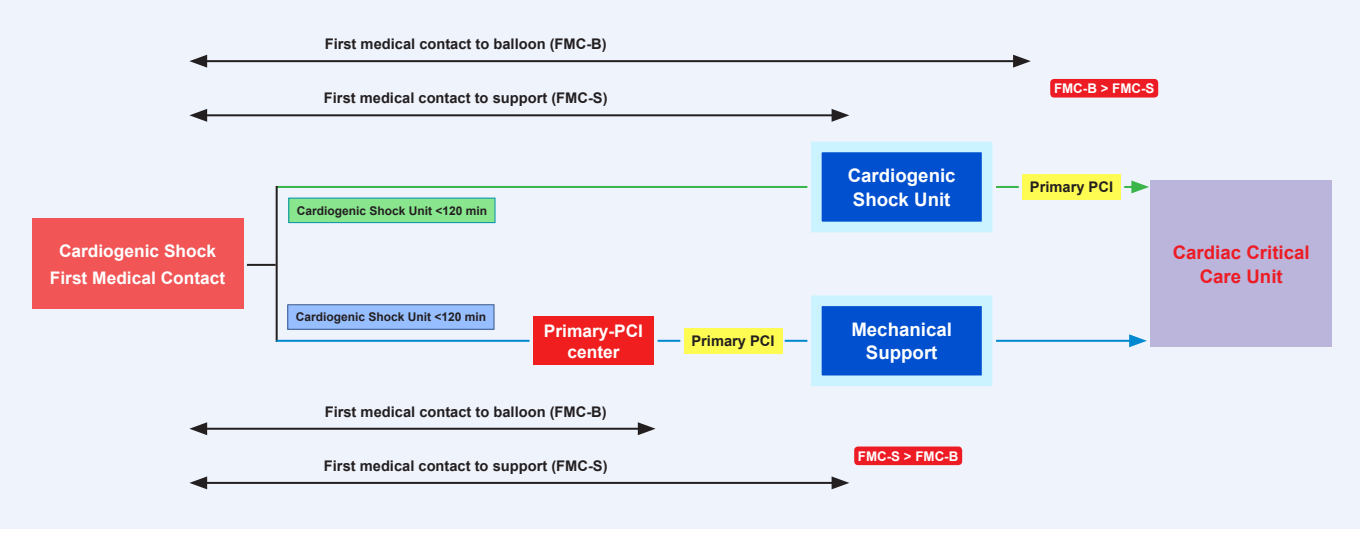

FIGURE 1. Proposed algorhythm for management of cardiogenic shock complicating acute myocardial infarction

significantly shorten time delays. These protocols can be applied in case of modern "shock networks", on the premise that the extension of the "network-integrated services" model beyond STEMI may bring similar benefits to other acute cardiovascular diseases.[56-60]

FMC is a cornerstone in the triage of patients. At this moment in time, the diagnosis of CS is highly demanding given the multitude of currently used definitions. Transport to a PCI-capable hospital without advanced CS treatment capabilities is acceptable if the estimated FMC-S time exceeds 120 min. As a result, the delay in primary PCI reperfusion will be avoided.[11]

Transfer to a specialized CS center is mandatory if FMC-S time is less than 120 min. If longer than 120 min, the destination would be a non-shock center catheterization laboratory in view of primary PCI (Figure 1). The Detroit protocol can be used and Impella CP inserted if left ventricular end-diastolic pressure exceeds 15 mmHg before the procedure.[43] This initial pressure determination can help the diagnosis of severe pump failure or pre-shock.

As a result of CS definition, some vasoactive support might be used, but the target of systolic blood pressure is merely speculative. Norepinephrine is the first choice, because of fewer side effects compared to dopamine.

The final destination of a patient with CS is a Level 1 CS Center, the most specialized facility in the algorithm proposed by Rab *et al*.[11] In this algorithm, a Level 1 CS center corresponds to a Level III cardiac critical care facility in Europe, as defined by the Acute Cardiovascular Care position paper.[61] Such a complex unit, usually located in a tertiary or university hospital with a 24/7 cardiac catheterization laboratory, should be able to provide advanced invasive and noninvasive monitoring, as well as all the necessary devices for extracorporeal life support, mechanical circulatory support, renal replacement therapy, and mechanical ventilation.[12] This is the place of Impella or Tandem Heart insertion in accordance with the previously mentioned Detroit protocol. After hemodynamic stabilization, the standard PCI procedure can be safely performed.

In Level I CS centers, rapid delivery of MS and the use of invasive hemodynamics are mandatory. The recorded hemodynamic parameters are more complex, and their values are used for the objective guidance of specific therapies, for weaning from vasoactive drugs and for escalation to more complex MS. These parameters include: cardiac index <2.2 L/min/m^2, pulmonary capillary wedge pressure >15 mmHg, cardiac power <0.6 watts, and pulmonary artery pulsatility index <0.9.

Several authors suggested the possibility to initiate advanced treatment for CS during transfer, with the help of ECMO mobile units. ECMO devices have been tested and validated as supportive measures in patients with out-of-hospital cardiac arrest (OHCA), integrated in a complex network that provides extracorporeal life support during transfer to a highly specialized tertiary care unit.[62-71] Such a system-wide approach has been demonstrated to improve neurological outcomes after cardiac arrest.[72-74] At the same time, such networks led to significant reduction in OHCA mortality, similar with the mortality reduction in AMI following the implementation of STEMI networks.[75-80] The cardiac-RESCUE pilot study demonstrated the effectiveness of transferring patients with CS to the most advanced cardiac care unit, in a network of 22 tertiary and 53 non-tertiary centers acting as spokes, which transferred patients to 3 hubs after ECMO initiation using a mobile ECMO unit.[81] Another study at Columbia University reported a survival rate of 49% after the use of a temporary mechanical support (ECMO, in 51% of cases), which was initiated by a shock team consisting of cardiothoracic surgeons, heart failure cardiologists, intensive care specialists, and nurse practitioners.[82,83]

CONCLUSIONS

Like every story worth telling, cardiogenic shock has its heroes and its villains. Mechanical support devices fight the complex, deleterious, interconnected mechanisms of cardiogenic shock and offer the necessary hemodynamic conditions for the primary PCI procedure to take place. Consequent restoration of coronary blood flow treats the cause of the index event and creates the foundation for the resolution of this high-mortality encumbered condition.

CONFLICT OF INTEREST

Nothing to disclose.

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