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Chapter 2

Cardiogenic Shock

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Abstract

Cardiogenic shock (CS) is an end-organ hypoperfusion associated with heart failure. Any reason impairing acute left ventricular (LV) or right ventricular (RV) function may cause CS. The only way to avoid CS is to provide early reperfusion in myocardial infarction (MI) patients. CS is characterized by permanent or transient rearrangement of the entire circulatory system. According to the current IABP-SHOCK II trial, 74% of the patients with CSMI are treated with norepinephrine, 53% of them with dobutamine, 26% of them with epinephrine, 4% of them with levosimendan, and 4% of them with dopamine. Percutaneous circulatory support devices such as intra-aortic balloon pump (IABP), LV assist device (LVAD), or extracorporeal life support (ECLS) create treatment options for selected patients such as CS, cardiopulmonary resuscitation, or high-risk pPCI and CABG. Extracorporeal Life Support Organization (ELSO, 2017) evaluated that the use of ECLS/VA-ECMO should be considered when the mortality risk exceeds 50% despite optimal conventional treatment in case of acute severe heart or pulmonary failure, whereas it should be assessed as a primary indication when it exceeds 80%. Early and effective revascularization is the best treatment option for CS. Thus, the organizations on the national and global basis will play the most effective role for the short- and long-term survival of patients.

Keywords: cardiogenic shock, multiple organ failure, inotropes, left ventricular assist devices

1. Introduction

Cardiogenic shock (CS) is one of the most important issues dealt by cardiologists today and still needs solutions. Prevention, accurate diagnosis, urgent intervention, effective support for heart failure, and multi-organ failure (MOF) are what this endeavor involves [1]. More than 90% of patients arriving at the hospital with acute myocardial infarction (MI) are likely

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to survive [2]. CS occurs in approximately 5–8% of inpatients with ST-elevation myocardial infarctions (STEMI) and has a mortality rate of more than 30% [1]. CS is caused by end-organ hypoperfusion due to impaired cardiac pump function. Although CS-related mortality has declined significantly over the past decade, it continues to remain high, especially in cases of its coexistence with ischemic heart disease. Acute coronary syndrome (ACS) is still the most common cause of CS despite significant advances that have been made in its diagnosis and treatment. The most successful form of treatment is primary percutaneous coronary intervention (pPCI), which is carried out as rapidly as possible [3]. The recent research has suggested that the peripheral vasculature and neurohormonal and cytokine systems also play a role in the pathogenesis and persistence of CS.

In cases where CS complicates MI (CSMI), only one in two patients survives after 1 year [4, 5]. In a large study including 5782 patients, CSMI had developed in 2.5% of the patients with STEMI before admission to hospital, in 4.3% of them on the first day of hospitalization, and in 2.3% of them afterward [6]. For non-STEMI (NSTEMI) patients, these ratios were 1.2% for each condition [6]. Mortality rates were 45.7% before the hospitalization, 32.8% in the early period, and 54.1% in the late period [7]. Of 1422 CSMI patients, in the SHOCK Trial Registry, a shock is developed following left ventricular failure in 78.5% of them, acute mitral insufficiency in 6.9% of them, acute ventricular septal defect in 3.9% of them, right ventricular failure in 2.8% of them, cardiac tamponade in 1.4% of them, and other reasons in 6.7% of them [8].

2. Diagnosis and causes

2.1. Definition

CS is an end-organ hypoperfusion associated with heart failure. In terms of the hemodynamic parameters used in the definition of CS, it is characterized by a systolic blood pressure of 80–90 mmHg, a cardiac index below 1.8 L min^{-1} m^{-2} without support and below 2.0–2.2 L min^{-1} m^{-2} with support, a mean arterial baseline under 30 mmHg, and a pulmonary capillary wedge pressure of 15 or >18 mmHg [9].

2.2. Diagnosis

However, it is not necessary to measure these parameters in order to make the diagnosis of CS. Hypotension is not observed at the start in one-fourth of the patients diagnosed with CSMI. In this case, the diagnosis is made according to the clinical findings of organ hypoperfusion including extremity coldness, oliguria, and changes in mental condition such as agitation. It is imperative to distinguish MI-related complications, from primarily mechanical complications. The main complications are ventricular septal defect, free wall, and papillary muscle rupture developing after MI. Usually, if it is the first MI event and there is no anterior involvement, it should be considered that mechanical complications may have occurred. First of all, diagnosing CSMI should begin by quickly obtaining a 12-lead ECG (STEMI) and examining the clinical findings with respect to CS. In rare instances, the diagnosis of NSTEMI can be made based on the clinical criteria and troponin levels. Performing a rapid echocardiography (ECHO) before PCI may discount these complications, and, at the same time, the

detection of any pre-angiographic valve disease may alter the revascularization approach. Bleeding, infection, and/or intestinal ischemia may also cause shock in cases of MI. In these situations, patient survivability depends on being skeptical and makes a rapid diagnosis along with correct intervention.

2.3. Causes

Anything that impairs acute left ventricular (LV) or right ventricular (RV) function may cause CS. In cases of acute myopericarditis, tako-tsubo, and hypertrophic cardiomyopathy, shock may present with ST elevation in which cardiac markers are released without coronary artery disease. Stress-induced cardiomyopathy, also known as apical ballooning or tako-tsubo cardiomyopathy, is a syndrome of acute LV dysfunction after emotional or respiratory distress leading to CS in 4.2% of cases [10]. Chordal rupture caused by degenerative diseases and trauma and acute valvular insufficiency caused by endocarditis may also cause CS. Severe aortic insufficiency (regurgitation) or coronary involvement developing as a result of aortic dissection may cause CS. Stress occurring in cases of severe aortic or mitral stenosis can cause shock. Cardiac tamponade and massive pulmonary embolism may cause shock without pulmonary congestion.

2.4. Risk identification

The only way to avoid CS is to provide early reperfusion in MI patients. In a randomized trial, CS occurred less frequently compared to PCI in STEMI patients treated with thrombolytic therapy within the first 2 hours of symptom onset before hospitalization (1.3 vs. 5.3%, $p = 0.032$) [11]. Low blood pressure and accelerated heart rhythm in patients admitted to hospital suggest shock. Advanced age, anterior MI, hypertension, diabetes mellitus, multivessel coronary artery disease, previous MI or angina, or being diagnosed with heart failure, STEMI, and left bundle branch block are risk factors for the development of CS [12].

3. Physiopathology

CS is characterized by permanent or transient rearrangement of the entire circulatory system. The primary cause of many CS instances is the failure of LV pump function, but other components of the circulatory system, inadequate compensation, or additional defects can also contribute to this condition. The fact that surviving patients demonstrate improved functionality explains that all or some of these changes are completely reversible.

3.1. Left ventricle

The degree of LV myocardial dysfunction usually initiates CS. In most cases, it is not severe. Left ventricular dysfunction reflects newly onset irreversible damage, reversible ischemia, and previous infarct-related injury in CS. Myocardial injury causes systolic and diastolic dysfunction. Low blood pressure helps by reducing afterload due to the unique position of the heart even though it causes damage at the same time by impairing the coronary blood flow. It can lead to an increase in ischemia and cell death at the border and remote zone of the infarct

area. Reduction in coronary perfusion causes deterioration in perfusion of the heart and other vital organs by causing a decline in cardiac output (CO). Metabolic impairments occur inside and outside of the infarct region. Hypoperfusion leads to catecholamine discharge, resulting in an increase in contractility and peripheral blood flow, while, at the same time, increased contractility causes increased oxygen demand on the part of the myocardium, as well as arrhythmia and myocardial toxic effects [13]. Systemic inflammation may play a limiting role in peripheral vascular compensatory response or may only be considered as an epiphenomenon. Revascularization makes the ischemia disappear, but increased CO or LV ejection fraction (LVEF) could not be shown as a benefit of revascularization. Revascularization significantly increases the quality of life as well as survival rates [14, 15].

Vasoconstrictors and inotropic agents are able to correct CO and peripheral circulation temporarily, but they do not break this vicious cycle. Although rapid intra-aortic balloon pump (IABP) application improves ischemia transiently and supports the circulation, it is not the final solution. Correcting coronary occlusion through surgery or PCI will break the vicious cycle and increase survival.

In the light of CS's complex pathophysiology, the cause of shock in many cases is a severe impairment in contractility and moderate disruption in the LVEF [16]. LVEF was found approximately 30% in the SHOCK trial [17]. In terms of LVEF value, the SHOCK trial obscures many post-MI studies in which LVEF decreases with or without heart failure. The LVEF in this study generally does not indicate that the magnitude of myocardial damage causes CS, although it is measured in patients with inotropic and/or IABP support. LVEF is the same in the acute phase of CS, and 2 weeks later, its functional status is different [18]. Even when there are conditions in which there is no serious mitral regurgitation and the LV is preserved, CS still develops in some patients [19]. LVEF is a prognostic indicator in patients who end up with shock. The size of the LV is small or normal in about half of patients with CS [19]. LV dilatation is an adaptive mechanism of failure in order to provide stroke volume in the early phase. LV dilatation in the chronic phase may be maladaptive. The LV end-diastolic volume was shown to increase slightly to 15 mL as a result of the serially performed echo within the first 2 weeks in the survivors of CS [18].

3.2. Right ventricle

The RV may cause or contribute to CS. Shock based on the dominance of the RV occurs in 5% of CSMI cases. RV insufficiency may limit CO, ventricular interdependence, or both of them by decreasing LV filling. The treatment of patients with RV dysfunction and shock focuses not on reducing CO and on maintaining adequate right heart filling pressure in order to provide adequate LV preload in the conventional sense. However, in these patients, there is usually a very high RV end-diastolic pressure above 20 mmHg due to RV dysfunction [20]. The increase in RV end-diastolic pressure shifts the interventricular septum to the left via mechanical pressure, thus impairing the functions by reducing the filling [21]. This means that aggressive fluid resuscitation in RV dysfunction is actually the incorrect method. Inotropic therapy should be initiated if it persists despite optimization of RV end-diastolic pressure in the CS secondary to the RV. Maintaining RV end-diastolic pressures between 10 and 15 mmHg provides the best CO [22]. Inhaled nitric oxide (NO) may be useful in reducing pulmonary vascular resistance and promoting forward flow. Shock secondary to RV dysfunction has a mortality rate as high

as that of shock secondary to LV dysfunction. The benefit of revascularization was similar in the SHOCK registry for patients with primarily RV dysfunction and those with primarily LV dysfunction [20].

Hypoperfusion of the extremities and vital organs is a sign of CS. MI-induced CO reduction and persistence of ischemia both result in the release of catecholamines leading to constriction of the peripheral arteries and, thus, affecting the maintenance of perfusion to the vital organs. Attempts to improve peripheral and coronary circulation at the expense of elevation in afterload by increasing the levels of vasopressin and angiotensin II at the beginning of MI and shock will subsequently lead to impairment in myocardial functions. The continuation of neurohormonal cascade activation will also increase acute pulmonary edema while attempting to improve perfusion by causing water and salt retention. The reflex increase of systemic vascular resistance (SVR) mechanism is not fully effective. The SHOCK trial showed that SVR was at mean levels during CS despite vasopressor treatment and that in some cases it was even as low as in a septic shock [23]. Sepsis was suspected in 18% of the cohort of the SHOCK trial, 74% of which developed positive bacterial cultures. SVR was lower in these patients, and low SVR preceded the clinical diagnosis of infection and culture positivity by days [23].

Findings and observations of MI may cause systemic inflammatory response syndrome (SIRS). Inappropriate vasodilation as part of SIRS results in impaired perfusion of the intestinal tract leading to the transmigration of bacteria and sepsis. As the duration of shock increases, so the possibility of SIRS increases [24].

Sometimes, the medications given can contribute to the development of CS. Numerous medications such as beta-blockers, angiotensin-converting enzyme inhibitors, and morphine were associated with the development of shock. The early use of these treatments contributes in a small way to increase the risk of CS. However, given the large patient population receiving this treatment, the number of incidents it causes significant [25, 26]. The timing of CS (early after medication initiation) in the placebo-controlled, randomized trials of β-blockage and angiotensin-converting enzyme inhibition combined with their mechanisms of action indicates that they may contribute to the development of CS in those at high risk.

Diuretics may also contribute to the development of post-MI shock [14]. The earliest effect of ischemia is usually a reduction in LV compliance. MI may cause pulmonary edema before a drop occurs in CO. The redistribution of intravascular volume to the lungs causes a clear decline in the volume of circulating plasma before heart failure. High-dose diuretics administered subsequently further reduce plasma volume. Low diuretic dose coupled with low-dose nitrates and positional measures to decrease preload (e.g., seated position with legs down) should be attempted in patients with MI and pulmonary edema to avoid precipitating shock. Excessive volume loading in patients with RV infarction may also cause or contribute to shock.

4. Treatment

4.1. Supportive treatment

For MI, giving aspirin and heparin routinely along with antithrombotic treatment is recommended. Since emergency coronary artery bypass grafting (CABG) therapy can be required

depending on the results of coronary angiography, clopidogrel therapy may be delayed to the period after emergency angiography. There are indications of clopidogrel in all patients who are to undergo PCI, and this will be useful in MI patients with shock depending on the information obtained from non-shock MI patients. The use of vasodilators including negative inotropes and nitroglycerin should be avoided. The arterial oxygen and pH levels should be kept within normal limits in order to minimize the ischemia. Intensive insulin therapy improves survival in critically ill patients with hyperglycemia and is a recommended course of action in complicated MI [27]. An easy indication should be established in order to initiate mechanical ventilation with mask or endotracheal intubation. Positive end-expiratory pressure reduces preload and afterload. Mechanical ventilation also reduces respiratory workload.

4.2. Hemodynamic management

Pulmonary artery (PA) (Swan-Ganz) catheterization is frequently recommended in order to confirm the diagnosis of CS. There has been a decline in the use of PA catheters following the controversy caused by a prospective observational study suggesting that PA catheters are associated with poor outcome [28]. The use of PA catheters in severely hypotensive patients with MI can be performed according to patient [27]. At present, many clinics do not prefer PA catheter for CS treatment anymore. Clinical assessment with ECHO is a reasonable alternative: Both PA systolic pressure and wedge pressure can be accurately estimated with Doppler ECHO. In particular, finding a short mitral deceleration time (≤140 ms) is highly predictive of pulmonary capillary wedge pressure ≥20 mmHg in CS [19].

4.3. Pharmacological treatment

According to the German-Austrian CSMI guideline, dobutamine should be preferred as an inotrope option, norepinephrine as a vasopressor option, and levosimendan over phosphodiesterase III inhibitors in case of refractiveness to catecholamines [29]. In the current IABP-SHOCK II trial, 74% of the patients with CSMI were treated with norepinephrine, 53% of them with dobutamine, 26% of them with epinephrine, 4% of them with levosimendan, and 4% of them with dopamine [5, 30].

Since the survival outcomes of high-dose vasopressor use are poor, pharmacological support including these agents should be kept to a minimum [31]. This indicates the underlying serious hemodynamic derangement and toxic effects. Inotropic agents play a central role in the treatment because the event initiating the shock is contractile dysfunction. Unfortunately, inotropes increase myocardial ATP consumption, so when the heart fails and supply is already limited, short-term hemodynamic healing occurs at the expense of increased oxygen demand. In order to provide coronary and systemic perfusion, the use of inotropic and vasopressor agents is required until IABP is placed or shock recovers. Norepinephrine is recommended in cardiac hypotension due to its high potential [27]. Both dopamine and norepinephrine have inotropic properties, but dobutamine is often required in addition.

4.3.1. Norepinephrine

The mean arterial pressure is effectively increased by intravenous infusions of norepinephrine at 0.1–1 μg/kg/min. According to the SOAP II study conducted using 1679 patients who

developed shock due to various etiologies, norepinephrine with a rate of 45.9% showed a 50.2% lower mortality rate compared to dopamine in the total population and produced significantly lower arrhythmia particularly atrial fibrillation (12.4 vs. 24.1%). Norepinephrine showed significantly better survival rates than dopamine treatment in the prospectively defined subgroup of CS patients [32].

4.3.2. Dobutamine

The inotropic dose range of dobutamine is between 2 and 20 μg/kg/min [33]. Based on the results of a multicenter cohort observational study on 1058 shock patients, following the German-Austrian guideline recommendations, the use of dopamine is an independent risk factor for mortality (p = 003), while this is not the case for dobutamine and norepinephrine [34]. Based on prospectively collected real-life data, epinephrine should be used only for resuscitation because it produces advanced organ damage and it is associated with higher mortality compared to dobutamine, levosimendan, and norepinephrine [35]. The European Association of Cardiology guidelines recommended the combination of levosimendan with a vasopressor agent in CSMI patients refractory to catecholamines or using it with a phosphodiesterase III inhibitor such as enoximone or milrinone, with or without dobutamine in intractable CS (ICS) patients [33]. The use of levosimendan or phosphodiesterase III inhibitors in shock patients who previously used chronic beta-blockers provides a better stabilization than dobutamine, and the results are similar to those with acute decompensated heart failure [36]. The German-Austrian CSMI guidelines recommend levosimendan, not PDE III inhibitors [29]. More importantly, PDE III inhibitors are not recommended at all in STEMI patients according to the guidelines of the European Society of Cardiology (ESC) [37].

4.3.3. Phosphodiesterase III inhibitors

Enoximone (Perfan™) and milrinone are selective PDE III inhibitors that increase inotropy and decrease systemic vascular resistance. They do not cause changes in myocardial oxygen consumption.

At the same time, they can be combined with dobutamine, because their combined inotropic effect is greater than that of dobutamine and PDE III inhibitor alone [38]. When "bridge to transplantation" was evaluated according to a prospective randomized trial, it did not prove superior to dobutamine, and it also caused high treatment costs [27].

4.3.4. Levosimendan (Simdax™)

Levosimendan, which has been used for the treatment of decompensated heart failure, is a calcium-sensitizing drug with inotropic agents. It increases the myocardial contractility with vasodilatory properties; meanwhile, diastolic relaxation is not impaired. It increased the cardiac contractility mediated by calcium sensation of troponin C, vasodilation through the opening of potassium channels on the sarcolemma of smooth muscle cells in the vasculature, and cardioprotection through the opening of mitochondrial potassium channels in the cardiomyocytes.

A single-center prospective randomized study comparing levosimendan and a PDE III inhibitor enoximone examined 88 patients with CSMI refractory to catecholamines. The endpoint

was identified as the resolution of shock, but the study was prematurely terminated by the ethics committee due to the significant superiority of levosimendan in the transient analyses. Only 32 CSMI patients could be evaluated. The primary endpoint of 30-day survival was found to be significantly higher in the levosimendan group than in the enoximone group (69% 11/16 vs. 37%, 6/16) [38]. According to nonrandomized trials, levosimendan has positive effects such as increasing CO, LV stroke work index, and systemic vascular resistance [39, 40]. It has also been documented to improve right ventricular function by increasing the RV cardiac power index (rVCPI) and decreasing pulmonary vascular resistance [39]. A small-scale study with 22 CSMI patients comparing levosimendan therapy with dobutamine treatment did not reveal any difference in 1-year mortality [41].

4.4. Percutaneous assist devices

Percutaneous circulatory support devices such as IABP, LV assist device (LVAD), or extracorporeal life support (ECLS) create treatment options for selected patients such as CS, cardiopulmonary resuscitation, or high-risk pPCI and CABG.

Percutaneous mechanical cardiac support (pMCS) devices, venoarterial extracorporeal membrane oxygenation (VA-ECMO), and ECLS applications are quite appealing for patients with CSMI because these therapeutic approaches offer an option that can improve cardiac output by avoiding the cardiotoxic effects of catecholamine therapy. IABP as passive pMCS and many active pMCS and VA-ECMO/ECLS are used [42–46]. However, in a review of an IABP-SHOCK II trial conducted on 600 patients with CSMI, it was observed that no benefit was provided in postinfarction CS treated with IABP and without mechanical complications compared to conventional treatment. This condition was downgraded from Class I (level of evidence C) to Class IIIA in the European guidelines [5, 47]. The use of active pMCS and VA-ECMO, and the advantages that they can create, should be respected. However, there are no high-quality RCTs supporting the general use of active pMCS in patients with refractory CSMI [48, 49]. As a result, ESC guidelines do not suggest the routine use of IABP in CS [33, 37, 50, 51]. It can be used simultaneously in refractory CS for a short term as a bridge leading to the implantation of a durable left ventricular assist device depending on the age, comorbid factors, and neurological status of the patient [52]. ECLS/VA-ECMO may provide a respiratory support in patients with the coexistence of severe cardiac and pulmonary insufficiency. Although there are no randomized trials that can assess ECLS/VA-ECMO in CS, observational studies have shown that it is useful in CS occurring during acute and chronic heart failure and cardiac arrest patients [53, 54]. Current ESC guidelines for heart failure suggest the use of ECLS/VA-ECMO or other support devices for the treatment of acute heart failure until cardiac and organ functions are improved in CS.

Extracorporeal Life Support Organization (ELSO) 2017 suggested that the use of ECLS/VA-ECMO should be considered when the mortality risk exceeds 50% despite optimal conventional treatment in case of acute severe heart or pulmonary failure, whereas it was suggested as a primary indication when the rate exceeds 80%. The main goal of the ECLS/VA-ECMO is to provide rapid circulatory and respiratory stabilization until an adequate improvement in cardiac loading is obtained in refractory CS. Although there are no controlled randomized

trials on the efficacy of ECLS/VA-ECMO, it was established as an indication of Class IIb in European guidelines and indication of Class IIa in American guidelines after observational studies demonstrated its beneficial effects on survival compared to conventional treatment [51, 54, 55]. Early application of ECLS/VA-ECMO was recommended to prevent imminent multi-organ failure since it maximizes cardiac recovery potential [46]. The ECLS VA-ECMO is also used in postcardiotomy CS occurring in the range 0.2–6% after cardiac operation [56].

There is a relative contraindication in patients that have recovered from life-incompatible conditions, in situations where preexisting conditions adversely affect the quality of life (the state of the central nervous system, end-stage malignancy, high-risk systemic bleeding complications), and in conditions that would not cause any benefit such as extreme old age or dependency; anatomical obstructions, if the treatment would take too long; or the existence of a fatal disease.

4.4.1. IABP

This has been the mainstay of mechanical CS treatment for a long period of time. IABP has become the most commonly used pMCS in the last decade. Some 10,000 IABPs were implanted in Germany alone in 2009 [57]. IABP, which is made of a polyurethane membrane mounted on a vascular 7.0–8.0 Fr catheter, is positioned in the descending thoracic aorta just distal to the left subclavian artery. This device matches its inflation and deflation times according to the cardiac cycle. The use of IABP improves coronary and peripheral circulation by increasing LV performance with diastolic balloon inflation and reduces afterload with systolic balloon deflation. IABP enables an increase in diastolic blood pressure and decrease in end-systolic pressure without affecting the mean blood pressure, cardiac output, cardiac power index, serum lactate levels, or by changing the doses of catecholamines. Accurate timing of inflation and deflation provides optimal support. Not all patients benefit from the support of IABP. It is a good prognostic indicator if it provides hemodynamic benefit [58]. If the procedure can be performed quickly, it should be applied as soon as possible before revascularization or transfer and in the presence of experienced operators. In the large National Registry of Myocardial Infarction, the use of IABP was independently associated with survival at centers with higher rates of IABP use [59], whether or not PCI, fibrinolytic therapy, or no reperfusion was used [43]. Some of the many nonrandomized trials on the use of IABP in CSMI are positive, but those with neutral outcomes have also been seen [46]. Sjauw et al. summarized the available data in a systematic review and meta-analysis on IABP in STEMI patients with and without CS including nine cohorts of patients with CSMI (n = 10,259). The use of IABP in patients treated with thrombolysis showed a significant decrease in 30-day mortality by 18% when compared to unsupported needs of highly revascularization rates. In contrast, the use of IABP in patients treated with pPCI showed a significant increase in 30-day mortality by 6% [60].

A randomized IABP-SHOCK trial conducted with 45 PCMI-treated patients with CSMI proved that the simultaneous administration of IABP did not correct multi-organ dysfunction syndrome (MODS) and hemodynamics [61]. When an IABP-SHOCK II trial that had been performed afterward was examined, it was seen that the administration of IABP along with early revascularization on 600 patients with CSMI had no effect on 30-day, 6-month, and

12-month mortality [5, 47]. In a review made by the Cochrane group, the treatment of IABP was compared with the standard treatment (n = 384) and three LVAD treatments (n = 45) in four randomized clinical trials covering a total of 790 patients with CSMI in which the majority of whom had been treated with the pPCI. No difference was noted in terms of 30-day mortality in the group treated with IABP compared to the group in which IABP was not used. It is thought that it can theoretically cause fewer complications and better support due to the improvement in the current technology coupled with improvements in automation, flexibility in treatment algorithms, and advances in placement speed and sheathless insertion thanks to its smaller catheter body, but there is no information to support these considerations.

IABP has rare but serious complications such as major bleeding, stroke, and local and systemic infections. When compared with LVAD and ECLS, it has the lowest complication rate. Limb ischemia is the most commonly occurring vascular complication, but their rates have been reduced due to its small-diameter catheter and sheathless insertion. Aortic dissection, retroperitoneal hemorrhage, femoral hematomas, arteriovenous fistulas, and femoral pseudoaneurysms, which may be seen in any femoral artery procedure, may also occur in IABP. Ischemia and necrosis in certain areas may occur with the embolization of aortic atherosclerotic components to the peripheral vascular bed. Visceral organs may be affected adversely as a result of inappropriate balloon catheter diameter and placement. In contrast to all of these clinical observations, randomized IABP-SHOCK II trial revealed that high complication rates secondary to IABP were not observed in patients treated with IABP.

4.4.2. LVADs

LV assist devices (LVADs) are theoretically appealing since they break the vicious ischemia cycle by providing temporary circulatory support, breaking hypotension and myocardial dysfunction, enabling recovery from the stunned and hibernating myocardium, and allowing the reversal of neurohumoral change. Active pMCS is hemodynamically more potent than IABP [42, 43, 46, 48]. However, device-related complications and permanent organ damage are the most important limiting factors. LVADs support the return of the oxygenated blood drained from the left side of the heart into the systemic arteries with pulsed circulation or continuous flow by circulating it through a device. Surgically implanted LVADs pump the blood taken from the apex of the left ventricle via a cannula.

4.4.2.1. The TandemHeart (CardiacAssist Inc., Pittsburgh, PA)

The TandemHeart is a left atrial-to-femoral arterial LVAD device. It drains the blood through a cannula placed in the left atrium entering from the femoral vein transseptally. The blood returns to a systemic artery, the femoral artery, and perfuses into the thoracic and abdominal aorta in a retrograde manner. The system is capable of delivering flow up to 4.0 L/min at 7500 rpm. The patients with CSMI treated with TandemHeart and Impella® family placed by passing through the aortic valve and pPCI were evaluated in small randomized clinical trials [48]. In the meta-analysis of four trials randomizing 148 patients treated with TandemHeart, Impella®, or Impella CP®, the results were compared with the patient group treated with IABP [48, 62–65]. Although hemodynamics were better in patients treated with pMCS, no

significant difference was detected in terms of mortality, but complications such as bleeding and leg ischemia were higher in that group.

4.4.2.2. The Impella® (Abiomed)

The Impella® pump is a nonpulsatile axial flow pump consisting of a suction cannula with a turbine positioned in the LV in order to push the blood into the ascending aorta. It has three versions 2.5, 5, and CP. Impella® is inserted through the femoral artery by 2.5 and CP standard catheterization procedures into the ascending aorta and then placed in the left ventricle by passing it through the aortic valve. The inlet area, located at the distal tip of the cannula, has four openings that allow the blood to be drained into the inlet and channeled through the cannula. The placement of Impella 5.0® is the same except that it requires surgical cutdown. The axial flow pump system reduces the left ventricular load and causes a reduction in the LV wall stress.

The Impella 2.5®, Impella CP®, Impella 5.0®, and Impella LD® catheters, in conjunction with the Automated Impella® Controller (collectively, "Impella® System Therapy"), are temporary ventricular support devices intended for short-term use (≤4 days for the Impella 2.5® and Impella CP® and ≤6 days for the Impella 5.0® and Impella LD®) and indicated for the treatment of ongoing cardiogenic shock that occurs immediately (<48 h) following acute myocardial infarction or open heart surgery or in the setting of cardiomyopathy, including peripartum cardiomyopathy, or myocarditis as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures (including volume loading and use of pressors and inotropes, with or without IABP). The intent of Impella® System Therapy is to reduce ventricular work and to provide the circulatory support necessary to allow heart recovery and early assessment of residual myocardial function (http://www.abiomed.com/impella/impella-25) (**Figure 1**).

4.4.2.3. HeartMate PHP (Thoratec Corporation)

This axial device system is composed of a percutaneously inserted, Nitinol-covered cannula through the femoral artery, integrated with a tribune (impeller) having a diameter of 13 Fr. Its major design feature is a collapsible elastomeric impeller and Nitinol cannula giving this device the lowest profile insertion cannula with the highest flow. When it is placed by passing through the aortic valve once, it may create a continuous flow of more than 4 L/min at reasonable operating speeds, resulting in reduced LV end-diastolic pressure and volume. When it has to be replaced again, the system collapsed by 13 Fr. The information is limited to a small registry trial made up of 46 patients, and the results of which have not been published yet.

4.4.2.4. The iVAC 2L (Terumo Interventional Systems)

The iVAC 2L system is introduced percutaneously through the femoral artery and can provide a pulsatile support of approximately 2 L/min using an extracorporeal membrane pump via a 17 Fr cannula. In the systolic phase of the heart, the blood is aspirated from the LV through the catheter lumen into the membrane pump. During the diastolic phase, the pump

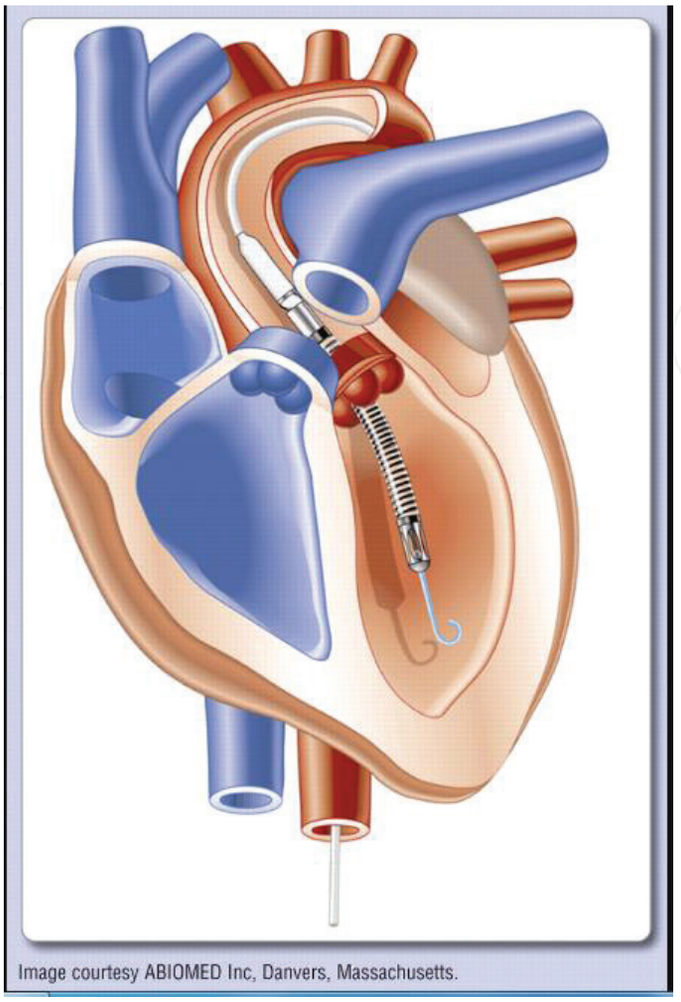


Figure 1. Installation of Impella®.

ejects the blood back through the catheter, then reopens the catheter valve, and delivers the blood to the ascending aorta through the side outflow port, thereby creating an "extra heart beat." Data are limited to a small case series, and the clinical impact of this device needs to be investigated further (**Figure 2**).

4.4.3. VA-ECMO

Advances made since the introduction of the first cardiopulmonary bypass system in 1953 have enabled the development of percutaneous devices. In fact, today's VA-ECLS devices consist of venous and arterial cannulas, tubing, a membrane oxygenator with gas blender, a continuous flow centrifugal pump, and a heat exchanger compensating for heat loss originating from extracorporeal circulation. Generally, a 16–19 Fr arterial cannula is placed in the ascending aorta, and an 18–21 Fr venous cannula is placed in the right atrium. The blood drained from the right atrium is pumped into the heat exchanger and membrane oxygenator and eventually returns to the femoral artery. The blood is drained from the main points separated from cardiopulmonary bypass (CPB) devices into an open reservoir passively, whereas there is a closed circuit in the VA-ECLS devices, and negative pressure is applied for venous blood

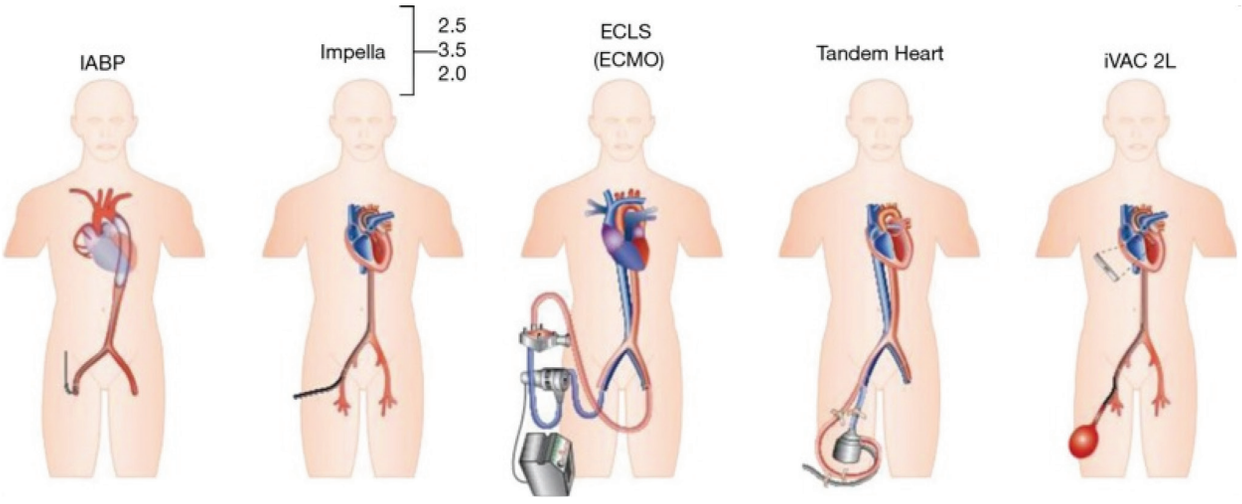


Figure 2. Mechanical cardiac support devices.

return [66]. The pump continues to provide pulsatile arterial blood pressure with the continuous flow until the circulation is fully supported by a cardiopulmonary bypass device. ECLS is used in LV, RV, and biventricular insufficiency with the flow exceeding 5 L/min.

Venoarterial extracorporeal oxygenation or its synonym extracorporeal life support (ECLS) and LVAD were commonly used as a bridge for heart transplantation in CS patients [67]. ECLS takes the blood circulation out of the body into a membrane oxygenator and takes some of the workload of the right and left heart and lungs. While anticoagulation is required for ECLS and percutaneous LVAD, it may be optional for surgically implanted LVADs. In reports concerning the large LVAD series, 74% of 49 surviving patients underwent transplantation, and 87% of the transplant patients in whom LVAD was placed surgically also survived and were discharged [68, 51]. Although early LVAD and extracorporeal life support and subsequently transplantation have been recommended as an alternative approach to emergency revascularization, these non-systematic direct comparative and observational studies have yielded contradictory results. In a study conducted with surgical LVAD with and without CABG, the mortality was found to be higher in patients with CABG in whom LVAD was inserted in the early period after MI [69].

While VA-ECMO may support pulmonary functions along with cardiac functions, they also have the advantage of being implanted in distant centers [46, 70]. After the publication of the neutral results of the IABP-SHOCK trial, the number of VA-ECMO applications increased dramatically [57]. The application number was 500 in Germany in 2012 increasing to 3000 in 2014 [57]. This worrisome increase in the use of VA-ECMO in CSMI patients is a very serious issue that needs to be assessed in more detail since it does not rely on concrete evidence but rather on conventional wisdom based on pathophysiology and the positive results published in observational studies [49, 71]. An increase of 3–6 L/min in the flow, which is provided by VA-ECMO and which is necessary, cannot ensure the survival of CSMI patients. There are drawbacks involved in using these devices as a result of the high rates of complications such as the large cannula sizes, major bleeding, lower extremity ischemia, compartment syndrome, amputation, stroke, severe infections, difficult weaning, lack of direct left ventricular unloading, and increase in afterload [72, 73]. Attempts to counteract the problem of left

ventricular loading and increase in afterload with VA-ECMO are being made with the combination of an unloading device such as IABP or the use of Impella® [74, 75]. Better weaning and lower in-hospital and 28-day mortality were reported with Impella® of VA-ECMO along with IABP in a propensity-matched national registry [74]. Considering the lack of RCTs, systematic reviews should be taken into account as well as two small nonrandomized registries (n = 95) comparing VA-ECMO with IABP and Impella® and two other studies (n = 140) conducted with Impella RD® and TandemHeart [54, 75]. Considering the 30-day survival rate of VA-ECMO, in this meta-analysis, it is obviously superior to IABP with 33% absolute survival rate. No benefit was observed when compared with ECLS and pMCS (Impella®, TandemHeart). In conclusion, the total meta-analysis did not indicate any significant benefits. When addressed as a whole, the meta-analysis data of VA-ECMOs/ECLS and pMCS are inconsistent: on the one hand, pMCSs are not better than IABP, whereas, on the other, VA-ECMOs/ECLS are better than IABP while they are not better than pMCSs. Of course, there is a need for higher-quality RCTs to be able to answer the questions about the routine use of VA-ECMO/ECLS in treatment-resistant CS patients [44, 49]. It is seen that 75% of the survivors after ECLS are able to go about their daily life, 25% of them return to work or school, and 57% of them are not limited in their usual activities. However, when compared to a normative age-matched population, significantly lower quality-of-life indices are reported [76].

4.5. Reperfusion

Coronary revascularization probably with pPCI should be planned as soon as possible in STEMI/NSTEMI patients with impaired pump function. In the IABP-SHOCK II trial conducted with 600 patients between 2009 and 2012, emergency coronary revascularizations were performed with pPCI in 95.8% of them and with CABG in 3.5% usually after unsuccessful pPCI, and revascularization was not performed only in 3.2% of them [5]. Early coronary revascularization is the key recommendation for treatment of CSMI patients [29, 32, 33, 37, 50, 51]. The SHOCK trial conducted with 302 CSMI patients between 1993 and 1998 revealed a tendency for early revascularization compared to conservative treatment whether with pPCI (64%) or CABG (36%) in terms of 30-day mortality (56.0 vs. 47.6%; $p = 0.11$) [77]. However, the 6-month (49.7 vs. 36.9%; $p = 0.027$), 12-month (46.7 vs. 33.6%; $p < 0.04$), and even 6-year (32.8 vs. 19.6%; $p = 0.03$) survival rates, for early revascularization, are significantly high [77–79]. SMASH (Swiss Multicenter Trial of Angioplasty for SHOCK) trial, which is the second study suitable for early coronary revascularization, was prematurely terminated due to low participation after only 55 CSMI patients were included. This study seemed neutral regarding 30-day mortality [5]. The low mortality rates of CSMI patients in the data registry reports of numerous countries such as France, Italy, Switzerland, Sweden, and the United States in the past 30 years were attributed to the increased rates of pPCI [3]. The "real-world" situation in Germany is reflected by the registry data addressing 2.818 CSMI-treated patients, of whom 85% were treated with pPCI, 4.2% with CABG, and 8.9% with noninterventional treatment. Hospital mortality rates were 42% for pPCI, 21.7% for CABG, and 47.8% for noninterventional treatment [80].

4.5.1. Types of revascularization

The preferred approach is primary percutaneous coronary intervention (pPCI). The decision to carry out revascularization in CSMI patients with multivessel disease or left main coronary

artery should be made depending on the patient's medical information, coronary anatomy, procedural risks, potential delays in treatment, and patient preferences in cooperation with a "heart team" composed of cardiologists and surgeons [32, 81, 82]. Registry data indicated similar mortality rates between pPCI and CABG, while they sometimes suggested that CABG was better [80, 81]. Chest pain units and shock centers in the network generated for MI patients should allow to rapid transfer of CSMI patients to those centers where cardiac catheterization and pPCI are performed [33, 37, 83]. Only in cases in which emergency cardiac catheterization cannot be performed in a reasonable time period, systemic fibrinolysis should be preferred as the second best option, and cardiac catheterization should be performed because systemic fibrinolysis is not as effective as catheter revascularization [84].

The standard concept for pPCI in CSMI patients is reopening only the culprit coronary lesion. Even though 70–80% of CSMI patients in fact have multivessel disease, the mortality rate of opening multiple vessels in the same session is high. According to the registry data of the IABP-SHOCKII trial, a significant difference could not be demonstrated between multivessel pPCI and the culprit lesion only pPCI in terms of 12-month mortality [85]. The European Society of Cardiology guidelines recommend the implantation of a drug-eluting stent (DES) over bare metal stents (BMS) in patients with STEMI and also in NSTEMI patients with acute coronary syndrome [29, 37]. However, the roles of DES and BMS are still indefinite. All the long-term causes of mortality were better in those who underwent DES implantation, while the other two were neutral in a retrospective analysis [86, 87]. Still, even though using DES instead of BMS does not have any adverse effect, the use of DES is still recommended in CSMI patients.

5. Conclusion

Examining the patients with CS, we can see that we have many problems to deal with and solve. Due to ever-increasing risk factors for MI, particularly due to rapidly increasing world population, aging populations, and tobacco use, the number of CS patients is increasing day by day despite the serious advances and solutions in ACS. Although pMCS devices manufactured specifically with advancing technology are considered to be good solutions, they do pose new and serious problems. They are not suitable for every country or society due to their high application and device costs and particularly due to the fact that they cannot guarantee life. We need to allocate more resources to the abovementioned problems for the sake of public health through the world, and we need to produce pMCS devices that are suitable for each population, easy to apply, inexpensive, transportable, permanent, and effective so that the patient can be transferred to a cardiac center no matter where the patient is. One clear fact revealed by this study is the lack of clarity with respect to pMCS indications due to a low number of controlled randomized clinical trials. Early and effective revascularization is the best treatment option for CS. To this end, those organizations operating on both national and global bases are going to play the most active role for the short-term and long-term survival of patients.

Conflict of interest

None declared.

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