UPDATES ON CARDIOGENIC SHOCK: DIAGNOSIS AND MANAGEMENT

Laksono S[1,2], Pandu Pratama A[3], Yogibuana Swastika Putri V[4], Astuti A[5], Kusharsamita H[6], and Halomoan R[7].
[1]Department of Cardiology and Vascular Medicine, Siloam Diagram Heart Hospital, Depok, Indonesia
[2]Faculty of Medicine, Universitas Muhammadiyah Prof. DR. Hamka, Tangerang, Indonesia
[3]Department of Cardiology and Vascular Medicine, RSUP Mohammad Hoesin, Palembang, Indonesia
[4]Department of Cardiology and Vascular Medicine, RSUD Saiful Anwar, Malang, East Java, Indonesia
[5]Department of Cardiology and Vascular Medicine, RSUP dr Hasan Sadikin, Bandung, West Java, Indonesia
[6]Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[7]Faculty of Medicine, Universitas Katolik Indonesia Atma Jaya, Jakarta, Indonesia

Correspondence:
Sidhi Laksono,
Faculty of Medicine, Universitas Muhammadiyah Prof. DR. Hamka,
Tangerang, Indonesia
Email: sidhilaksono@uhamka.ac.id

Abstract

Cardiogenic shock (CS) is a complex condition causing end-organ hypoperfusion and high mortality rates especially in patients with acute myocardial infarction. It remains a challenge for clinician to provide good outcomes despite the development of evidence-based therapeutic strategies, especially for interventional management. Although there has been an improvement in survival, the mortality remains high. There are still many uncertainties regarding the best treatment, as clinicians need to weigh the risks and benefits. This review aims to elaborate the latest updates in the field of CS. To enhance contractility and systemic vascular resistance and hence avoid organ damage, inotropic and vasopressin agents are often administered in the therapy of CS. Despite their usefulness and widespread use, administration of these medicines requires close monitoring and the lowest effective dosage administered in the shortest amount of time possible to prevent adverse effects including increased oxygen demand, arrhythmia, and impaired microcirculation of the tissue. When pharmacological agents fail to provide an adequate response, mechanical circulatory support (MCS) devices like the intraaortic balloon pump (IABP), left ventricular assist devices (LVAD), venoarterial extracorporeal membrane oxygenation (VA-ECMO), and revascularization become an option to provide haemodynamic support.

Keywords: Cardiogenic Shock, Classification, Diagnosis, Management

Introduction

Cardiogenic shock (CS) is usually defined as physiological state in which cardiac pump function is inadequate for tissue perfusion resulting in reduced cardiac output, end-organ hypoperfusion, and hypoxia (1, 2). Acute myocardial infarction (AMI) is often the cause of cardiogenic shock, which is around 70%, and also occur in 5-8% patient with ST segment elevation myocardial infarction (STEMI) (3-5). CS also occurs more often in STEMI than non-STEMI (NSTEMI) patients (6). Clinical presentation is usually characterized by persistent hypotension despite appropriate fluid replacement and is accompanied by signs of end-organ hypoperfusion requiring pharmacological or mechanical intervention (2). Although the reperfusion therapy and percutaneous mechanical circulatory support (MCS) devices have markedly improved, the mortality in CS remains high at 25% to 50% (7, 8). Albeit the accurate pathophysiology of the disease is less understood, early diagnosis and intervention are crucial for survival. This article aims to review and update the definition, pathophysiology, diagnosis, and management of CS.

Definition

CS is defined by clinical features dan reduced cardiac output and associated hemodynamic findings. Clinical findings of reduce cardiac output includes cool extremities, weak distal pulse, altered mental status (AMS), and decreased urine output (UO) (< 30 mL/h) (2). Hemodynamic findings on CS are reduced cardiac output without the evidence of hypovolemia. The hemodynamic criteria that is often used is from Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, consists of: (1) systolic blood pressure (SBP) < 90mmHg for at least 30 minutes (or requires medications or devices to maintain SBP ≥ 90 mmHg), (2) Pulmonary capillary wedge pressure (PCWP) > 15 mmHg (which excludes hypovolemia), and (3) a cardiac index (CI) of < 2.2 L/min/m^2. (9, 10). Whereas the intra-aortic balloon pump (IABP)-SHOCK II trial is the

same with SHOCK trial criteria but without cardiac index (Table 1) (11).

Table 1: Cardiogenic shock defined by guidelines and trials.

Guidelines/Trials	Criteria
SHOCK trial (1999) (10)	• SBP < 90mmHg for > 30 minutes or vasopressor support to maintain SBP > 90 mmHg • Signs of end-organ damage (UO < 30 mL/h or cool extremities) • Hemodynamic criteria: CI < 2,2 and PCWP > 15 mmHg
IABP-SHOCK II (2012) (11)	• Mean arterial pressure (MAP < 70mmHg or SBP < 100 mmHg despite adequate fluid resuscitation (at least 1 L of crystalloids or 500 mL of colloids) • Evidence of end-organ damage (AMS, mottled skin, UO < 0,5 mL/kg/h, or serum lactate > 2 mmol/L)
Euro Heart Survey Percutaneous Coronary Intervention Registry (EHS-PCI) (2012) (12)	• SBP < 90 mmHg for 30 minutes or inotropes use to maintain SBP > 90 mmHg • Signs of end-organ damage and increased filling pressure
European Society of Cardiology Heart Failure (ESC-HF) guideline (2016) (13)	• SBP < 90 mmHg with appropriate fluid resuscitation with clinical and laboratory evidence of end-organ damage • Clinical signs: cold extremities, oliguria, AMS, narrow pulse pressure. Laboratory findings: metabolic acidosis, elevated serum lactate, elevated serum creatinine
Korean Acute Myocardial Infarction Registry-National Institute of Health (KAMIR-NIH) (2018) (14)	• SBP < 90 mmHg for > 30 minutes or supportive intervention to maintain SBP > 90 mmHg • Evidence of end-organ damage (AMS, UO < 30 ml/h, cool extremities)

AMS: altered mental status
SBP: systolic blood pressure
UO: urine output

Society for Cardiac Angiography and Interventions (SCAI) proposed a new classification of cardiogenic shock to allow easier way to differentiate patient subsets, which mean there is no need for calculation and also suitable for rapid assessment (Figure 1). The SCAI classification was based on Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification (INTERMACS). INTERMACS classification is also easy to use but it does not distinguish between patients who were placed on extracorporeal membrane oxygenation (ECMO) support and patients that are stable on inotropes, on IABP, nor those who received an Impella catheter to improve cardiac output while on inotropes (15).

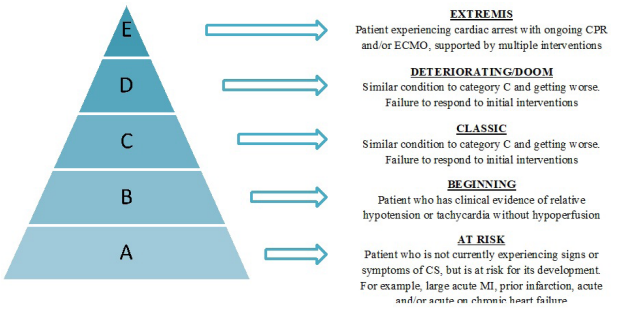


Figure 1. SCAI cardiogenic shock classification[15]

CPR: Cardiopulmonary Resuscitation; CS: Cardiogenic Shock; ECMO: Extracorporeal Membrane Oxygenation; MI: Myocardial Infarction

Figure 1: SCAI Cardiogenic shock classification (15)

Epidemiology

CS incidence among patients with AMI remains stable at 3-10%, but the case proportion associated with AMI decreased over time to 30% and CS and CS cases caused by decompensated heart failure has steadily increased (16). A study by Berg et al. (4) that was done on cardiac intensive care units (CICU) in North America reported among 667 patients admitted with shock, 66% were assessed as cardiogenic shock. And among the patients with CS, 30% were caused by AMI complicated by CS (AMICS), 28% by non-ischemic cardiomyopathy, 18% by ischemic cardiomyopathy, and 17% were caused by other than primary myocardial dysfunction. While other study by Lang et al. (17) the CS incidence has increased up to 65.6% from 2007 until 2017, and 38.5% patients were women and had mean age of 71 years. Kolte et al. (18), also have similar reports where CS was more common in patients older than 75 years old than in those younger than 75 years old (9.4% versus 7.3%; P < 0.001), in women than in men (8.5% versus 7.6%; P < 0.001), and in Asians and Pacific Islanders than in whites, African-Americans, and Hispanics (11.4% versus 8%, 6.9%, and 8.6%, respectively). In-hospital mortality in contemporary registries was estimated to be around 30%-40%, which suggest an improvement in CS outcomes over the last decades (16).

Pathophysiology and etiologies of cardiogenic shock

Generally, CS is an acute disturbance that leads to impaired cardiac output, preceded by gradual damage that results in insufficient and maladaptive compensatory mechanisms and rapid degradation to end-organ hypoperfusion (6, 19). Compensatory peripheral vasoconstriction may enhance coronary and peripheral perfusion initially, but it will result in blood mobilization from the splanchnic region, which results in increased cardiac afterload and burdens injured myocardium (2). As a result, oxygenated blood flow to peripheral tissue and eventually the cardiac (20).

Furthermore, fluid from the interstitium is migrated into the blood. Decreased kidney perfusion causes

the renin–angiotensin–aldosterone axis to become activated. An inflammation-like response occurs following hypotension and blood pressure restoration, or ischemia and reperfusion, resulting in the activation of many inflammatory pathways (21). Pathological vasodilation is caused by systemic inflammation, which releases nitric oxide synthase and peroxynitrite, which have cardiotoxic inotropic effects (21). Interleukins and tumor necrosis factor-alpha (TNF-α) are two systemic inflammatory mediators that cause vasodilation and contribute to death in CS patients (22).

The most frequent cardiac cause of cardiogenic shock is an acute left ventricular failure in the presence of a STEMI. This is commonly related to anterior wall myocardial infarction and occurs in about 79% of cardiogenic shock patients (23). When a significant portion of the left ventricular myocardium becomes ischemic or necrotic and fails to pump, stroke volume and cardiac output decline. Hypotension and tachycardia compensate for myocardial perfusion, which relies on the pressure gradient between the coronary artery system and the left ventricle and the duration of diastole, worsening ischemia. The increased ventricular diastolic pressures induced by pump failure further decrease coronary perfusion pressures, and the added wall stress raises myocardial oxygen needs, exacerbating ischemia further. Reduced ventricular output also impairs systemic perfusion, resulting in lactic acidosis and subsequent deterioration of systolic function (24).

When the myocardial function is impaired, numerous compensating responses such as sympathetic stimulation to raise heart rate and contractility and renal fluid retention to enhance preload are activated. When cardiogenic shock develops, these compensating responses might become ineffective and exacerbate the condition. Elevated heart rate and contractility increase myocardial oxygen demand and worsen ischemia (24). Tachycardia and ischemia can produce fluid retention and poor diastolic filling, leading to pulmonary congestion and hypoxia. Vasoconstriction to maintain blood pressure raises myocardial afterload, further decreasing cardiac function and raising myocardial oxygen demand. This increasing demand, along with insufficient perfusion, increases ischemia and initiates a vicious cycle that, if not terminated, results in death. The cessation of this cycle of myocardial dysfunction and ischemia serves as the foundation for cardiogenic shock treatment (24).

The incidence of mechanical complications of ischemic heart disease are severe mitral regurgitation (7%), ventricular septal rupture (4%), right ventricular failure (3%), and tamponade (1.4%). The most fatal of these cardiac causes is ventricular septal rupture (6). Nonischemic cardiac disorders might also cause cardiogenic shock (Table 2). It is essential to explore these nonischemic etiologies in patients with classic cardiogenic shock signs and symptoms without specific electrocardiogram (ECG) abnormalities and negative laboratory values for myocardial infarction (1). Consideration of these non-ischaemic etiologies highlight that cardiogenic shock is generally associated with abruptly decreased ejection fraction, and cardiogenic shock is a physiological state of depressed cardiac output that is anatomically not well defined and can exist with just mildly impaired ejection fraction (25).

Table 2: Nonischaemic aetiologies of cardiogenic shock (1)

Etiology	Example
Pharmacologic	• Beta-blockers • Calcium channel blockers • Digoxin toxicity
Primary ventricular dysfunction	• Acute myocarditis • Stress cardiomyopathy (i.e., Takotsubo • cardiomyopathy) • Nonischaemic cardiomyopathy (e.g., sarcoidosis, amyloidosis, hemochromatosis)
Outflow obstruction	• Valvular stenosis • Left ventricular outflow obstruction (e.g., in hypertrophic cardiomyopathy)
Acute valvular regurgitation	• Trauma • Degenerative disease • Endocarditis
Endocrine	• Severe hypothyroidism
Pericardial disease	• • Cardiac tamponade Pericardial constriction
Tachyarrhythmias	• Supraventricular/atrial tachyarrhythmias • Monomorphic VT Polymorphic VT (i.e., Torsades de Pointes)
Bradyarrhythmias	• Sinus node dysfunction (e.g., sick sinus syndrome) • AV node dysfunction (e.g., AV nodal block)

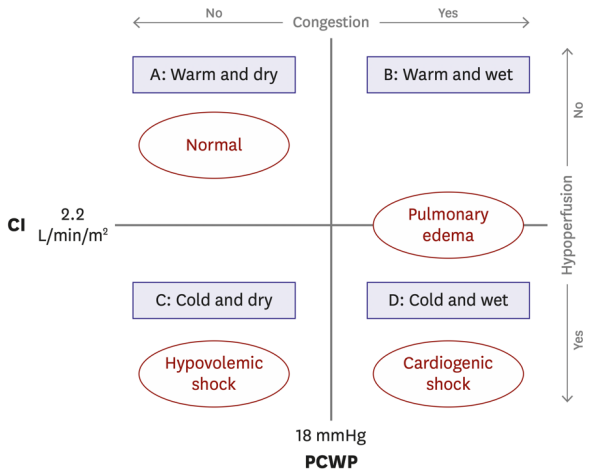
AV: atrioventricular
VT: ventricular tachycardia

Large regions of non-functional but viable myocardium, on the other hand, might induce or contribute to the development of cardiogenic shock in individuals following myocardial infarction. Myocardial stunning is a kind of postischemic dysfunction that continues after restoring normal blood flow; nonetheless, myocardial performance recovers entirely. Initially described in animal models of ischemia and reperfusion, stunning is now acknowledged in therapeutic settings. In patients with persistent wall motion abnormalities following angioplasty for acute coronary syndromes, direct evidence for myocardial stunning was identified using positron emission tomography; perfusion assessed by 13N-ammonia was normal in the context of persistent contractile dysfunction (26). The etiology of stunning is unknown, although it appears to include a combination of oxidative stress, disruptions of calcium

homeostasis, and reduced myofilament response to calcium (27).

Diagnosis

The symptoms developed on CS depend on the cause. Patients with AMI often have typical history of acute onset of chest pain, possibly in the setting of known coronary artery disease (9). Patients with CS usually present with cool extremities and evidence of pulmonary congestion. This presentation is termed "cold and wet" that indicates a reduced cardiac index, increased systemic vascular resistance, and increased PCWP. There is also a "dry and cold" that implicate an euvolemic state indicating reduced CI, increased systemic vascular resistance and normal PCWP. Patients with euvolemic presentations were less likely to have previous history of MI or chronic kidney disease compared with patients with the classic "cold and wet" features. Another presentation of CS is the "wet and warm" subtype that indicates reduced CI, low-to-normal systemic vascular resistance and an increased PCWP which is often under-recognized (Figure 2) (28).



CI = cardiac index; PCWP = pulmonary capillary wedge pressure.

Figure 2: Clinical classification of acute heart failure (28)

Cardiac catheterization is both used as definitive diagnostic investigation and guides therapeutic intervention in AMICS (20). Before cardiac catheterization is done, patient need to undergo several initial investigations and non-interventional management strategies. Electrocardiogram (ECG) should be ordered within 10 minutes of presentation. The ECG is useful to differentiate the cause of CS. Patient with coronary disease and AMI may show both STEMI (new infarct) or Q wave (old infarct). NSTEMI can also results in CS. ECG can also help with diagnosing arrhythmia contributing to CS. Chest radiography can show cardiomegaly and signs of pulmonary congestion in patients with severe left heart failure (9).

Laboratory investigations such as complete blood counts and metabolic panels should be ordered every 12 to 24 hours. N-terminal pro-B-type natriuretic peptide (NT-proBNP) will increase during an acute decompensated heart failure. In CS caused by acute coronary syndrome (ACS), elevated levels of natriuretic peptides are associated with higher mortality. Troponins are usually trended every 6 hours starting from initial clinical suspicion. Lactic acid should also be trended every 1-6 hours to evaluate response to initial resuscitation. Echocardiography assessment is very helpful in diagnosing CS as it can be done rapidly at bedside and is noninvasive. Complication from acute infarction and other additional information such as valvular stenosis or regurgitation can be detected. But all the initial investigations should not delay cardiac catheterization (20).

Management of cardiogenic shock

Initial treatment

Early stabilisation is a crucial step for clinical improvement. Oxygen should be given for hypoxic patients to maintain the oxygen saturation above 90%. Oxygenation in non-hypoxic patient is potentially harmful due to the elevation of coronary vascular resistance (29). Oxygenation should be accompanied by monitoring for saturation using pulse oximetry. In a setting which non-invasive oxygenation is not adequate, switching to invasive technique is required. Low tidal volume should be administered to prevent pulmonary complications and right ventricular failure (RVF). Assessment of volume status should be done to rule out hypovolemia. The presence of hypovolemia in CS should be corrected with fluid loading (21).

Inotropes and vasopressors

Inotropic and vasopressin agent are commonly used in management of CS to increase contractility and systemic vascular resistance, prevent any organ damage. Despite their benefit and frequent use, administration of these agents should be carefully monitored and given at the lowest dose in a short time as they might increase the demand for oxygen, induce arrhythmia, and impair microcirculation of the tissue.

For patients with severe hypotension (systolic blood pressure less than 70 mmHg) or hypotension refractory to previous drugs, norepinephrine is the drug of choice over dopamine because of an increased risk of arrhythmias and mortality. Patients who have recently had a myocardial infarction should be especially cautious when given norepinephrine because of the risk of tachycardia and increased myocardial oxygen demand. Dobutamine is often utilized because it exhibits beta-1 and beta-2 agonist characteristics that increase myocardial contractility, decrease left ventricular end-diastolic pressure, and raise cardiac output (30).

There is still uncertainty and a lack of evidence regarding which agents are most effective in treating CS (31). In Sepsis Occurrence in Acutely III Patients (SOAP II trial) comparing

dopamine and norepinephrine in CS patients, dopamine was more harmful as it was related to higher risk of mortality after 28 days. There were significantly more cases of arrhythmia, mainly atrial fibrillation, in the dopamine group compared to the norepinephrine group (32). However, the result of this study might be confusing due to the lack in stating the definition, evaluate the different management between various CS phenotypes, and did not report any important prognostic variables. Another study by Rui et al., comparing dopamine and norepinephrine, showed that norepinephrine was less harmful with lower mortality and lower risk of arrhythmia. Dopamine and norepinephrine both belong to the catecholamine group and may raise blood pressure to correct CS, but their primary mechanisms of action are quite different. In the sympathetic nervous system, norepinephrine acts as an endogenous agent that strongly stimulates the a-adrenergic receptor and has a less impact on the b-adrenergic receptor. As a potent vasoconstrictor, norepinephrine has a dose-dependent impact on the cardiovascular system. Doses between 0.01 and 3.3 mg/kg/min are advised. Dopamine is a precursor to norepinephrine, the effect of which also depends on how many doses are used. Doses between 2 and 10 mg/kg/min cause b receptor stimulation and a rise in heart rate and cardiac contractility (33).

Other option to combine dobutamine and norepinephrine is also available to improve haemodynamic status in CS patients with lower risk of developing rhythm disorder, lower heart rate, and less lactate acidosis (34). Levosimendan, a Ca^{2+}-sensitising agent, could improve cardiac contractility without increasing the oxygen demand and promote vasodilation (reducing afterload) (35). Levosimendan administration also provides the ability to modulate oxidant-antioxidant balance. This ability in mitochondrial level would benefit CS patients to exert cardioprotective effect (36). In CS patients with evidence of RVF, vasopressin is preferred as it is associated with less constriction of pulmonary vasculature (1). Clinical judgement by the physicians is essential in deciding the treatment strategy.

Mechanical Circulatory Support (MCS)

Despite the frequent use of inotropes and vasopressors, the effort to maintain perfusion pressure and prevent organ damage remain a challenge. Furthermore, increased use of inotropes and vasopressors are related to higher mortality. MCS devices become the option to provide haemodynamic support without increased risk of myocardial damage and in condition where pharmacological agents failed to give adequate response. Options for MCS devices used in CS are presented below (Figure 3).

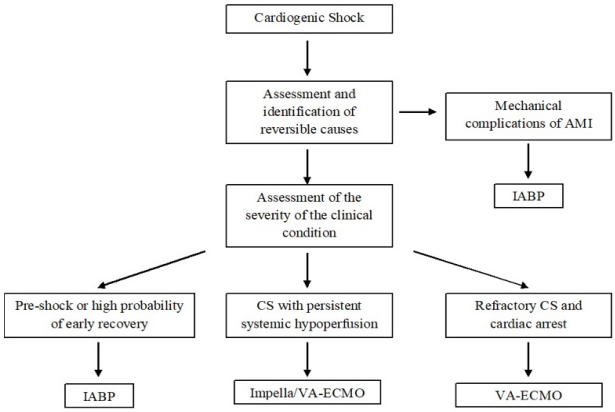


Figure 2. Algorithm for selecting the proper MCS device in CS patients

AMI: Acute Myocardial Infarction; CS: Cardiogenic Shock; IABP: Intra-aortic Balloon Pump; VA-ECMO: Venoarterial Extracorporeal Membrane Oxygenation

Figure 3: Algorithm for selecting the proper MCS device in CS patients

Intraaortic balloon pump

For many years, the intraaortic ballon pump (IABP) remain the most commonly used device in CS, especially due to acute myocardial infarction. Early result from SHOCK trial was able to show higher rate of survival in patients with improved haemodynamic after IABP procedure (37). However, in the largest randomised multicentre IABP SHOCK-II trial in 600 CS patients, IABP failed to show any outcome benefits in haemodynamic status, length of stay in the intensive care unit, and 30-day mortality (11). Further long-term follow-up (6.2 years) for IABP-SHOCK II trial was performed and the mortality was not significantly different between the IABP group and control group (38). The result of this recent study supported the recommendation to not routinely perform IABP and the procedure should be performed in selective patients.

Left-ventricular assist devices

There are numerous LVAD available for mechanical cardiac support. Impella is among the most widely used in CS. Impella devices are axial flow pumps, inserted through femoral artery and passed into the left ventricle. The Impella devices have the ability to maintain circulatory support by 2.5-5.0 L/min, depends on their size. Compared to IABP, Impella works independent of cardiac function--could unload the left ventricle and support arterial pressure at the same time (20).

Despite the ability to maintain adequate circulation, real-world data are sparse. A clinical study of 250 patients from

2004-2016 did show that Impella as a treatment for CS after acute myocardial infarction was feasible, despite the 30-day mortality was 56.2% and 6-month mortality was even higher (60.7%). Several complications also occurred including bleeding, haemolysis, vascular complications, and stroke (39). High mortality is also shown from a recent single-center retrospective study of Impella in severe CS patients. The hospital mortality was 81% and associated with age (> 66 years) and lactate levels (3.3 mmol/L). This study suggests the importance of patient selection with consideration of age and lactate levels (40). A meta-analysis of Impella in 671 CS patients following myocardial infarction also showed a high 30-day mortality of 54.6%. This study also analysed the survival difference if the Impella was placed prior or after percutaneous coronary intervention (PCI). Impella initiation before PCI showed significant risk reduction related to 30-day mortality compared to after PCI (41).

TandemHeart is another percutaneous MCS device that works by aspirating oxygenated blood from the left atrium to the femoral arteries. This device can provide adequate flow by 3.5-4.5 L/min. TandemHeart can be considered in patients with severe CS refractory to IABP and vasopressors as it was able to improve cardiac index, systolic blood pressure, mixed venous oxygen saturation, decrease pulmonary capillary wedge pressure (PCWP), reduced ventricular filling pressure, and oxygen demand. Similar to Impella devices, although TandemHeart was beneficial for haemodynamic support, the 30-day and 6-months mortality was still high (42).

Venous Arterial-Extracorporeal Membrane Oxygenation (VA-ECMO)

VA-ECMO is a temporary MCS and used as a salvage treatment for refractory CS. VA-ECMO creates a right-to-left shunt for venous blood drainage from the right atrium to the oxygenator and pumping the oxygenated blood to the systemic circulation (ascending aorta or iliac artery). This mechanism provides adequate flow support that can reach 7 L/min (30). In a retrospective observational study, which VA-ECMO used as rescue therapy in CS patients, it showed a quite high survival rate (51%). Mortality rate was still high and was associated with respiratory and genitourinary comorbidities (43). A systematic review of 1998 adults with CS were performed. The result showed poor longer-term survival rate at 12 months (23.2-36.1%) (44). These data presented a challenge in VA-ECMO therapy, potentially due to LV overload during therapy, especially in patients with very low systolic LV function (30).

To overcome this challenge, VA-ECMO can be combined with additional treatment. IABP can enhance aortic valve opening and increase LV ejection. Additional IABP in VA-ECMO would help to reduce PCWP by 4 mmHg. IABP also helped reducing LV afterload (45). However, a contrary result was shown from a meta-analysis by Vallabhajosyula et al. The use of IABP as additional therapy in CS patients who required VA-ECMO did not affect the short-term mortality in the total cohort (patients with AMI and post cardiotomy patients) but was associated with 18.5% lower mortality compared to VA-ECMO alone in AMI patients (46). Combination of VA-ECMO with Impella was associated with lower hospital mortality and showed more benefit for bridging to next therapy in refractory CS. The benefit might be related to the ability of Impella to reduce LV overload due to VA-ECMO therapy (47).

Revascularization

In patients with MI presenting with CS, reperfusion strategy becomes the intervention of choice. Most of the patients who have CS present with multivessel coronary artery disease, with higher mortality risk than the patients with single-vessel disease (48). This raised a concern whether reperfusion should be done on the culprit vessel only or also in the nonculprit vessel in multivessel disease. A recent randomised trial, Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial aimed to figure out the better reperfusion strategy. This trial showed a clinical benefit when reperfusion was only done on the culprit lesion compared to the multivessel reperfusion strategy, showing a lower 30-day mortality (45.9% vs 55.4% respectively, $P < 0.01$) or severe renal failure requiring renal replacement therapy (49). The result from CULPRIT-SHOCK trial was also in accordance with two meta-analyses showing that multivessel PCI carry higher risk of mortality (48, 50). However, a contradictory result was shown later from KAMIR-NIH (Korea Acute Myocardial Infarction-National Institutes of Health) Registry. This study showed a lower risk of mortality in patients who underwent multivessel PCI after 1 year of follow-up. Multivessel PCI was also associated with lower risk of MI and also the need for repeat revascularization (14). Given these data, larger trials are essential to clarify the dissimilarity between previous studies.

Conclusion

Cardiogenic shock is a challenging entity. Despite early treatment, the mortality rate is still high. Available drugs and devices provide benefit in clinical outcomes and survival rate. However, the evidence is still scarce. Further and bigger randomized trials are needed to make proper recommendation regarding therapy in cardiogenic shock.

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Competing interests

The authors declare that they have no competing interests.

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Ethical Clearance

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