Cardiogenic Shock

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9.1 Case Report

A 60-year-old man with a known dilated valvular cardiomyopathy was admitted to the emergency department (ED) for worsening dyspnea and fatigue. The patient and his wife referred the onset of dyspnea a week before, firstly exercise related and then at rest. The patient also referred weight gain (4 kg in 5 days) despite usual food consumption and water restriction and decrease in urine output within the last day.

His vital signs were 80/45 mmHg and 125 beats per minute and his oxygen saturation was 89 %.

Few minutes after his arrival in the ED, while waiting for medical visit, patient's condition rapidly deteriorated with further desaturation and hypotension. He required prompt intubation and mechanical ventilation. Inotropic support with dopamine was started, and the patient was immediately transferred to our ICU for further evaluation and treatment.

Medical History and Cardiovascular Risk Factors

- Cardiovascular risk factors: dyslipidemia and type II diabetes mellitus.
- Family history: no family history of structural heart disease.
- 1999: diagnosis of severe mitral regurgitation due to rheumatic valvular disease. Concomitant diagnosis of left ventricular dilatation and moderate left ventricular systolic dysfunction (LVEF 40 %).
- 2000: hospital admission for acute pulmonary edema during atrial fibrillation episode with rapid ventricular response. After the acute phase, the patient underwent an echocardiographic evaluation that confirmed severe mitral regurgitation together with the increase in systolic pulmonary artery pressure (PAP 55 mmHg), severe left atrial enlargement, and moderate to severe left ventricular systolic dysfunction (LVEF 38 %). A coronary angiography did not reveal any coronary disease.

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The patient was evaluated and accepted for mitral valve surgery.
- 2001: mitral valve replacement with mechanical prosthesis. Surgical atrial fibrillation ablation was ineffective.
- 2006: hospital admission for hypotensive acute heart failure with renal and hepatic impairment treated with IV diuretics and inotropes. The echocardiogram revealed correct prosthesis function but further worsening of left ventricular function (FEVS 30 %). The patient referred an NYHA class III. The patient was discharged on optimal medical therapy with indication to a follow-up visit after 3 months.
- 2007: cardiac resynchronization therapy with defibrillator (CRT-D) implantation.
- 2010–2013: frequent hospital admissions for acute heart failure. An evaluation for heart transplantation was proposed, but the patient refused.

Allergies

None.

Medications

Furosemide 125 mg in the morning + 75 mg in the evening, ramipril 2.5 mg o.d., bisoprolol 3.75 mg o.d., spironolactone 100 mg o.d., atorvastatin 20 mg o.d., and metformin 500 mg b.i.d.

Vital Signs

- Temperature: 36 °C
- Heart rate: 125 bpm
- Arterial blood pressure: 85/55 mmHg
- Respiratory rate: 16 breaths/min
- Oxygen saturation: 98 %

Physical Examination

- *General:* intubated, sedated; cold sweats and pallor
- *Neck:* jugular venous distention, no lymphadenopathy, no carotid bruit
- *Cardiovascular:* irregular and tachycardic rhythm, apical soft proto-mesosystolic murmur (2/6 at Levine scale)
- *Lungs:* decreased tactile fremitus and dullness to percussion at right pulmonary basis, bilateral medio-basal rales
- *Abdomen:* moderate hepatomegaly, no splenomegaly, no ascites, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness
- *Extremities:* cold, mild cyanosis, peripheral edema

Laboratory Tests

White blood cells 8800/mmc, hemoglobin 10.5 g/l, hematocrit 32 %, platelets 138,000/mmc, creatinine 2.4 mg/dl, blood urea nitrogen 112 mg/dl, AST 288 U/L, ALT 204 U/L, γGT 110 U/L, total bilirubin 2.1 mg/dl with direct bilirubin of 1.6 mg/dl, INR 4.2, uric acid 9.4 mg/ml, potassium 4.8 mEq/l, sodium 134 mEq/l, magnesium 1.2 mg/dl, blood glucose 254 mg/dl

Arterial Blood Gas Analysis

Before orotracheal intubation and mechanical ventilation: pH 7.28, PO_2 55 mmHg, PCO_2 52, lactate 6.7 mmol/L with decreased serum bicarbonate (HCO_3 18 mmol/L)

Instrumental Examination

The ECG (Fig. 9.1) revealed atrial fibrillation with rapid ventricular response (130 bpm).

The echocardiographic examination showed severely dilated left ventricle (LV end-diastolic volume of 280 ml, LV end-diastolic diameter 78 mm), impaired LV function with an estimated ejection fraction (EF) of 20 % because of global hypokinesia, correct function of the mitral prosthesis with a mild intraprosthetic regurgitation, right ventricle dilatation and dysfunction (TAPSE 12 mm, FAC area 25 %), and severe tricuspid regurgitation with

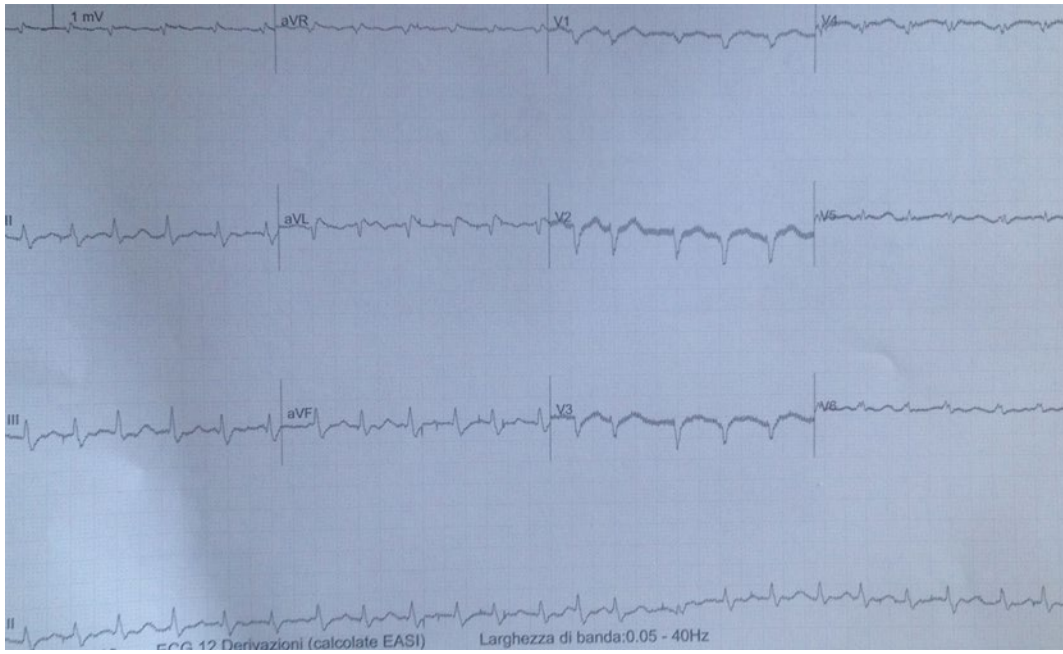

Fig. 9.1 ECG showing atrial fibrillation with rapid ventricular response

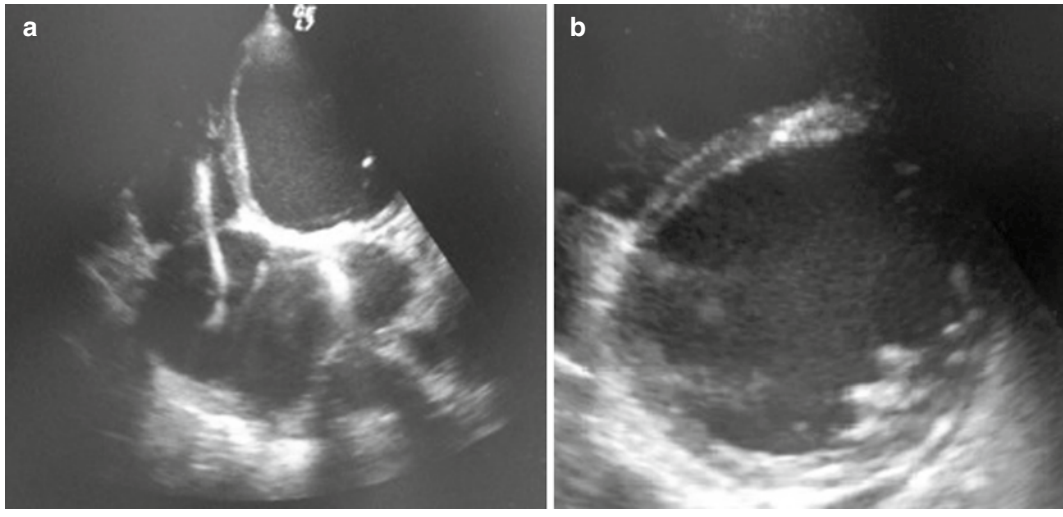

Fig. 9.2 Echocardiographic images: apical four-chamber view (**a**) and parasternal short axis at papillary level (**b**) showing chamber dilation, mitral valve prosthesis, and presence of lead in right chambers

systolic pulmonary artery pressure of 50 mmHg (Fig. 9.2). The cardiac output and the cardiac index as estimated by echocardiography were, respectively, 2.8 l/min and 1.3 l/min/m^2.

Urgent chest radiography was performed showing pulmonary vascular congestion with alveolar infiltrates and right moderate pleural effusion.

Clinical Course and Therapeutic Management

The patient underwent insertion of a radial arterial catheter for invasive measurement of blood pressure and arterial blood gas testing, insertion of central venous catheter at right subclavian site

for drug infusions, measurement of central venous pressure and blood sampling, and determination of central venous oxygen saturation.

Clinical, instrumental, and laboratory data (hypotension <90 mmHg, tissue hypoperfusion with increase in arterial lactate and renal and hepatic impairment, cardiac index of 1.3 l/min/m^2) allow us to make the diagnosis of cardiogenic shock in a patient with advanced heart failure.

Inotropic support with dopamine (5 mcg/kg/min) was continued, and also adrenaline was started at a dose of 0.05 up to 0.08 mcg/kg/min because of persistent hypotension, increase in arterial lactate (7.8 mmol/l), and oliguria.

Continuous infusion of loop diuretics (furosemide, 500 mg/24 h) was started with progressive improvement in diuresis. Intravenous digoxin was administered in the acute phase for AF rate control, and unfractionated heparin was introduced. Insulin infusion was started to correct hyperglycemia and on the following days switched to bolus insulin injection.

The patient's clinical status gradually improved, with normalization of arterial lactate on day 2 and also the central venous oxygen saturation (from baseline 56–63 % on day 2). On day 5, pulmonary congestion significantly improved and the patient was extubated. The patient was gradually weaned from inotropes until interruption on day 7. Therefore, an echocardiography was repeated confirming severe left ventricular dysfunction (FEVS 25 %) and mild to moderate right ventricle dysfunction (TAPSE 15 mm, FAC area 32 %), reducing pulmonary artery pressure (35 mmHg).

A beta-blocker and an angiotensin-converting enzyme inhibitor were started on day 8 and uptitrated (ramipril 2.5 mg o.d., bisoprolol 3.75 mg o.d.). Loop diuretics were switched from IV to oral administration (furosemide 125 mg b.i.d., spironolactone 100 mg o.d.). Oral digoxin was continued to achieve a better rate control. Oral anticoagulation was reintroduced on day 9. Laboratory tests showed improvement of kidney and hepatic function (creatinine 1.4 mg/dl, total bilirubin 1.3 mg/dl, normalization of AST, ALT, and γGT).

Cardiac rehabilitation was started on day 12 with progressive improvement of functional capacity.

Considering the end-stage HF despite optimal pharmacological and device treatment and the recent episode of cardiogenic shock, the possibility to an evaluation for advanced treatment options, as heart transplant or left ventricular assistive device implantation, was offered to the patient who agreed, and a visit in a national reference hospital was therefore planned. The patient was discharged on day 25.

9.2 Cardiogenic Shock

Definition and Epidemiology

Cardiogenic shock (CS) is a complex clinical condition characterized by inadequate end-organ perfusion due to the inability of the heart to provide adequate flow. The tissue hypoperfusion, if prolonged, could result in end-organ damage and finally in multiorgan failure. Cardiogenic shock is a fatal condition if not early diagnosed and treated. The in-hospital mortality approaches 50 % and is related to the severity of hemodynamic impairment, the promptness of diagnosis, and the type of management (medical therapy, mechanical support) [1]. Mortality decreased significantly during the last years because of the wide use of revascularization.

The diagnosis of CS results from multiparametric evaluation and could be made in the presence of:

- Hypotension defined as systolic blood pressure ≤90 mmHg or when vasopressors are required to maintain SBP ≥90 mmHg or mean arterial pressure is 30 mmHg lower than baseline
- Evidence of organ hypoperfusion: resting tachycardia, altered mental status, oliguria, poor capillary refill, cold/diaphoretic extremities
- A reduction in cardiac index (<1.8 L/min/mq without support or <2.2 l/min/mq with support) with evidence of increase in pulmonary capillary wedge pressure (>18 mmHg)

Any cause of severe left or right ventricle dysfunction may cause cardiogenic shock; however,

acute coronary syndrome (ACS) with left ventricular failure is mostly involved. The incidence of CS complicating ACS is approximately 7 % in ST elevation myocardial infarction (STEMI) and 2.5 % in non-STEMI [2]. In those patients presenting with ACS and CS, mechanical complications as ventricular septal or free wall rupture and papillary muscle rupture should be suspected and searched.

Other less frequent causes are acute myopericarditis, stress-induced cardiomyopathy, acute valvular regurgitation or prior severe valvular disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, drugs and medications, arrhythmias, and traumatic cardiac injury.

Cardiogenic shock due exclusively to right ventricle involvement represents only 5 % of cases, and it is characterized by a similar mortality to LV shock [3].

In the ischemic setting, CS could be present acutely or could develop later, within the first days. It seems that later CS is associated with a higher mortality than earlier development of CS [4].

Different risk factors for CS in ischemic patients have been recognized: anterior STEMI, multivessel disease, advanced age, female sex, previous diagnosis of diabetes and hypertension, prior cardiovascular disease, heart failure at admission, systolic blood pressure <120 mmHg, heart rate >90 bpm, and presence of left branch block [5, 6].

Pathophysiology

Systemic perfusion and blood pressure are related to cardiac output (CO) and systemic vascular resistance (SVR):

$$\text{MAP}\left(\text{mean arterial pressure}\right)=\text{CO}\times\text{SVR}$$
$$\text{SVR}=8\eta L/\pi r^4$$
$$\text{CO}=\text{SV}\times\text{HR}$$

η = viscosity, L = vessel length, r = vessel radius, SV = stroke volume, HR = heart rate

The stroke volume depends on the preload, afterload, and myocardial contractility as explained by the Frank–Starling and Hill mechanisms. The initial response to a decrease in blood pressure is mediated by arterial baroreceptors that cause an enhancement in sympathetic activity (via IX and X cranial nerves) with a consequent increase in HR, myocardial contractility, and SVR. More slowly acting mechanisms are the activation of renin/angiotensin/aldosterone system and fluid retention. The reduction in tissue perfusion leads to a reduced oxygen delivery with a shift to anaerobic metabolism and an increase in lactate levels with a possible consequent metabolic acidosis.

Cardiogenic shock (CS) may be precipitated by different cardiac and extracardiac causes as listed below:

- Cardiomyopathies: acute myocardial infarction (MI) involving >40 % of the left ventricular myocardium or dilated cardiomyopathy with cardiac pump failure.
- Arrhythmias: supraventricular arrhythmias may cause cardiogenic shock through an impairment of left ventricular filling. Bradyarrhythmias or ventricular tachycardia/fibrillation may reduce or abolish CO due to an ineffective cardiac contraction.
- Mechanical: valvulopathies (mitral or aortic regurgitation) or intracardiac shunt.
- Extracardiac: any condition that causes a significant reduction in preload or acute increase in afterload (i.e., cardiac tamponade, pulmonary embolism, tension pneumothorax, constrictive pericarditis).

The CS pathophysiology is very complex with differences from patient to patient. Cardiogenic shock evolves through different stages that represent a physiologic continuum from an initially compensated status (pre-shock or shock impending) till multiorgan failure.

Regardless of the precipitating cause, the main feature consists of a reduction of cardiac output with consequent hypotension, unable to maintain an adequate systemic perfusion (Fig. 9.3). The reduction of blood pressure triggers the activation of compensatory mechanisms through sympathetic system and renin/angiotensin/aldosterone system with consequent tachycardia,

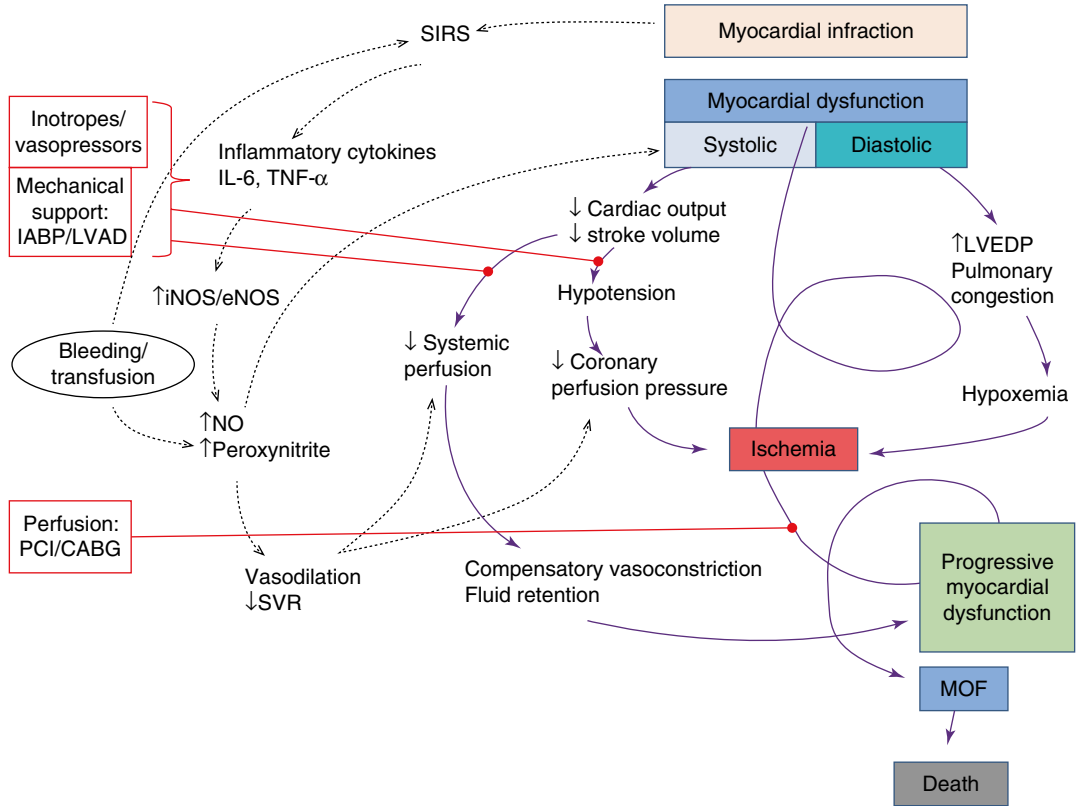

Fig. 9.3 Concept of CS pathophysiology. This is the "downward spiral," induced by left ventricle (LV) systolic dysfunction that leads to reduced stroke volume and cardiac output with consequent hypotension. Coronary blood flow is therefore reduced with ischemia and further myocardial dysfunction. Even diastolic dysfunction with increased left ventricular end-diastolic pressure (*LVEDP*) and pulmonary edema leads to hypoxemia and consequent ischemia. The reduced systemic perfusion activates compensatory mechanisms that cause vasoconstriction and fluid retention, increasing left ventricle after- and preload and aggravating myocardial dysfunction. The systemic inflammatory response syndrome (*SIRS*) characterized by cytokine (interleukin-6 (*IL-6*) and tumor necrosis factor (*TNF*)) production and consequent endothelial and inducible nitric oxide synthase (*eNOS*, *iNOS*) activation leads to nitric oxide (*NO*) and peroxynitrite production that causes reduced systemic vascular resistance (*SVR*) with vasodilatation and further myocardial depression. Bleeding complications and subsequent transfusions have a negative role in the shock spiral. If there is not a prompt intervention with treatment options shown in red (inotropes/vasopressors, mechanical support with intra-aortic balloon pumping (*IABP*) and left ventricular assist device (*L-VAD*), reperfusion by percutaneous coronary intervention (*PCI*) or coronary artery bypass (*CABG*)), the vicious circle leads to multiorgan failure (*MOF*) and death

increased contractility, a marked systemic vascular resistance (SVR) elevation increasing LV afterload, and fluid retention with increase in preload. These compensatory mechanisms in the long term become maladaptive and result in a further marked reduction in tissue perfusion. Hypotension, vasoconstriction, tachycardia, and increased myocardial contractility reduce myocardial perfusion and increase myocardial oxygen demand, exacerbating ischemia.

Pump failure causes diastolic dysfunction with increased ventricular diastolic pressure that further reduces coronary perfusion pressure, worsening ischemia. The increased ventricular diastolic pressure increases left atrial pressure which may cause pulmonary congestion leading to hypoxia, further exacerbating myocardial ischemia. Ischemia worsening aggravates myocardial dysfunction and begins a vicious cycle that leads to progressive

end-organ hypoperfusion with multiorgan failure (MOF) and death when not interrupted (Fig. 9.3). Reduced systemic perfusion leads to anaerobic metabolism and consequently to lactic acidosis that further depresses myocardial function.

Some patients do not have elevated SVR, suggesting that the compensatory vasoconstriction is not universal, and moreover, a systemic inflammatory response may be involved [7], contributing to myocardial dysfunction and hypotension (via vasodilatation). In fact, in the presence of myocardial infarct, cytokines (interleukin-6 (IL-6), tumor necrosis factor (TNF)) that activate inducible nitric oxide synthase (iNOS) are released, leading to increased levels of nitric oxide (NO) with consequent vasodilatation and worsening hypotension [8]. Nitric oxide and superoxide lead to peroxynitrite production that impairs myocardial contractility [9]. The inflammatory mediators lead to microcirculatory abnormalities like regional heterogeneity in blood flow which plays a very important role in organ failure pathogenesis. In fact data shows that IL-6 levels correlate with organ failure and mortality [10].

Even if severe LV failure is the principal cause of CS, other factors, here below listed, may contribute to hypotension:

- Hypovolemia due to bleeding with a hemorrhagic shock superimposition or due to diuretic therapy
- Septic shock superimposition
- Severe preexistent valvular heart disease like critical aortic stenosis or new-onset valvular disease like severe mitral regurgitation
- Important bradycardia that causes low cardiac output and hypotension in patients with reduced LV function due to acute MI
- Atrial arrhythmias with rapid ventricular response or ventricular tachycardia
- Drugs lowering blood pressure (nitrates, beta-blocker, calcium antagonists, ACE inhibitors, diuretics, and morphine)

These factors should be promptly detected and, when possible, corrected.

Diagnosis

The diagnostic evaluation during cardiogenic shock must not delay resuscitation if needed and must be conducted at the same time. Diagnostic efforts should be made to recognize the stage of pre-shock to prevent loss of the compensatory mechanisms and progression to shock and multiorgan dysfunction.

Medical History and Physical Examination

Medical history may be collected from the patient or relatives in case of advanced shock. The presence of cardiovascular risk factors or the history of chest pain may suggest acute myocardial infarction (MI). Additional information about comorbidities or allergies should be recorded.

Cardinal findings on physical examination are:

- Hypotension: defined as absolute (PAS <90 mmHg or PAM <65 mmHg) or relative ($\Delta P > 30$ mmHg). Prominent and persistent hypotension (>30 min), despite volemic correction, may require inotropes to ensure adequate systemic perfusion.
- Oliguria: decreased urine output (diuresis <0.5 mg/kg/h), consequence of renal hypoperfusion related to reduced cardiac output and blood redistribution to other vital organs.
- Cool and clammy skin: compensatory vasoconstriction to redirect blood flow to vital organs, causes cold, mottled, or diaphoretic skin.
- Altered mental status: ranges from agitation to delirium and coma.

Dyspnea, chest pain with tachycardia, and tachypnea are often present. On cardiac auscultation, gallop rhythm or new murmurs may be found. Pulmonary congestion with diffuse crackles is also a typical finding but may lack in about one-third of patients at presentation [11]. Jugular venous distension and hepatomegaly are clinical signs related to an increased preload, especially during right ventricular failure. A capillary refill time >2 s is a frequent finding and should be

associated with low mixed venous oxygen saturation.

Electrocardiogram

Electrocardiogram (ECG) suggests the diagnosis of acute MI in the presence of ST-T alterations. Supraventricular and ventricular tachy- or brady-arrhythmias may cause shock and can be diagnosed by ECG monitoring. Shocked patients usually present sinus tachycardia.

Echocardiogram

Echocardiography may confirm the diagnosis of cardiogenic shock, showing marked depression of left or right ventricular function with low stroke volume and elevated filling pressures. It is also useful in evaluating cardiac chambers, regional wall motion, the pericardium, and valves: it could detect causes or contributing factors as regional wall motion abnormalities, the presence of cardiac tamponade, or severe mitral or aortic regurgitation. In acute MI, echocardiogram should be repeated to exclude the presence of mechanical complications as ventricular septal, free wall, or papillary muscle rupture [12]. Transthoracic echocardiography (TTE) is the first step, but transesophageal echocardiography (TEE) should be used when TTE images are suboptimal especially in patients with mechanical ventilation.

TTE plays also a role as a less invasive tool for evaluating hemodynamic parameters with Doppler-based methods. Small ventricles ("kissing ventricles") usually suggest the use of fluid challenge, while a dilated and hypokinetic right ventricle should be related to pulmonary embolism.

Hemodynamic Monitoring

Hemodynamic monitoring through a pulmonary artery catheter adds further details in the diagnosis, establishing cardiac output, pulmonary artery occlusion pressure (PCWP), systemic vascular resistance, and continuous mixed venous oxygen saturation (SvO_2) [13]. These parameters are also helpful in guiding inotropic/vasopressor therapy or fluid resuscitation and in assessing mechanical ventilation settings [14]. Pulmonary artery catheterization has never shown to improve patient's outcomes in clinical trials [2, 3, 15]. The diagnosis of cardiogenic shock is confirmed in the presence of a reduced cardiac index (<2.2 l/min with inotropic support or <1.8 without therapy), an increased PCWP (>15–18 mmHg), and/or a reduction in SvO_2/$SvcO_2$ (<70 % and <65 %, respectively). A fall in SvO_2 is suggestive for a reduced oxygen delivery or an increase in oxygen consumption and may reflect inadequate tissue perfusion even in a pre-shock stage. According to guidelines [12], an invasive hemodynamic monitoring is recommended in a patient with persistent hypotension refractory to pharmacological treatment with uncertain left filling pressures.

Laboratory Evaluation

Laboratory tests are useful in identifying causes of shock and in evaluation of organ failure. Basic chemistry tests, complete blood count, liver and renal function tests, amylase and lipase, and arterial blood gas should be evaluated. Cardiac biomarkers (troponin T/I, CK-MB) are useful in the diagnosis of acute MI and correlate with infarction extension. Arterial or venous lactates complete the picture because an increased serum lactate level may correlate with a reduced oxygen delivery with a shift to anaerobic metabolism. Elevated lactate serum levels (>1.5 mmol/l at admission, >1 mmol/l after 24 h) are also associated with increased mortality [16].

Coronary Angiography

Coronary angiography should be performed early in patients with suspected acute MI. Revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) is also recommended without any delay in patients with cardiac pump failure related to an ischemic cause [12].

Differential Diagnosis

The differential diagnosis for shock may be challenging and must be focused on underlying causes of inadequate tissue perfusion.

1. *Hypovolemic shock* – hypovolemic shock is related to an intravascular volume loss due to hemorrhage or third-space loss with a reduced preload that leads to a reduction in CO and an increase in systemic vascular resistance to maintain adequate perfusion. Dry mucous and decreased jugular and central venous pressure with low PCWP are typical findings.
2. *Distributive shock* – distributive shock is related to vasodilatation with a consequent drop in SVR. The CO is increased as a compensatory mechanism, while the PCWP may be low or normal. Possible causes of distributive shock are sepsis or systemic inflammatory response syndrome, anaphylaxis, neurogenic disease, and toxic problems.
3. *Cardiogenic shock* – as discussed previously, cardiogenic shock is related to a cardiac pump failure and may be divided in to four categories in relation to etiology.
4. *Combined shock* – different mechanisms contribute to generate shock (i.e., septic shock may coexist with a cardiac pump failure due to myocardial stunning related to sepsis).

Management

The initial approach consists of:

- Identification of patients with high risk to develop CS (they should be transferred to the nearest tertiary center)
- Early diagnosis (before a frank hypotension is being manifested) with a consequent rapid stabilization
- Identification/treatment of reversible causes

Invasive blood pressure, heart rate, rhythm, and oxygen saturation should be continuously monitored. Right heart catheterization is not routinely recommended, but it can be very useful in a subgroup of patients (persistently hypotensive patients or patients with uncertain LV filling pressure) to guide optimal treatment decisions.

The principal therapeutic targets in these patients are:

- MAP >65 mmHg in order to restore tissue perfusion and to prevent multiorgan dysfunction (MOF)
- Systemic vascular resistances: 800–1000 dyn/s/cm^{-5}
- CI >2.5 l/min/m^2
- FC <110 bpm
- SVO_2 >65 %
- Lactate <2 mmol/l

These parameters should be monitored every 90 min.

Reversible causes should be detected and treated emergently, for instance, revascularization in acute coronary syndromes, surgery for mechanical complications of MI or acute valvular disease, and pericardial drainage in tamponade.

In patients with evidence of ACS (ongoing ischemia, persistent ST elevation, new LBBB), early revascularization with either PCI or CABG must be considered. In the SHOCK trial, CS patients treated emergently with PCI or CABG had an improved long-term survival than patients who did not or underwent revascularization later [17]. The CS is the only situation in which an emergency multivessel revascularization can be performed [17, 18]. Fibrinolysis should be considered when PCI or CABG is not available [19]. Indications for antiplatelet/antithrombin therapies are similar to those in STEMI patient without CS (see Chap. 1).

When a reversible underlying cause is not present, the medical management role is primarily supportive, serving as a bridge to mechanical circulatory support, heart transplantation, or recovery, because there is lack of evidence that the medical management alone improves survival.

Even if there are only a few clinical trials with discording results, sympathomimetic inotropic and vasopressor agents are the mainstay of the medical first-line therapy. These agents interact with specific receptors (Table 9.1) and activate adrenergic pathways, increasing myocardial

contractility and modifying vascular tone. The principal inotropes and vasopressors that we commonly use in CS are (Table 9.2):

Dobutamine: It is predominantly a β-adrenergic agonist with a β1/β2 ratio of 3:1. It increases HR, SV, and CO with a modest decrease in blood pressure and SVR [20]. It also has a mild α1-adrenergic agonism, and this is the reason why vascular resistance decrease does not persist at higher doses. These beneficial effects are limited by myocardial oxygen consumption increase that worsens myocardial ischemia, precipitates tachyarrhythmias, and increases mortality. The ESC guidelines recommend dobutamine and dopamine as the first-line inotropic therapy in CS.

Epinephrine (adrenaline): It is a potent agonist of all adrenoreceptors. Its use results in HR, SV, CO, and coronary blood flow increase. At low doses, a passive pulmonary vessel stretching accommodates CO increase, but at high doses, it determines a pulmonary vascular resistance increase and so a right ventricle afterload increase. Even adrenaline increases myocardial oxygen consumption due to increase in HR and stroke work. It has metabolic effects like increased plasma glucose and lactate concentration. The lactate concentration increase seems not to be harmful.

Norepinephrine (noradrenaline): It is a potent α-agonist that also stimulates β1 receptors, with an increase in blood pressure, SVR, and SV. Like adrenaline, it increases right ventricle afterload. Either cerebral circulation or coronary circulation is protected to a certain extent from these vasoconstrictor effects due to the relative paucity of the vascular adrenoreceptors, while pulmonary, renal, splanchnic, and cutaneous blood flow is not spared. The ESC guidelines recommend noradrenaline as second-line therapy in CS patients.

Dopamine: It has a dose-dependent action. At low doses (≤2 γ/kg/min), it activates dopaminergic receptors with splanchnic and renal vasodilatation. At medium doses (5–10 γ/kg/min), it activates β1 receptors with HR and CO increase. At intermediate doses (2–5 γ/kg/min), either dopaminergic or β1 receptors are stimulated. At high doses, it predominates α-adrenergic action with

Table 9.1 Location and response of adrenergic receptors

Receptor	Location	Activity
α1	Vascular smooth muscle Heart	Contraction Increase force of contraction
α2	Vascular smooth muscle	Contraction
β1	Heart	Increase force of contraction Increase AV nodal conduction velocity
β2	Smooth muscle (vascular, bronchial, GI, and GU)	Relaxation
D	Vascular smooth muscle	Relaxation

AV node atrioventricular node, *GI* gastrointestinal, *GU* genitourinary

Table 9.2 Inotropes and vasopressors used in CS

Medication	Receptor/mechanism	Doses	BP	HR	CO	SVR
Dobutamine	β1 > β2 > α	2–15 γ/kg/min	↓	↑	↑↑	↓
Milrinone	PDE II inhibitor	0.375–0.75 γ/kg/min	↓↓	↑	↑↑	↓↓
Levosimendan	Ca sensitizer	0.05–0.2 γ/kg/min	0	0	↑↑	↓↓
Epinephrine	β1 = β2 > α	0.01–0.03 γ/kg/min, max 0.1–0.3 γ/kg/min	↑	↑	↑↑↑	↓
Norepinephrine	α > β1 > β2	0.01–0.03 γ/kg/min, max 0.1 γ/kg/min	↑↑	0 or ↓	0	↑↑
Dopamine	Moderate dose β	5–10 γ/kg/min	↑↑	↑	↑↑	0 or ↓
Dopamine	High dose α	10–20 γ/kg/min	↑↑	↑↑	↑	↑↑
Phenylephrine	α1	60–60 γ/min	↑↑	↓	↓	↑
Vasopressin	V1	0.01–0.04 units/min	↑↑	0	0	↑↑

BP blood pressure, *CO* cardiac output, *HR* heart rate, *SVR* systemic vascular resistance

vasoconstriction and increase in SVR that may cause a CO decrease. De Backey et al. showed in a subgroup analysis that in CS patients dopamine increased 28-day mortality rate compared with norepinephrine, but in this study dopamine doses in CS patients are not specified, and this may be a reasonable explanation of these results because high-dose dopamine causes a CO decrease [21].

Milrinone: It inhibits phosphodiesterase-3 and prevents cyclic adenosine monophosphate (cAMP) degradation that activates protein kinase A which results in increased calcium influx into the cardiomyocyte with increased contractility. In the smooth muscle, elevated cAMP causes relaxation (vasodilatation) because it inhibits myosin light-chain kinase. Milrinone has a similar cardiovascular profile to dobutamine. In fact it increases HR, SV, and CO and decreases mean blood pressure, SVR, and pulmonary artery resistances, reducing preload and afterload and consequently ventricular wall stress. Although milrinone affects hemodynamics, the OPTIME-CHF trial did not show a difference in days of hospitalization between decompensated heart failure patients treated with 48 h administration of milrinone and placebo. In this study, there was not an increase in in-hospital mortality in the milrinone group [22]. Actually milrinone is recommended only for refractory CS patients.

Levosimendan: It is a calcium-sensitizing agent that binds troponin C, at systolic calcium concentrations, and prolongs myosin–actin interaction due to troponin I inhibition. So levosimendan does not increase cellular calcium concentration and consequently does not impair diastolic function and cardiac rhythm. It has phosphodiesterase III inhibitory effects and causes blood pressure decrease. Levosimendan has an active metabolite so its inotropic effects continue even after infusion is stopped. The SURVIVE study did not show a 180-day mortality rate through short-term levosimendan and dobutamine infusion in acute decompensated heart failure [23], but deaths in the first weeks were significantly fewer in the levosimendan group. There are only few data (limited to case reports) on the role of levosimendan in CS patients. The ESC guidelines recommend levosimendan infusion to reverse beta-blocker effects if the last ones are thought to contribute to hypotension.

Phenylephrine: It is an α1-selective agonist that causes an increase in SVR and blood pressure and a reflex bradycardia that determines a decrease in CO. This is the reason why its utilization in CS is very rare.

Vasopressin: It activates V1 vascular smooth receptors and causes vasoconstriction. In refractory CS, vasopressin has been utilized, increasing MAP without effects on CI, pulmonary capillary wedge pressure, or urine output [24].

Assessment and optimization of cardiac filling pressure enhance hemodynamic improvement in CS. Hypovolemia should be treated with intravenous fluid replacement, and this should be guided by PCWP, systemic arterial pressure, arterial oxygen saturation, central venous pressure (target value 8–10 mmHg if there is no right ventricle (RV) dysfunction, 10–12 mmHg if RV dysfunction), and cardiac output measurement.

When hypervolemia with pulmonary and peripheral edema is present, diuretics (loop diuretics or combining loop with thiazide diuretic when patient becomes resistant to the first ones) should be used.

Actually the intra-aortic balloon pumping (IABP) may be considered in patients with acute myocardial infarction complicated by CS. The evidence does not support the IABP routine use because the IABP SHOCK II trial did not show a 30-day mortality difference between the IABP and control groups in patients with CS complicating MI, probably due to high rate of patient shift from the control to the IABP group [25].

In patients with refractory shock, LV mechanical device may be considered. The percutaneous circulatory support devices can be distinguished in four categories:

- Mechanical left ventricle support that unloads LV pressure (IABP)
- Mechanical left ventricle support that unloads LV volume (TandemHeart and Impella Recover 2.5 l/min or 4 l/min)
- Mechanical biventricular support (combination of right and left ventricle support)
- Mechanical biventricular support with membrane oxygenation (ECMO)

Oxygen or mechanical respiratory support is indicated according to clinical and blood gas asset.

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