Pharmacological therapies for acute cardiogenic shock

Radić, Marija

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Marija Radić

Pharmacological therapies for acute cardiogenic shock

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Summary

Title: Pharmacological therapies for acute cardiogenic shock

Author: Marija Radić

Cardiogenic shock (CS) is a life threatening condition, a state of end-organ hypoperfusion, caused by cardiac failure leading to low cardiac output and inability of cardiovascular system to provide adequate flow of oxygen-rich blood to body-extremities and vital organs. This is a clinical syndrome characterized by a systemic hypotension <90 mmHg, and signs of tissue hypoperfusion, usually as a sequela of an acute myocardial infarction. Cardiogenic shock can also arise from non-ischemic causes, like myocarditis, endocarditis and pericardial tamponade. The incidence of cardiogenic shock is in decline, which reflects increased use of coronary reperfusion strategies for MI, including primary percutaneous coronary intervention (PCI) and fibrinolytic therapy which by limiting the infarct size also reduces the risk of shock development. Initial medical treatment includes IVFs, inotropes and vasopressors. Inotropes are divided into subgroups, according to their mechanism of action we distinguish beta-agonists, phosphodiesterase III inhibitors and Ca^{2+} sensitizers. Inotropes act on heart contractility, vasopressors increase vasoconstriction, consequently causing increase in mean arterial pressure (MAP) and Ca^{2+} sensitizers, among other pharmacological agents, are used to increase sensitivity of myocardiocytes on intracellular Ca^{2+} level. Pathophysiology of CS is not fully understood, it is a vicious cycle: when it is caused by infarction, ischemia leads to myocardial dysfunction which causes left ventricular systolic and diastolic dysfunction manifested with elevated left ventricular end diastolic pressure (LVEDP), decreased cardiac output and decreased coronary perfusion. Systemic hypoperfusion causes compensatory vasoconstriction and tachycardia which increases myocardial oxygen demand and subsequently worsens myocardial ischemia. This self-perpetuating cycle leads to progressive myocardial dysfunction and finally to the multi-organ failure unless it is interrupted by an adequate therapy. CS is an emergency condition requiring rapid diagnosis with prompt initiation of supportive pharmacological therapy, etiologic treatment and careful patient monitoring are of a vital importance. The goal of medical management is to restore heart function and tissue perfusion and with the aim of prevention end-organ damage.

Keywords: • Cardiogenic shock •Pharmacological therapy •Myocardial infarction

Sažetak

Naslov: Farmakološko liječenje u akutnom kardiogenom šoku

Autor: Marija Radić

Kardiogeni šok (KŠ) je po život opasno stanje koje karakterizira nedostatna perfuzija ciljnih organa nastala kao posljedica preniskog minutnog volumena, odnosno nesposobnosti srca da održi potreban protok krvi u tijelu. To je klinički sindrom karakteriziran sustavnom hipotenzijom <90 mmHg i znakovima tkivne hipoperfuzije. Najčešće nastaje kao posljedica akutnog infarkta miokarda. KŠ može biti uzrokovan i neishemijskom bolešću srca, kao posljedica bolesti srčanih zalistaka, miokarditisa, endokarditisa ili tamponade. Učestalost KŠ je u padu, što se objašnjava povećanom upotrebom koronarne reperfuzije u liječenju infarkta miokarda, uključujući perkutanu koronarnu intervenciju i fibrinolitičku terapiju koje smanjuju područje infarkta, time smanjujući rizik nastanka šoka. Temeljni principi farmakološkog liječenja KŠ uključuju intravensku tekućinu, odnosno održavanje adekvatnog volumena, inotrope i vazopresore. Inotropi su prema načinu djelovanja podijeljeni u tri skupine: beta-agoniste, inhibitore fosfodiesteraze tipa 3 i Ca^{2+} senzitizere. Inotropi pojačavaju kontraktilnost miokarda time povećavajući udarni i minutno volumen, vazopresori uzrokujući vazokonstrikciju dovode do porasta sustavnog arterijskog tlaka.
Patofiziologija kardiogenog šoka nije u potpusti objašnjena – ona predstavlja circulus vitiosus: kada je KŠ uzrokovan infarktom, ishemija miokarda uzrokuje dijastoličku i sistoličku disfunkciju lijeve klijetke, što ima za posljedicu povišeni end-dijastolički tlak lijeve klijetke, smanjeni minutni volumen i dodatno smanjenu koronarnu perfuziju čime se perpetuira ishemijom uzrokovana disfunkcija miokarda. Sistemska hipoperfuzija uzrokuje aktiviranje kompenzatornih mehanizama, dovodeći do vazokonstrickije i tahikardije koje povećavaju potrebe mikoarda za kisikom. Posljedica svega je daljnje pogoršanje ishemije i disfunkcije srca, hipoperfuzije organa, te ukoliko se odgovarajućim liječenjem ne postigne poboljšanje hemodinamskog stanja bolesnika, krajnji rezulatat je zatajivanje ciljnih organa i smrt bolesnika. KŠ je zbog navedenog hitno stanje koje zahtijeva brzu dijagnozu i suportivnu farmakološku terapiju. Cilj liječenja je popraviti funkciju srca i time poboljšati perfuziju tkiva kako bi se spriječilo zatajivanje organa.

Ključne riječi: •Kardiogeni šok •Farmakološka terapija •Infarkt miokarda

1. INTRODUCTION

Cardiogenic shock (CS) is hemodynamically unstable state, often associated with multiorgan failure. CS represents a state of hemodynamic instability in patients diagnosed with cardiovascular disease (1). It may result from a number of disorders, such as those that impair functions of the myocardium, heart valves or pericardium, as well as disorders of conducting system. The most common cause of CS is acute ST-elevation (STEMI), of which 5%-15% are complicated by CS (2). CS is a pathological state in which the most important cardiac function, blood pumping into the rest of the body to perfuse the tissues, fails and oxygen and energy supply to the tissues becomes inadequate. CS has to be diagnosed and treat promptly, otherwise, tissue hypoperfusion will cause multiorgan failure with fatal consequences (3).

1.1 EPIDEMIOLOGY AND ETIOLOGY

In 5% to 15% of cases CS is a complication of acute MI and it is a leading cause of death after MI (4). Acute on chronic heart failure is the second most common cause of CS (5). The 1-year mortality is between 50% and 60% (6). Higher mortality rate is reported in patients diagnosed with other acute noncardiovascular illnesses, acute respiratory failure and acute kidney disease, respectively (5). CS is a complication related more to the STEMI than to the non-ST-segment elevation myocardial infarction (NSTEMI). Risk factors for developing CS are patients of older age (>75 years), female gender, patients having diabetes (DM) or those with a history of hypertension (HTN), previous acute coronary syndrome and rapid heart rate (>100 beats/min). Noncoronary causes of CS occur as a consequence of some primary cardiac conditions, such as myocardial, valvular or pericardial abnormalities (1).
Due to the high mortality rate it is difficult to determine the true incidence of CS (3). The shock mostly develops in the first 24 hours from the hospital admission (7). Unfortunately, the mortality rate has not much changed in the past years despite advances in medicine, and it remains unsatisfactory high. The best way to prevent CS is to prevent ischemic heart disease with lifestyle change of the population. Some basic lifestyle changes could make a big difference in a health of an individual, such as to quit smoking as well as to avoid secondhand smoke, eat healthier food and educate the patient to exercise regularly.

1.2 CLINICAL PRESENTATION

Contemporary trials and guidelines define clinical criteria for CS (8). The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) and the other trial, the intra-aortic balloon pump (IABP)-SHOCK II, use evidence of end-organ damage or hemodynamical instability to establish a diagnosis of cardiogenic shock. Laboratory and physiological evidences are indicated as values of serum lactate >2 mmol/L, pulmonary capillary wedge pressure (PCWP) >15 mm Hg or urine output <30 mL/h and systolic blood pressure measurements (SBP) <90 mmHg measured for >30 min or the use of pharmacological therapy to maintain SBP >90 mm Hg (9).

Important signs of end-organ perfusion are altered mental status and cold extremities. Not often mentioned but blood glucose level of >11.1 mmol/L has high prediction value for the development of CS in patients with acute coronary syndrome (ACS) (10). Unresponsiveness to fluid resuscitation is one of the specificities of SBP in CS. Interestingly, no differences were seen in clinical presentation between genders, despite the higher prevalence of CS in women (11).

It was suggested that the diagnosis of CS should be based mainly on the signs of tissue hypoperfusion (12) and status of three organs easily accessible for clinical examination. Skin perfusion, kidney function and state of consciousness, all three known as “windows of the body” clearly show the early signs of CS development (13). Early diagnosis and prompt treatment ensure more favorable outcome, for easier assessment of the risk, symptoms scale was developed. Four symptoms such as pale skin, fainting, impaired consciousness, and glycemia >11.1 mmol/l form 4 Simple Symptoms Shock Scale (4S) that might enable easier diagnosis of a possible development of CS in patients with ACS (10). Sinus tachycardia seen in many patients is a compensatory mechanism for reduced stroke volume (14).

1.3 DIAGNOSIS

CS has to be diagnosed promptly, otherwise if is it not treated on time, tissue hypoperfusion can be fatal (3). CS is usually diagnosed in an emergency setting. The signs such as rapid, weak or even absent pulse, irregular heartbeat, S3 or S4 heart sound, cool skin, rapid and irregular breathing, dilated pupils, chest pain, confusion can be found on physical examination. Other signs of CS can also be found on physical examination, such as oliguria,

decreased capillary refill, clammy extremities or the signs of increased intravascular volume such as elevated jugular venous pressure, hepatojugular reflex and peripheral edema. Aforementioned signs directly represent the manifestation of decreased organ perfusion (15). Acute kidney injury (AKI) caused by reduced glomerular filtration rate occurs as a consequence of decreased renal blood flow due to kidney hypoperfusion and venous hypertension, latter commonly present in shock. AKI may be taken as an indicator of shock severity (14).

Not a single test is sufficient to diagnose CS, but for the complement clinical assessment of the tissue hypoperfusion and for the evaluation and prognosis of CS it is preferable to do a complete laboratory work and diagnostic studies (14). Complete blood cell count, arterial lactate level, NT-pro-BNP, kidney and liver function tests, mental status, urine output combined with invasive blood pressure (IBP) monitoring (5). Laboratory abnormalities may reveal metabolic acidosis, hypoalbuminemia or increased troponin as an indication of cardiac ischemia.

For the patients with instable hemodynamics, it is advised to use invasive arterial blood pressure (IABP) monitoring over the standard non-invasive blood pressure monitoring (NIABP), as the NIABP does not provide continuous pressure monitoring and the wave of the pressure. Invasive monitoring in terms of heart catheterization besides providing information of end-organ perfusion, may enable more proper identification of the etiology of the shock state (5). Swan-Ganz catheter is the most commonly used, and allows continuous evaluation of the hemodynamic responses to various pharmacological therapies (5). Swan-Ganz in CS catheter shows an increase in RA pressure, RV systolic and diastolic pressures as well as increase in PCWP with decrease in CO. Knowing that the most common cause of CS is acute myocardial infarction (AMI), it is important to perform ECG as soon as possible and measure troponin level as well, to evaluate for signs of arrhythmia and/or myocardial ischemia. ECG gives not only diagnostic but also prognostic information. Standard 12-lead ECG does not include recordings of right precordial leads, they are only recorded as a part of electrocardiographic evaluations in patients with inferior myocardial infarction. STE in leads V3R and V4R is an ECG sign of right ventricular myocardial infarction. Right coronary artery supplies inferior and posterior parts of the left ventricle, therefore right ventricular myocardial infarction (RVMI) commonly occurs in conjunction with inferior MI. Increased in-hospital mortality is directly linked with at least 0.5 mm ST-segment elevation (STE) in lead V4R in patients diagnosed with inferior myocardial infarction (15).

ECG also provides information of some nonischemic etiologies, such as damage of the heart muscle or cardiac tamponade .Acute pericarditis as a cause of pericardial effusion may cause diffuse elevation of ST segments, hence the possibility of MI must be considered (16). It is advisable to continue ECG monitoring (6). Arterial hypoperfusion and venous congestion may lead to hepatic injury, presented with increased alanine transaminase (AST). Early increase in ALT values is associated with increased CS mortality (17).
To exclude other causes of chest pain, chest radiography should be performed. Patients diagnosed with CS mostly have signs of LV failure, findings include Kerley B-lines, pulmonary edema and pleural effusions, all highly specific for dyspneic patient (14). However, normal chest X-ray does not exclude CS.

It is mandatory to perform bedside cardiac ultrasonography (US) in all patients with undifferentiated shock in ED. US examination helps to diagnose the etiology of the shock, it simply assesses heart, inferior vena cava, pleural compartments and aorta. It can easily rule out tamponade, and evaluates left and right ventricular functions as well as volume and inferior vena cava status. IVC diameter is a reliable indicator of intravascular volume status, if it collapses with respiration, it indicates hypovolemia. IVC measurements may be inaccurate in patient who has already received vasodilators or diuretics as a part of a treatment, (14). Nonetheless US can also identify pulmonary edema or ascites.(18)
Echocardiography provides a wide range of helpful information about the general status of the heart, including information about the size and shape of the heart, myocardial contractility, possible papillary muscle rupture, mitral regurgitation, ventricular septal defect and cardiac tamponade. Typical finding in CS is dilated LV with poor contractility. If hyperdynamic LV is found, echocardiogram may suggest some other causes of shock like sepsis. Reduced ejection fraction (EF) as a marker of decreased LV contractility, is not necessary diagnostic factor to make a diagnosis of CS (14).
Coronary angiography should be urgently performed in patients diagnosed with CS and suspected for acute coronary syndrome or its complications. Angiography gives an information of the presence and the extent of coronary artery disease, i.e the need for revascularization. It may be proceeded with percutaneous coronary intervention or suggest for the need of urgent surgical revascularization.
Some nonspecific symptoms such as dyspnea, chest pain, tachycardia, hypoxia and elevated jugular venous pressure might represent another important emergency known as pulmonary embolism (PE). PE is the third most common cause of cardiovascular death worldwide; it

activates several different pathophysiological changes that can cause severe hemodynamic compromise. Impact of the PE to RV and its response to it, are the most important factors which determine the outcomes of PE. Due to the nonspecific symptoms, diagnosis of PE is challenging, therefore laboratory test such as increased D-dimer is of a great help when a suspicion to PE is high. Typical ECG pattern "S1Q3T3" is present in 25% of patients commonly accompanied with increased D-dimer alongside with hemoptysis, dyspnea, tachycardia and chest pain. All aforementioned symptoms are clinically valid indications for a further diagnostic procedures (19). CT pulmonary angiography (CTPA) provides accurate information on the presence of PE, but it also gives information on other chest pathologies (20). Another highly specific and sensitive diagnostic procedure is ventilation-perfusion (V/Q) scan also known as V/Q scintigraphy, usually indicated in patients who have contraindications for CTPA such as kidney failure or allergy to a contrast media.

2. PATHOPHYSIOLOGY

Complex pathophysiology of CS can be explained as a vicious cycle, in which failing heart, leads to decrease in cardiac output (CO) and stroke volume (SV) further connected to the lower blood pressure and increase in the pulmonary blood volume. Decrease in CO results in hypotension and systemic hypoperfusion. Sequel of the hypotension is a reduction of coronary artery perfusion, further leading to inadequate supply of the heart muscle with oxygen, facilitating the development of myocardial ischemia.

Division of the vicious cycle leads to the increased pulmonary blood volume and subsequently increased intrapulmonary pressure, i.e. pulmonary congestion leading to insufficient lung gas exchange and hypoxemia. This leads to the decrease in oxygen supply of the heart muscle causing development of the myocardial ischemia and further decrease in the contractility of the heart. Activation of compensatory mechanism further aggravates end-organ perfusion by causing systemic vasoconstriction with the aim of controlling oxygen rich blood redistribution.

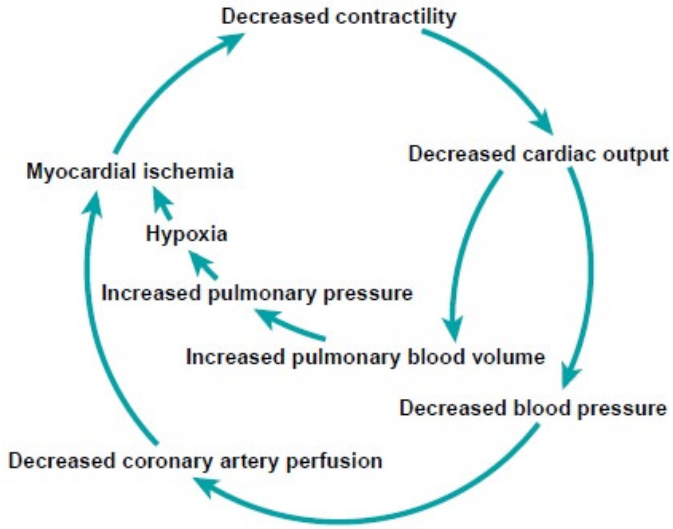

Figure 2.1 Pathophysiology of cardiogenic shock (4)

For the easier understanding of pathophysiology of CS, pressure- volume (PV) loops can be exceptionally helpful. Correct placement of miniaturized conductance catheter in the ventricle is essential for obtaining of an accurate data which are then projected into PV loops graph for better understanding and visualization. Left ventricular PV loops are considered to be a gold standard of hemodynamic assessment and are commonly used to asses cardiac performance. A single PV loop is a summation of the pressure and volume changes that occur within a ventricle during every cardiac cycle. Ventricular volume is presented on the x axes, and y axes represent ventricular pressure. From the PV loops we can measure end diastolic and end systolic volumes, and from these volumes it is easy to asses stroke volume, ejection fraction and cardiac output.

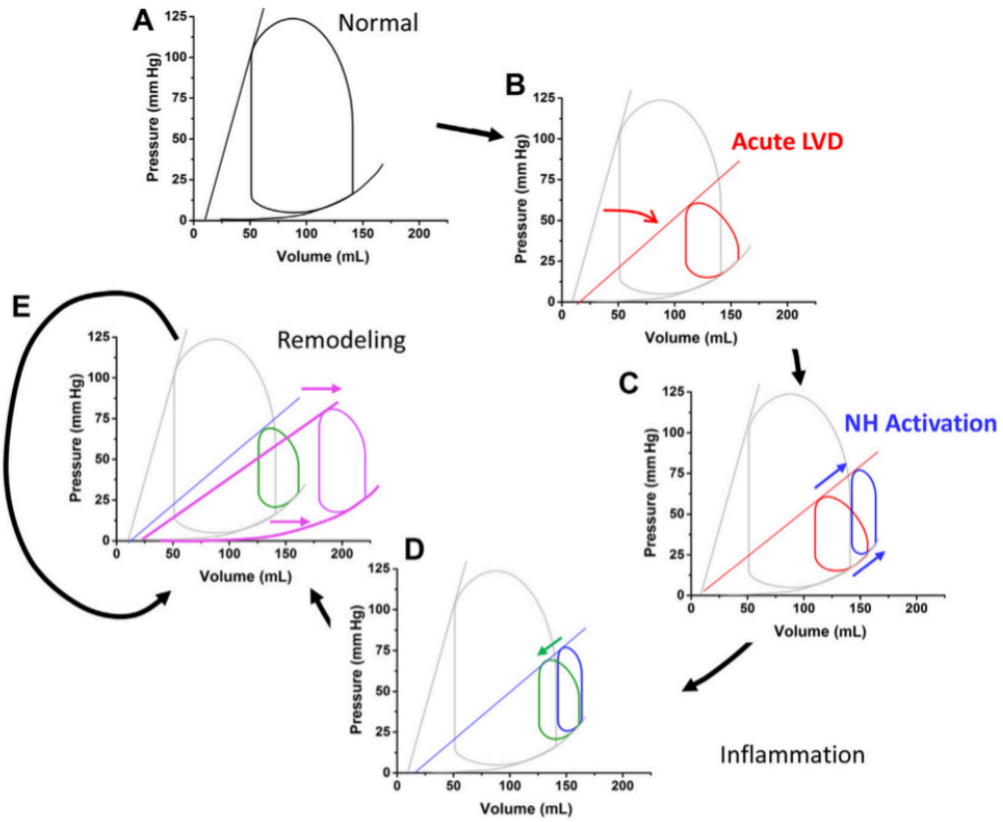

Figure 2.2 Pathophysiology of CS illustrated by use of PV loops (1)

Fig.2.2 A represents the PV loop of a normal, healthy person. Reduction of ventricular contractility, represented as a change in end-systolic pressure-volume relationship (ESPVR) which shifts the curve downward and rightward leading to decline in blood pressure and a reduction of cardiac output are changes commonly present in MI, is easily visualized with PV loop graph (Fig.2.2 B) (1).

The end-systolic pressure-volume relationship is a measure of cardiac contractility and represents the maximal pressure developed by the LV. The slope of ESPVR provides an information of the innate ability of the myocardium to contract. Consequently, the change in the slope of ESPVR can be observed as a change in myocardial contractility. An increase in slope demonstrates increase in contractility also known as positive inotropic response, therefore ventricle can generate greater pressure at any given volume while negative inotropic response meaning decrease in contractility, is demonstrated as less steep ESPVR curve.

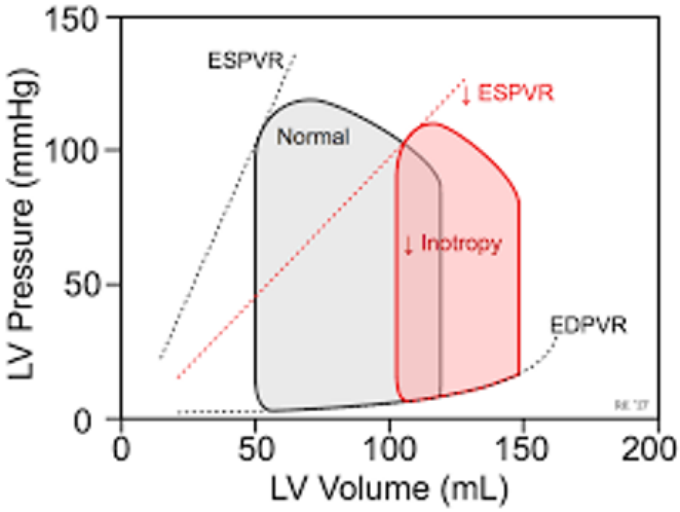

Figure 2.3 Inotropic effects on end-systolic pressure-volume relationship slope(21)

Autonomic response to decreased myocardial contractility is the first compensatory response manifested as activation of neurohormones with the aim of maintaining mean arterial pressure (MAP). Mechanism begins when baroreceptors recognize decrease in MAP and activate efferent autonomic nerve fibers to stimulate release of catecholamines from the adrenal gland. Enhanced autonomic tone increases heart rate, while catecholamines promote vasoconstriction causing increase in total peripheral resistance (TPR). As a result, volume redistribution occurs, increase in sympathetic tone shifts fluid out from the splanchnic compartment into effective circulation, resulting in increased functional circulation, consequently raise in central venous pressure and pulmonary venous pressure is noted (22). Increased blood pressure is seen as a rightward shift of the PV loop, closer to the point of higher end-diastolic volumes and pressure (Fig. 2.2 C). After the neurohormonal activation, another compensatory mechanism takes a place in a form of an inflammatory process. The clinical picture commonly present in patients who suffered MI shows reduced contractility, smaller SV, lower BP and elevated LV end-diastolic volume, shown on PV loops graph with a flatter ESPVR and narrower PV loop shifted to the right
(Fig. 2.2 D)(1). With time, cardiac remodeling occurs (Fig. 2.2 E). As myocyte hypertrophy happens, end-diastolic pressure volume relation (EDPVR) shifts towards the larger volumes, shifting with itself a ESPVR, additionally worsening LV function (1). The whole process of remodeling continues as long as a pharmacological or mechanical therapy begins to show its effects.

3. MANAGEMENT

Treatment of CS is based on the treatment of its cause (etiological treatment), but also supportive therapy with the aim of preserving the perfusion of tissues and organs of the patient. Early revascularization therapy with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is of a crucial importance for patients diagnosed with CS after acute MI. Emergent PCI or CABG reduce mortality (3) and limit multiorgan dysfunction. Patients with CS treated with coronary angiography alone, without revascularization compared to those treated with conservative strategy, had a lower in-hospital mortality rate (23).

The concept of using mechanical circulatory support (MCS) such as axial flow pumps (Impella LP 2.5, Impella CP, Impella LP 5.0), left atrial-to-femoral arterial ventricular devices (TandemHeart) and venous-arterial extracorporeal membrane oxygenation (ECMO) ameliorate survival rate (4). Intra-aortic balloon pump (IABP) support is recommended in patients with CS due to mechanical complications of myocardial infarction like acute mitral regurgitation or ventricular septal defect. Extracorporeal membrane oxygenation and lung protective ventilation, used due to the reduced oxygen supply and decreased perfusion, have the goal of providing oxygenation as well as end organ perfusion. ECMO showed some beneficial results in providing necessary circulatory support, but one cannot expect from EMCO to improve cardiac functions (24). Availability, relatively easy and fast insertion of veno-arterial (VA) ECMO favors its use (25), but ECMO support in the case of left ventricular (LV) failure has some disadvantages: it increases left ventricular afterload and additionally increases stress on an already poorly functioning LV, making unloading of the left ventricle more difficult and thus may lead to lung congestion ("ECMO lung") and worsening the state of a patient (26).

However, before consideration for mechanical circulatory support it is mandatory do achieve optimal non-invasive hemodynamic support including "appropriate" ventricular preload, i.e. volume status as well as vasoactive/inotrope drugs to improve cardiac output and maintain tissue perfusion.

3.1 PHARMACOLOGICAL THERAPY

The advance stages of CS are characterized by vasodilatation, regional circulatory and microcirculatory abnormalities and hypoxia at the cellular level. Decreased cardiac output is initially treated with IV infusions of fluids and plasma, with a goal of maintaining euvolemia (27). The initial treatment should be focused on restoring CO that can be achieved with medical therapies or their combination with mechanical circulatory support.

3.1.1. Medical therapies

Initial step taken in the treatment of CS is to review the medications and to discontinue those that might be contributing in causing hypotension and negative inotropy (5). Medical management, which is primarily of a supportive type, includes; IVFs, inotropes and vasopressors. For the easier control of the adequacy of tissues oxygen delivery, central venous catheter should be inserted. Insertion of the central venous catheter allows easer administration of vasoactive elements and facilitates monitoring of CVP and central venous oxygen saturation ($S_{CV}O_2$) as a response to pharmacological therapy (8).
Pulmonary artery catheter (PAC) used for hemodynamic monitoring plays an important role in the management of patients with CS (28), since small changes in hemodynamic parameters can have a significant impact on patient stability.
Medical therapy of patients with CS is principally based on inotropic and vasoactive substances attributable to their ability to increase cardiac contractility or vascular tone.

3.1.2. Inotropes

Inotropes are pharmaceutical agents, due to their enhancing effect on cardiac contractility they are recommended to be used as the initial treatment of patients presenting with CS (7). Their positive inotropic effect is also amplified by their chronotropic and peripheral vascular effects. They are administered for a short period until hemodynamic stabilization and restoration of peripheral perfusion occur. Reported inotropic adverse side effects require cautious use of inotropes, on one hand they are required to stabilize hemodynamics, but on the other hand they increase myocardial oxygen consumption and may lead to the development of arrhythmias and myocardial ischemia. Most commonly inotropes are used in treatment of patients with peripheral organ hypoperfusion and critical decline of CO (29).

Inotropes are divided into subgroups based on their mechanisms of action; therefore, we differentiate three groups: beta-agonists, phosphodiesterase III inhibitors and Ca^{2+} sensitizers. According to different mechanism of action, different groups produce different side effects.

a) Beta-agonists

Dobutamine is a sympathomimetic agent approved for the temporary use in patients with decreased contractility caused by the heart failure. Its recommended use is only as a short-term intravenous support until the introduction of a more definitive treatment. It has a higher affinity for beta-1 than for beta-2 receptors therefore, strong beta-1 receptor affinity encourages its strong chronotropic and inotropic effects (5). Its weaker action on beta-2 receptors produces mild peripheral vasodilation, contributing to the reduction in the systemic vascular resistance. Combined effects of dobutamine on increased inotropy and decreased afterload, induce a notable increase in CO with minimal effect in BP. Peripheral vasodilation produced by dobutamine might cause problems for patients already presented with moderate or severe hypotension (<80 mm Hg) that's why it should be administered with caution and it is sometimes given in conjunction with norepinephrine (NE). It has a rapid onset of action and a half- life of 2 minutes, but recently it was noted that the therapeutic effect of dobutamine is prolonged, persisting for 4-10 weeks after infusion over a period of 48-72 hours (30). It has a minimal alpha-1 receptor activity, whose vasoconstrictive effects are negated by the baroreceptor mediated response and its stronger beta-2 activity (31). Utilization of dobutamine for the management of patients in shock requires continuous monitoring with electrocardiogram and repeated blood pressure checks. Initial dosage is 2.5μg/kg/min and increased every 10 minutes until end-organ perfusion improves or until adverse effects or the maximal infusion rate of 20 μg/kg/min are achieved. Except from the usual adverse side effects caused by inotropes such as hypotension, dobutamine specifically may cause hypokalemia and its prolonged use is associated with increased mortality (32).

Dopamine is as a precursor of norepinephrine (NE) and epinephrine, and acts in dose-dependent fashion on receptors. It has a stronger action on dopa receptor but as its concentration in plasma rises it also becomes adrenergic agonist acting on beta receptors, while to exert an action on alpha receptors even higher concentrations are required (33). Interestingly dopamine at low concentration of only <3 μg/kg/min causes vasodilation,

identified primarily at the renal level. Strong inotropic effect is accomplished at the dosage of 3-5 μg/kg/min. According to the guidelines dose of dopamine greater than 5 μg/kg/min is going to produce vasoconstriction; at that plasma concentration level it is able to act on alpha receptors. Like for the other inotropes, dose should be titrated until the end organ perfusion improves.
Previously it was used for a long period as a treatment for acute heart failure, until its connection with a harmful side effect - Takatsubo syndrome was proven (33). Higher doses are associated with vasoconstriction, i.e. increased afterload to the left ventricle. Tachyarrhythmias and myocardial ischemia are also reported as side effects. Consequently, dobutamine is preferred over dopamine.

Norepinephrine (NE) is a catecholamine that functions as a hormone and a neurotransmitter in the body with a mixed alpha-1 and beta activity. It has the strongest activity on alpha receptors, subsequently on beta-1 receptors, while it demonstrates the poorest activity on beta-2 receptors. In a dosage of 0.2-10.0 μg/kg/min it shows a strong vasoconstrictive activity hence producing a significant increase in blood pressure. Its ability to mildly increase cardiac contractility is accomplished by its action on beta-1 receptors (34). Guidelines endorse usage of NE over dopamine to reach the target mean arterial pressure (MAP) (35), and therefore it is most commonly used as a first line agent for the treatment of shock when patient is presented with hypotension <90 mm Hg. Treatment of a patient in shock with high dosage of NE might lead to discrepancy in the values of BP measured invasively with non-invasive blood pressure measurements. Hypotensive patients treated with higher doses of NE usually show lower BP for more than 10 mmHg when IBP monitoring method is used than NIBP (36). Thus, patients treated with NA should have invasively measured blood pressure.

Epinephrine is also known as adrenalin, and is a sympathomimetic catecholamine. It exerts pharmacological effects acting as an agonist on alpha-1, beta-1 and beta-2 receptors. When present in small concentration in plasma it shows greater affinity for beta receptors, while in larger doses it exerts action on alpha receptors. Through its action on beta-1 receptors it causes an increase in heart rate and myocardial contractility while its action on alpha-1 receptors induces increased vascular smooth muscle contraction. Epinephrine can be administered through different routes such a through the endotracheal tube when it is used for neonatal resuscitation, intravenously is administered when it is used during the advanced

cardiovascular life support (ACLS) or intramuscularly for the treatment of anaphylaxis (37). Epinephrine has a rapid onset, but its duration of action is short. Cardiovascular side effects include: arrythmias, chest pain, hypertension, palpitations and tachycardia. When epinephrine is administered intravenously, tachycardia and hypertension are expected side effects, that's why it is important to titrate the drug thoroughly while monitoring hemodynamics. Epinephrine is not the first line pharmacological agent because of its increased risk of causing tachyarrhythmias, splanchnic vasoconstriction, prolonged acidemia and hyperlactatemia (38). Even though the use of epinephrine showed very transient improvement in cardiac index, its use is associated with marked safety issues, including refractory shock (39).

Both epinephrine and norepinephrine are efficient in increasing MAP, nonetheless the use of epinephrine was associated with an increase in heart rate, most probably due to higher number of beta-2 adrenoreceptors present in atria (39). Norepinephrine increases the contractile force of the myocardium, requiring greater utilization of energy and as a consequence has a lower cardiac efficiency (39). Treatment with norepinephrine is advised over treatment with epinephrine due to more frequent adverse effects associated with the use of epinephrine, such as lactic acidosis, gastric hypoperfusion and arrhythmias (40). Dopamine acts in a dose-dependent fashion on many receptors and exerts some favorable actions such as one on the renal vasculature, however, its high mortality rate reported as its major adverse effect places norepinephrine as a better choice for therapy.

b) Phosphodiesterase III inhibitors

Milrinone is widely used positive inotropic agent in patients with CS (41). It decreases the degradation of cyclic adenosine monophosphate (cAMP) and increases influx of Ca^{2+} into the cell and thus contributes to myocardial contractility. Accompanying its inotropic properties, it also causes peripheral vasodilation (42). As its mechanism of action and its ability to increase myocardial contractility is not mediated through beta- blockers, it differs from dopamine and dobutamine. Its unique mechanism of action within a group of inotropes enables the use of this pharmacological agent in patients who are receiving beta blockers, like in patients with chronic heart failure whose optimal medical therapy consists of beta blockers (43). Through its mechanism of action, the same intracellular processes are activated in smooth muscle cells

of peripheral and pulmonary vasculature. By decreasing the pulmonary vascular resistance, it may cause improvement in right ventricular function. Alongside with its already mentioned effect of decreasing pulmonary vascular resistance it also decreases systemic vascular resistance but interestingly it increases CO without much affecting the BP. This pharmacological agent should be avoided in patients with renal failure since its renal clearance (44). Possible side effects are hypotension, chest pain, arrhythmias, tremor, bronchospasm and hypokalemia (4).

c) Ca^{2+} sensitizers

Levosimendan has favorable properties in patients with CS. It exerts its effects by acting on troponin C, increasing the sensitivity of cardiomyocytes to already present intracellular calcium levels, resulting in increased contractility. Due to its increased sensitivity to already present Ca^{2+}, arrhythmia reported as its side effect is not hazardous (45). Aside from inotropic effect it also exerts inodilatory properties by opening adenosine triphosphate (ATP)-sensitive potassium channels, leading to vascular smooth muscle relaxation (46) therefore it is often administered in combination with a vasopressor (40). The combined vasodilatory and inotropic effects result in reduced preload and afterload which is of a great help in treatment of patients with decompensated heart failure.
Administration is usually in a rate of 0.05-0.20μg/kg/min. Levosimendans' active metabolite has a long half-life of 7-9 days, hence it is perforable pharmaceutical agent in the process of weaning patients off inotropes or mechanical circulatory support (40). Other reasons for its favorable use in CS is its ability to reduce inflammatory mediators and markers of oxidative stress (40). Reported side effects are hypokalemia, headache, hypotension, and atrial fibrillation. Improvement of hemodynamic parameters were seen, but no study reported lower mortality rate in patients treated with levosimendan, therefore it is preferred as a second-line inotropic agent (40).

Table 3.1 Main characteristics of pharmacological therapy of cardiogenic shock (40)

Inotrope	Mechanism	Dosing	Inotropy	Vasoconstriction	Vasodilation	BP	Diuresis	Recommendation/ Level of Evidence	Possible Side-effects
Beta-agonists									
Dobutamine	Beta-1>beta-2>alpha	2–20 µg/kg/min (–) bolus dose	++	+ High doses	+	+	Neutral	IIb/C	Tachyarrhythmias Hypotension Headache Eosinophilic myocarditis (rare) Peripheral blood eosinophilia
Dopamine	Dopa>beta, alpha in high doses	Renal effect <3 µg/kg/min Inotropic effect 3–5 µg/kg/min Vasoconstriction >5 µg/kg/min (–) bolus dose	++	++ High doses	++ Low doses	+ High doses	++ Low doses	IIb/C	Tachyarrhythmias Hypertension Myocardial ischaemia
Norepinephrine	Beta-1> alpha>beta-2	0.2–10.0 µg/kg/min (–) bolus dose	+	++	Neutral	+	+	IIb/C	Tachyarrhythmias Hypertension Headache
Epinephrine	Beta-1> beta-2>alpha	0.05–0.50 µg/kg/min (+) bolus dose: 1 mg IV every 3–5 min during resuscitation	++	++ High doses	+	Neutral/+	Neutral	IIb/C	Tachyarrhythmias Headache Anxiety Cold extremities Pulmonary oedema Cerebral haemorrhage
Phosphodiesterase III inhibitors									
Milrinone	PDE3 inhibition	0.375–0.750 µg/kg/min (+) bolus dose: 25–75 µg/kg over 10–20 min (optional)	+	Neutral	++	–	Neutral	IIb/C	Tachyarrhythmias Hypotension Headache
Ca^{2+} sensitisers									
Levosimendan	Calcium sensitiser PDE3 inhibition, opening of vascular K_{atp} channels Inhibition in high doses	0.05–0.20 µg/kg/min (+) bolus dose 12 µg/kg over 10 min (optional, not routinely recommended)	+	Neutral	++	–	+	IIb/C	Hypotension Atrial and ventricular tachyarrhythmias Headache

BP = blood pressure; PDE3 = phosphodiesterase type 3.

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Biography

Marija Radić was born in 1995 in Zagreb, Croatia. In 2014 she began to follow her dream and started to study medicine at the University of Zagreb. Her interests lie in the fields of internal medicine and cardiology.