Cardiogenic shock: causes, diagnosis and treatment

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Cardiogenic shock: Causes, Diagnosis and Treatment

GRADUATE THESIS

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Abbreviations:

- ACEI: Angiotensin-Converting-Enzyme Inhibitor
- AV: Arteriovenous
- CBC: Complete Blood Count
- CF: Coagulation Factor
- CVP: Central Venous Pressure
- CS: Cardiogenic Shock
- CHF: Congestive heart failure
- CI: Cardiac Index
- CMP: Comprehensive Metabolic Panel
- CPI: Cardiac Power Index
- CCB: Calcium Channel Blocker
- ECHO: Echocardiography
- IHD: Ischemic Heart Disease
- MI: Myocardial Infarction
- LV: Left Ventricle
- LVEF: Left Ventricular Ejection Fraction
- HF: Heart Failure
- JVP: Jugular Venous Pressure
- MI: Myocardial Infarction
- MAP: Mean Arterial Pressure
- MR: Mitral Regurgitation
- NSTEMI: Non-ST-Elevation Myocardial Infarction
- NO: Nitric Oxide
- NS: Normal Saline
- NTG: Nitroglycerin
- PRBC's: Packed Red Blood Cells
- PiCCO: Pulse Contour Cardiac Output
- RV: Right Ventricle
- S3: The Third Heart Sound
- SV: Stroke Volume
- SVR: Systemic Venous Resistance
- STEMI: ST-elevation Myocardial Infarction
- SBP: Systolic Blood Pressure
- NSTEMI: non-ST-elevation Myocardial Infarction
- MAP: Mean Arterial Pressure
- SBP: Systolic Blood Pressure
- US: Ultrasound
- CI: Cardiac Index
- CPI: Cardiac Power Index

- IHD: Ischemic Heart Disease

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1.SUMMARY

Title: Cardiogenic Shock: Causes, Diagnosis and Treatment

Keywords: Cardiogenic Shock, Myocardial Infarction, Acute Coronary Syndrome,

Author: Marko Ilari Kavilo

The most common cause for CS is LV failure in the setting of STEMI. The infarct is located most likely in the anterior wall. Currently CS is complicating between 8 to 9% of patients with STEMI and 2,5% of patients with NSTEMI. Mortality is high with 50%.

CS has a complex pathophysiology. It results from permanent or temporary disruptions in the whole circulatory system. In addition to mechanical disruptions, neurohormones, inflammation and peripheral vasculature also play a major role in the pathophysiology of CS.

Diagnosis of CS can be usually made by easy-to-access criteria. Detailed physical examination, electrocardiogram, laboratory studies and echocardiography play all a major role in assessing the patients. PA catheters may be used for diagnosis and advanced hemodynamic monitoring, but it is not obligatory.

Treatment of CS involves several different aspects from which the first one is intensive care treatment with fluids, vasopressors and inotropes. The goals of the treatment of CS are optimizing MAP and CO while keeping the risk of pulmonary edema low. Therapeutic hypothermia has also proven its benefit in treating CS patients after resuscitation. Prevention and treatments of multiorgan system dysfunction should be also emphasized since it greatly affects the patients prognosis.

Modern medicine has also made available several different mechanical circulatory support devices that can work either as a bridge to therapeutic resolution, as a bridge to transplant or as a bridge to long-term mechanical circulatory support device. The IABP didn’t prove its usefulness in patients with CS. On the other side, despite the expectations and optimistic first results, the use of pVADs didn’t decrease the short or long-term mortality when compared to IABP in patients with CS.

2. SAŽETAK

Najčešći uzrok kardiogenog šoka (engl. cardiogenic shock – CS) je akutno zatajivanje srca u kontekstu akutnog infarkta miokarda, osobito prednje stijenke. U današnje vrijeme CS prisutan je u 8-9% bolesnika s infarktom miokarda sa ST elevacijom (STEMI) i u 2,5% bolesnika s infarktom miokarda bez ST elevacije. Smrtnost je visoka i iznosi oko 50%.

Patofiziologija CS je kompleksna. Dolazi do privremenih ili trajnih poremećaja u cijelom cirkulacijskom sustavu. Osim mehaničkih poremećaja, neurohormoni, upala i periferna vaskulatura također igraju važnu ulogu u patofiziologiji CS. Dijagnoza CS može se postaviti na temelju jednostavnih kriterija. Detaljni fizikalni pregled, elektrokardiogram, laboratorijske pretrage i ehokardiografija su ključni u inicijalnoj procjeni bolesnika. Kateterizacija plućne arterije može se koristiti za dijagnozu i napredno hemodinamičko praćenje, ali nije nužna.

Liječenje CS uključuje nekoliko različitih aspekata, ali osnova je intenzivna skrb uz primjenu volumena, vasopresora i inotropa. Ciljevi liječenja CS su optimiziranje tlaka u plućnoj arteriji i minutnog volumena, održavajući rizik od plućnog edema na najnižoj mogućoj razini. Terapeutska hipotermija također je dokazala svoju korist kod liječenja bolesnika sa CS nakon oživljavanja. Važna je i prevencija i liječenje multiorganskog zatajivanja koje uvelike utječe na prognozu bolesnika.

U modernom liječenju danas je dostupno nekoliko različitih mehaničkih cirkulacijskih uređaja za podršku koji mogu služiti kao premoštenje do oporavka, transplantacije ili kao premoštenje do ugradnje dugoročnog mehaničkog cirkulacijskog uređaja za podršku. Nije dokazana korist od primjene intra-aortne balon pumpe (IABP) kod bolesnika u CS. S druge strane, unatoč očekivanjima i optimističnim prvim rezultatima, uporaba pVADs nije smanjila kratkotrajnu ili dugoročnu smrtnost u usporedbi s IABP-om u bolesnika s CS.

3. PREFACE

Cardiogenic shock is a serious disorder with high early death rate. However, it is treatable, and early aggressive treatment can result in full recovery. Cardiogenic shock occurs occasionally on hospitalized patients, especially in patient population hospitalized with acute coronary syndrome. Recent evidence suggests that neurohumoral and cytokine mechanisms, as well as peripheral vasculature, play a substantial role in pathogenesis of cardiogenic shock. Survivability of cardiogenic shock can be substantially improved by early revascularization therapy. Modern medicine knows several mechanical interventions available for this patient group. Also, clinical studies are feasible in this high-risk patient population. Hospital survivors have an excellent chance for long-term survival with good quality of life. This review will focus on the causes, diagnosis and treatment of cardiogenic shock.

4. ETIOLOGY & EPIDEMIOLOGY

4.1 ETIOLOGY

The largest data set to assess the various etiologies of CS is The SHOCK Trial Registry.[1] LV failure in the setting of STEMI is the most common cardiac cause. It accounts 79% of patients with CS and is most often due to STEMI in the anterior wall. Causes around mechanical complications of IHD include severe MR (7%), ventricular septal rupture (4%), RV failure (3%) and tamponade (1,3%).[1] Among these cardiogenic causes ventricular septal rupture carries the highest mortality.

Non-ischemic cardiac conditions can also lead to CS. Among the pharmacologic causes β-blockers, CCB's and Digoxin toxicity are associated with CS. Acute myocarditis, stress cardiomyopathy (i.e. Takotsubo's cardiomyopathy) and nonischemic cardiomyopathies (i.e. sarcoidosis, amyloidosis and hemochromatosis)

lead to primary ventricular dysfunction and possibly further to CS. Outflow obstruction and CS can be result of valvular stenosis or left ventricular outflow obstruction (i.e. hypertrophic cardiomyopathy). Trauma, degenerative disease and endocarditis can lead to acute valvular regurgitation and further to CS. From endocrine causes hypothyroidism is associated with CS. From tachyarrhythmias supraventricular tachyarrhythmias, monomorphic VT and polymorphic VT (i.e. Torsades de Pointes) and from bradyarrhythmias sinus node dysfunction (i.e. sick sinus syndrome) and AV node dysfunction (i.e. AV nodal block) can be causes of CS.[1]

4.2 EPIDEMIOLOGY

Patients with CS often die before the arrival to the hospital. Therefore, the true incidence of CS is difficult to determine. However, over the 15 years, there has been doubling from 4% to 8% in the proportion of intensive care admission rates of patients with CS.[2] Currently CS is complicating approximately 8% to 9% of patients with STEMI and 2,5% of patients with NSTEMI. Mortality in CS patients have stayed few years unchanged and remains very high with 50%.[3]

5. PATHOPHYSIOLOGY

Pathophysiology of CS is complex. It is result of permanent or temporary derangements of the entire circulatory system. Most common primary insult is the LV pump failure. However, other parts of circulatory system contribute to event with inadequate compensation or other defects. Often these abnormalities are partially or completely reversible, and this might explain the good functional outcome in most survivors.

5.1 LEFT VENTRICLE

The dysfunction initiating CS is often severe, although not always. The insults in Figure 1 initiating LV dysfunction in CS represent MI or systolic or diastolic dysfunction. Therefore initiating factors of LV dysfunction in CS can reflect either irreversible injury of varying reasons, reversible ischemia or damage from prior infarction, or some combination of these. Due to the location and function of the heart, the changes of blood pressure can be simultaneously either beneficial or detrimental. Lower blood pressure is beneficial to heart's pumping capacity by afterload reduction, but lower blood pressure also decreases coronary perfusion diminishing oxygen delivery to the cardiac muscle.

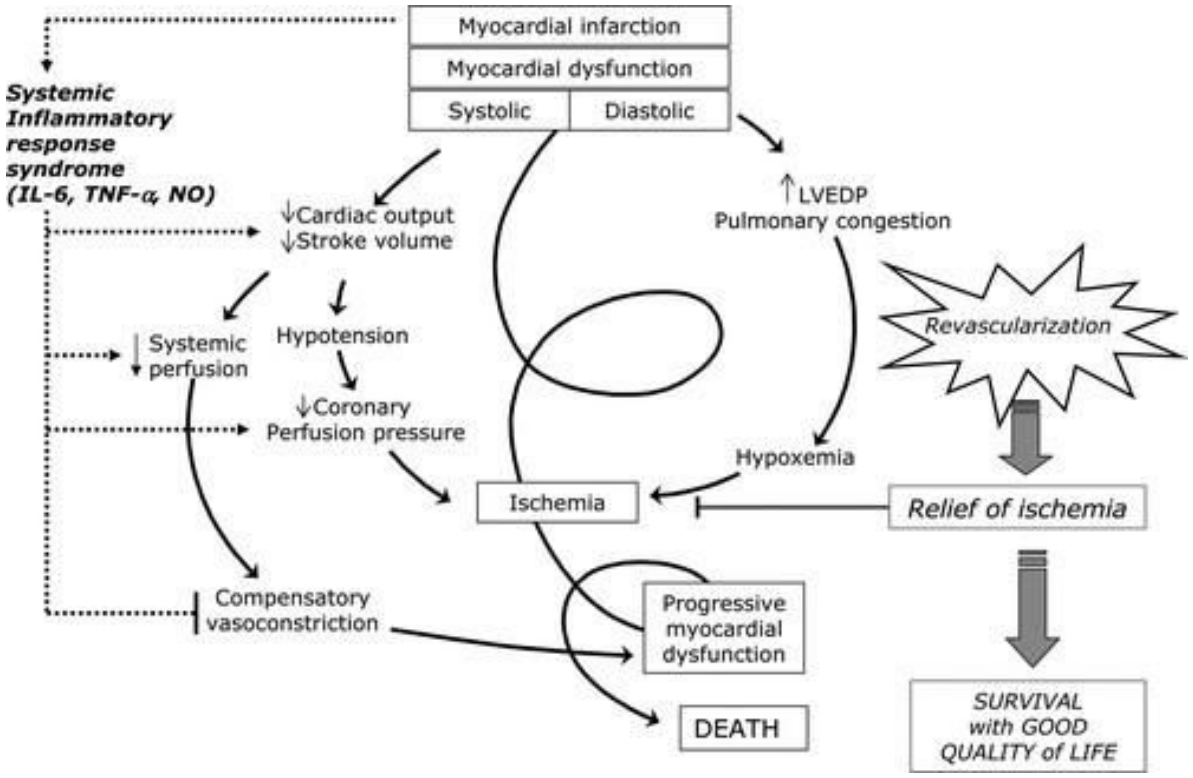

Figure 1 shows the classic description of CS pathogenesis. Myocardial injury causes systolic and diastolic dysfunction. Systolic myocardial dysfunction manifests

as decreased CO and SV, leading to hypotension. Hypotension decreases coronary perfusion pressure leading to ischemia of the myocardial muscle and further deteriorating myocardial function. The ischemia causes cell death in the infarct border zone and in the remote zone of myocardium. Decreasing CO and SV also simultaneously lead to decreased systemic perfusion, initiating vasoconstriction and furthermore impairing myocardial function. Myocardial infarction, in addition to the impairment of myocardial muscle, affect hemodynamics via systemic inflammatory response. Systemic inflammation may play a role by limiting the peripheral vascular compensatory response and therefore may contribute to myocardial dysfunction. It remains unclear if inflammation plays a key role in causation or if it's just an epiphenom. Diastolic aspects of cardiac dysfunction cause pulmonary congestion due to increased LVEDP and add into hypoxemia by decreased oxygenation of the blood in lungs.[4,5]

Due to the complex pathophysiology of CS, in many cases LVEF may be only moderately depressed in CS and often severe impairment in contractility doesn't lead to CS.[6]

5.2 RIGHT VENTRICLE

RV dysfunction can be a direct cause or a contributor to CS. However, a shock predominantly caused by RV represents only 5% of CS complicating MI's.[7] Isolated RV dysfunction caused shock carries almost equal mortality compared to LV shock.[7] In the SHOCK registry, the benefit of revascularization was similar to patients with primarily a RV dysfunction compared to patients with primarily a LV dysfunction.[7]

LV filling might decrease as a result of decrease in right sided cardiac output or ventricular interdependence. Patients with RV failure caused CS have typically very high RV end-diastolic pressure (>20 mmHg).[7] The elevation of RV end-diastolic pressure causes interventricular septum to move toward the left atrium impairing both LV filling and LV systolic function.[8] This is especially important since aggressive

fluid resuscitation is a common practice in treating RV failure in shock. Higher CO is associated with LV end-diastolic pressures of 10-15 mmHg.[9] Promotion of forward flow and decrease of pulmonary resistance can be achieved with inhaled NO. Rarely creation of atrial septal defects and pericardiectomy have been used in difficult cases.

5.4 NEUROHORMONES, INFLAMMATION AND PERIPHERAL VASCULATURE

CS causes a hypoperfusion of vital organs and peripheral tissues. The decrease in CO leads to release of catecholamines that in turn constrict arterioles with a goal to maintain perfusion in the vital organs. Shock also leads in to an increase in angiotensin II and vasopressin levels, and this improves coronary and peripheral perfusion. However this improvement is done with the expense of increased afterload. Activation of neurohumoral mechanisms in shock also leads to salt and water retention. Water retention might help with perfusion but it can also aggravate pulmonary edema. The reflex mechanism of increasing SVR might not be fully effective. This was demonstrated by variable SVR, with median SVR in CS in the normal range despite vasopressor therapy in the SHOCK trial.[10] It is also possible that SVR is low in CS patients.

In the SHOCK cohort trial 18% of the patients had a low SVR in the similar pattern to septic shock. 74% of these patients later developed positive blood cultures.[10] However, the low SVR preceded any clinical diagnosis of sepsis or culture positivity by days. These findings support the observation that MI can cause SIRS. This inappropriate vasodilation that happens as a part of SIRS impairs the perfusion of the GI system and allows this way the transmigration of bacteria to the bloodstream. Levels of tumor necrosis factor-α and interleukin-6 have been found in patients admitted with MI and initially in Kilip class I but later developed CS.[11] However SIRS is more common with increased duration of shock.[12] The highest levels of cytokines are typically found after 24-72h from MI. Both tumor necrosis factor-α and interleukin-6 have depressant action on the myocardium and

interleukin-6 might also disrupt coronary blood flow since it has a property to cause endothelial damage on blood vessels.[13] There are also other circulating factors that have been reported to contribute to SIRS in MI (e.g. c-reactive protein, procalcitonin, neopterin, complement). There was a phase-2 study about complement (C5) inhibitor pexelizumab in MI patients, however in the results it was found that this aforementioned drug did not reduce the development of shock or mortality.[14,15]

Excessive amounts of NO might also have a contributory effect on SIRS. Increased expression of NO synthase is associated with MI, and excess NO leads to vasodilation, depression of myocardial function and interference of catecholamine action. Isoform nonselective NO synthase inhibitors appeared to improve outcomes and haemodynamics in small studies of CS patients but NG-monomethyl-L-arginine was not found to reduce mortality in large multi-center trial.[16] The latter however resulted in early blood pressure rise in patient population that had persistent hypotension despite vasopressors and after opening the infarct artery.[17] This suggests that excess NO contributes to hypotension. Regardless, more studies are needed on this topic.

6. DIAGNOSIS

CS is a state of end-organ hypoperfusion due to cardiac failure. CS forms a spectrum that ranges from mild hypoperfusion to profound shock. Hemodynamic parameters are included in the definition of CS: persistent hypotension (SBP <80 to <90 mmHg or MAP 30 mmHg lower than the baseline) with severe reduction in the cardiac index (<1.8 L x min^{-1} x m^{-2} without support or <2.0 to 2.2 L x min^{-1} x m^{-2} with support) and adequate or elevated filling pressure (e.g. LV end-diastolic pressure >18 mmHg or RV end-diastolic pressure >10 to 15 mmHg). Doppler echocardiography is usually used in the confirmation of elevated LV filling pressures and establishing the cause.[18]

PA catheterization is occasionally used in diagnosis. However, diagnosis of CS can usually be made based on the basis of easy to access criteria without advanced haemodynamic monitoring.[19] Established criteria for diagnosis are (1) SBP

<90 mmHg for >30 min or vasopressors required to achieve BP >90 mmHg (2) pulmonary congestion or elevated left-ventricular filling pressures (3) signs of impaired organ perfusion with at least one of the following criteria: (a) altered mental status; (b) cold, clammy skin; (c) oliguria; (d) increased serum lactate.

Immediate detailed physical examination is critical in a patient suspected of CS. The main focus should be identifying the poor tissue perfusion and finding out the etiology of CS. Findings from physical examination, ECG, chest X-ray, ECHO and lab results greatly help in this.

6.1 PHYSICAL EXAMINATION

Classical findings in case of decreased cardiac function can be divided into signs of abnormal abnormal cardiac function, signs of increased intravascular volume and signs of decreased organ perfusion. Findings suggestive of abnormal cardiac function are S3 or S4 heart sounds, murmurs of valvular disease or mechanical complications of ischaemia, and bibasilar rales. Increased intravascular volume would be suggested by presence of pedal edema, hepatojugular reflux and elevated jugular venous pressure. Typical signs of decreased organ perfusion would be oliguria, cool and clammy extremities, decreased capillary refill and altered mental status.

Presence of elevated JVP, S3 and displaced cardiac apex are strongly suggestive of heart failure.[20] However, findings from physical examination generally lack sensitivity. JVP can be used to roughly estimate CVP. Hepatojugular reflux (applying pressure on the patient's right upper quadrant of abdomen) can be used in order to locate the patient's JVP location. Hepatojugular reflux has a positive likelihood ratio of 8.0 for elevations in left heart filling pressures.[18] It is practical to roughly estimate if JVP is high, normal or low. Central veins and filling pressures can be assessed also with bedside ultrasound in case if JVP cannot be assessed from other measurements.

6.2 ELECTROCARDIOGRAM

ECG is a standard measure in anyone suspected suffering from coronary ischaemia. ECG can provide valuable information in addition to showing STEMI. For patients with inferior MI 0,5 mm ST elevation in V4R in right sided ECG has been shown to be a independent indicator of increased in-hospital mortality.[21,22] Also inferior infarction with ST depression in V1, V2 and/or V3 is suggestive of posterior infarction and also indicative of increased morbidity and mortality.[23] Nonischemic etiologies (e.g. tamponade) can be also suggested from ECG. Due to the limited specificity and negative predictive value of signs like PR depression, low QRS voltage and electrical alternans presence of these signs can lead the way to US evaluation.[24,25] Also it has been found that lead aVR may provide important additional information in diagnosis of coronary artery disease even though it's occasionally ignored by clinicians. It may provide a clue to the location of the lesion (left main disease) and also provide hints when suspecting a triple-vessel disease.[62]

6.3 LABORATORY STUDIES

Standard laboratory studies (CBC, BMP, CF's, lactate, venous blood gas and troponin) often show derangement in case of CS due to the hypoperfusion. Lactate is in a great role because it can cause metabolic acidosis in CS patients. Abnormal liver enzymes and coagulation factors can possibly be seen due to hepatic congestion. It's important to assess the relationship between electrolytes and arrhythmias. Elevated natriuretic peptide levels have high high sensitivity for acute HF and B-type natriuretic peptide levels less than 100 pg/mL or an N-terminal B-type natriuretic peptide levels less than 300 pg/mL are excluding acute HF.[26]

6.4 ECHOCARDIOGRAPHY

Echocardiography is used as a evaluation measure in suspicion of CS in order to assess LVEF, valve function, intravascular volume status and pericardial effusion or obstructive lesion.[27] Intravascular volume status and RA pressure can be determined by assessing IVC.

Determining LVEF is critical when suspecting CS. It can be simply determined as hyperkinetic, normal or poor. Diagnosis of CS can be excluded if the LVEF is either hyperkinetic or normal, and there is no coexisting valvular disease, arrhythmia or tamponade. However, poor LVEF is not sufficient for diagnosis of CS and it should be used as a part of overall evaluation of the patient. Echocardiography is also great when visualizing pathologic valve function, especially in secondary ischemic mitral valve dysfunction.

Also, echocardiography is very helpful when diagnosing pericardial effusion or tamponade. Echocardiography is able to visualize an effusion and determine its shape and location. Early right ventricular diastolic collapse and end-diastolic right atrial collapse are indicative of cardiac tamponade. Also, a greater than 30% decrease in mitral-inflow velocity in inspiration is associated with cardiac tamponade.[28] Obstructive lesions, like different stenoses, can be visualized with echocardiography.

7. TREATMENT

Goals in CS are to optimize both MAP and CO while decreasing the risk for pulmonary edema. MAP equals CO x SVR and CO can be determined by equation HR x SV. Stroke volume is depending on preload, afterload and contractility. Pulmonary edema might be expected when PCWP is over 20-25 mmHg, however increased pressures might be tolerated in chronic HF. Hepatic and renal congestion often happens when CVP/RAP is over 15 mmHg.

7.1 REVASCULARIZATION

Like shown in the SHould we emergently revascularize Occluded Coronary arteries for cardiogenic shocK (SHOCK) trial, early revascularization is proven to be the most important treatment approach in CS complicating AMI.[29] The trial failed to show the superiority of revascularization therapy versus medical therapy on 30-day mortality. However there was a significant reduction mortality with longer follow ups (½, 1 & 6 years).[30,31] The number needed to save one life is <8 when early revascularization is compared to medical therapy. Current treatment guidelines are using class 1B for early revascularization and CABG.[32,33] More efforts are needed to have the clinicians to recognize the importance of early revascularization since the rates of application are still in quite unsatisfactory levels ranging from 50-70% in registries. [34,35,36] Overall, early revascularization has however markedly increased in clinical practice.

7.1.2 REVASCULARIZATION IN MULTIVESSEL CORONARY ARTERY DISEASE

Around 70-80% of CS patients are presenting with multivessel disease.[30,37,38] Multivessel disease is defined as stenosis/occlusion in more than one vessel.[30,37,38] Multivessel disease is correlated with higher mortality in comparison to the single vessel disease.[39] Current guidelines recommend either PCI or CABG depending on amenability to PCI and coronary anatomy.[32] There is still large uncertainty considering the choice of reperfusion therapy and correlating outcome since all the trials in the past haven't specified the type of reperfusion chosen. Current limited data suggests similar mortality rates for CABG and PCI.[40] In the case of CS patients CABG is rarely performed (the rates are <5 % in registries and trials).[36,37]

Recent CULPRIT-SHOCK trial showed that in patients with multivessel disease and acute MI with CS, the strategy consisting of PCI on the culprit lesion only with possible staged revascularization determined a lower 30-day risk of the

composite of all cause mortality or severe renal failure compared with multivessel PCI.[63] This was driven by a significant risk reduction in 30-day all cause mortality by the culprit lesion-only strategy compared with immediate multivessel PCI (43.3 vs. 51.6%; HR 0.84, 95% CI 0.72–0.98, P = 0.03). These findings should be interpreted in in light of a low 12,5% (43 out of 344 patients) crossover rate from culprit-lesion only to immediate multivessel PCI based on physicians' judgement. Due to these aforementioned findings, it is now recommended that patients with acute MI with CS should be treated with culprit lesion-only PCI.

7.2 PERI-INTERVENTIONAL ANTITHROMBOTIC THERAPY

Antithrombotic (anticoagulation & antiplatelet) therapy has a very important role when considering PCI. Currently, in case of PCI, it is recommended to treat with aspirin and P2Y12 inhibitor (either clopidogrel, ticagrelor or prasugrel). There are currently no trials for oral antiplatelet therapy in case of CS. However it should be noted, that the enteral absorption is limited in CS, and the bioavailability of these drugs could be also limited by mechanical ventilation impairing the patient's ability to swallow the drugs. In intubated patients the tablets should be crushed and administered through the nasogastric tube. In case that CABG may be required, the use of P2Y12 inhibitors should be avoided. Recently, it could have been shown that crushed Ticagrelor could have superior antiplatelet action compared to non-crushed tablets.[42] Anticoagulant therapy (either UFH, enoxaparin or bivalirudin) should be also used in case of PCI. The recommendations in case of anticoagulation are same as in other types of coronary syndromes because evidence from specific randomized trials in CS is still missing.

It is known that failure to achieve normal flow affects negatively to mortality and that success in restoration of normal epicardial flow in CS is lower than in non-CS cases.[43] Oral antiplatelet glycoprotein IIb/IIIa-inhibitors may be beneficial in CS. There is existing observational data suggesting that potential mortality benefit could be reached by using intravenous IIb/IIIa platelet inhibitors.[14] However in the CS setting there is only one randomized trial of 80 patients (with 35% cross-over in

standard treatment group) which failed to confirm that routine upstream abciximab usage is superior in comparison with standard treatment with optional abciximab use left at the discretion of the interventionist.[15]

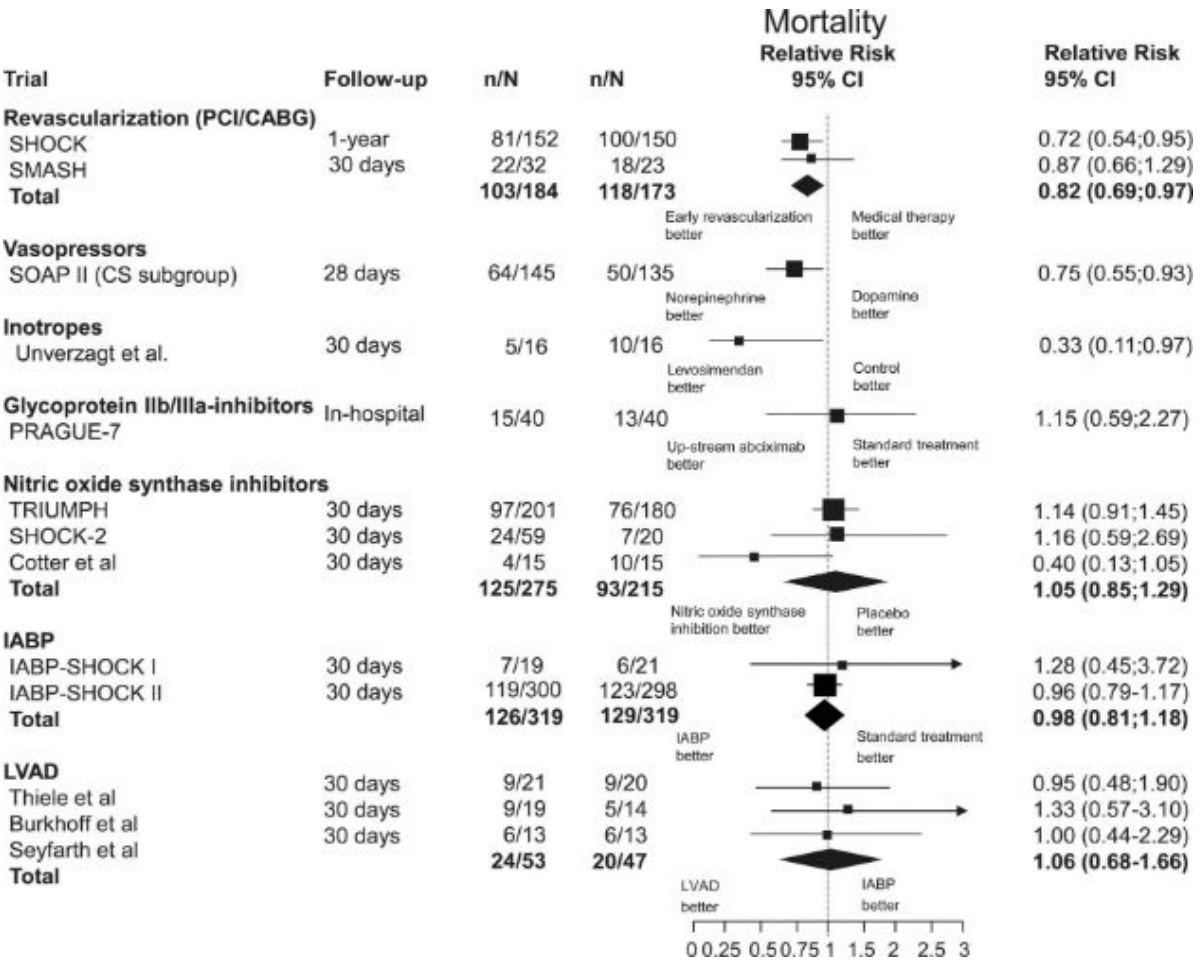

Figure 2 Current evidence from randomized clinical trials in CS in the PCI era.

7.3 INTENSIVE CARE UNIT TREATMENT

7.3.1 FLUIDS, VASOPRESSORS, INOTROPES

Like mentioned before, goals in treatment of CS are optimizing MAP and CO while keeping the risk of pulmonary edema low. Treatment can be approached by assessing and optimizing preload, afterload and contractility.

Preload can be assessed by measuring PCWP which roughly equals LVEDP and LVEDV. Current goals for PCWP are 14-18 in acute MI and less than/or equal to 14 in acute decompensated HF. Preload should be optimized individually with every patient by measuring SV with different PCWP to create Starling curve. Preload can be increased by giving patients NS. Albumin hasn't shown any clinical benefit over NS. PRBC's can be given instead of NS in patients with significant anemia. Preload can be decreased by diuresis. Ultrafiltration or dialysis can be used in patients who are refractory to diuretics.

Afterload is often represented as the wall stress during LV ejection. Wall stress during LV ejection can be represented as $(-SBP\ x\ radius) / (2\ x\ wall\ thickness)$ and is therefore proportional to MAP and proportional to SVR, which can be calculated by SVR = MAP - CVP/CO. Established goals in CS are MAP over 60 mmHg and SVR between 800 and 1200. With MAP over 60 and high SVR it is recommended to use vasodilators (eg NTG, ACEI, nitroprusside, hydralazine) or to wean vasopressors. With MAP less than 60 mmHg, high SVR and subsequently lower CO it is recommended to temporize and stabilize the patient with vasopressors until the CO can be increased. MAP of less than 60 mmHg and low SVR (and therefore inappropriate vasoplegia) should be treated with vasopressors (eg dopamine, phenylephrine, norepinephrine, or vasopressin if refractory). Norepinephrine has better outcomes compared to dopamine even in CS.[44]

Contractility should also be optimized. Contractility is proportional to CO for given preload and afterload. Goal CI (CO/BSA) is over 2.2. There are several methods that can be used in case CI is too low despite optimal preload and

vasodilators (as MAP permits). Inotropes and mechanical circulatory support can both be used. Inotropes include epinephrine (strong inotrope and pressor), milrinone (strong inotrope & vasodilator, including pulmonary vessels) and dobutamine (moderate inotrope & mild vasodilator). Both dobutamine and milrinone are proarrhythmic. Often dobutamine and norepinephrine are given together in order to improve cardiac contractility.[37] Other inotropes (levosimendan & phosphodiesterase inhibitors) have been recently under study based on their improvement of myocardial contractility without increase in oxygen demand and also due to their potential for vasodilation. However recent Cochrane review showed that the current evidence for inotropes and vasodilators in CS is very limited.[45] Only four very small studies were eligible for this meta-analysis and three trials with a total of 63 participants with high overall risk of bias compared levosimendan to standard treatment (enoximone or dobutamine) or placebo. Levosimendan showed a borderline survival benefit in comparison with enoximone (Hazard ratio 0.33; 95% confidence interval 0.11–0.97; Figure 3). Only small differences in haemodynamics, length of hospital stay, and frequency of major adverse cardiac events were observed. Catecholamines increase myocardial oxygen consumption and they should be administered with as low dose as possible and for as short duration as possible.

Catecholamines are administered in approximately 90% of CS patients.[37] However, the evidence from randomized trials is very limited considering catecholamines in CS. Even though it is known that catecholamines have a positive effect in hemodynamics, there exists no randomized data showing the prognostic benefit. The significantly higher rate of arrhythmic events with dopamine versus epinephrine was shown in randomized comparison of 1679 patients with shock including 280 CS patients treated with dopamine. There was also lack of significant decrease in mortality. The predefined CS subgroup had lower mortality with norepinephrine (Figure 3). Therefore epinephrine should be chosen as the vasopressor agent in CS patients who have low blood pressure. Optimal range for BP is between 65 and 70 mmHg, higher pressures are not associated with improved outcomes.

7.3.2 MULTIORGAN SYSTEM DYSFUNCTION

Multiorgan system dysfunction (MODS) should be emphasized as well even though there's not specific guidelines for treatment of MODS in CS. It has a strong impact on prognosis. There are several measures that are recommended.[46] Pulmonary catheters, PiCCO or other systems should be used in all complicated cases due to fact that haemodynamic management is dependent on optimal filling pressures. It is important to try to avoid pulmonary injury by using lung protective ventilation in case invasive ventilation in needed. Urinary production should be measured. Continuous renal replacement therapy should be administered in case of acute renal failure with signs of uraemia, metabolic acidosis, refractory hyperkalemia and/or hydropic decompensation. Prophylaxis for stress ulcers and thromboembolism should be provided. Glycemic control to less than 11.0 mmol/L and optimal nutrition are also in great role.

It is also common to encounter moderate or severe bleeding in CS patients. It is also influenced by concomitant use of ventilation techniques.[30,37,47,48] Blood transfusions in coronary syndromes increase mortality.[49] The explanation might lie in alterations of nitric oxide biology in erythrocytes in stored blood. This would lead into initial vasoconstriction, platelet aggregation and ineffective oxygen delivery. This contradicts the past belief that increase of hemoglobin and oxygen delivery would improve outcomes in ischemia. Bleeding and transfusions are also contributing to inflammation.

7.3.3 HYPOTHERMIA

Hypothermia is established in patients who are suffering from cardiac arrest patients with shockable rhythm outside the hospital settings. It is used in order to prevent brain injury and improve survival.[50] CS patients have been excluded in the relevant hypothermia trials but hypothermia is often applied to CS patients after resuscitation.

Over 40% of the CS patients were resuscitated in the IABP-SHOCK II trial before the randomization with subsequent induced hypothermia. The relevance of this induced hypothermia was shown.[37] The reduction of use of catecholamines and the improvement of hemodynamics in the settings of CS were shown in the first non-randomized human trials and animal trials.[51] It could be also beneficial to induce hypothermia in non-resuscitated CS patients.[51]

7.4 MECHANICAL SUPPORT

Table 1: Technical features of percutaneous support devices

	iVAC 2L®	TandemHeart™	Impella® 5.0	Impella® 2.5	Impella® CP	ECLS (multiple systems)
Catheter size (F)	11 (expandable)	—	9	9	9	
Cannula size (F)	17	21 venous 12–19 arterial	21	12		17–21 venous 16–19 arterial
Flow (L/min)	Max 2.8	Max. 4.0	Max. 5.0	Max. 2.5	3.7–4.0	Max. 7.0
Pump speed (rpm)	Pulsatile, 40 mL/beat	Max. 7500	Max. 33 000	Max. 51 000	Max. 51 000	Max. 5000
Insertion/Placement	Percutaneous (femoral artery)	Percutaneous (femoral artery + vein for left atrium)	Peripheral surgical (femoral artery)	Percutaneous (femoral artery)	Percutaneous (femoral artery)	Percutaneous (femoral artery + vein)
LV unloading	+	++	++	+	+	–
Anticoagulation	+	+	+	+	+	+
Recommended duration of use	−21 days	−14 days	10 days	10 days	10 days	−7 days
CE-certification	+	+	+	+	+	+
FDA	–	+	+	+	+	+
Relative costs	++	+++++	++++	+++	++++	+(+)

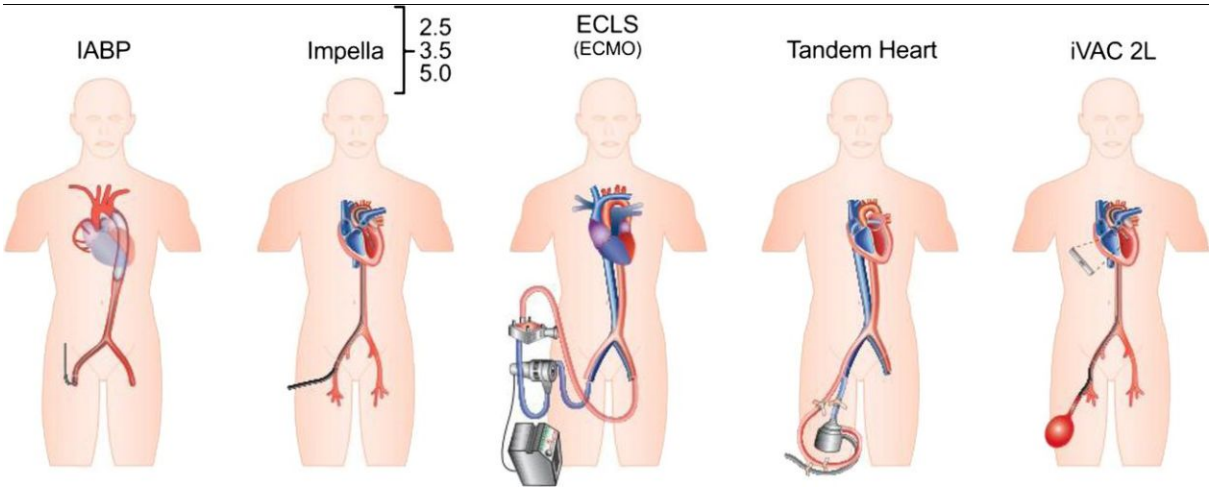

Figure 3: Schematic drawings of percutaneous support devices for CS

7.4.1 EXTRACORPOREAL LIFE SUPPORT

ECLS is a novel mechanical support therapy that is used in many acute care settings with positive results. Core parts of ECLS systems are the blood pump, heat exchanger and membrane oxygenator.[52] In a single center series of approximately 200 patients with STEMI and CS, the use of ECLS in patients undergoing cardiac catheterization demonstrated a 33% decrease in 30-day mortality in comparison with people not receiving ECLS. The most common ECLS is ECMO. There are two types of ECMO, namely veno-arterial ECMO (VA-ECMO) and veno-venous ECMO. VA-ECMO can be used to provide full cardiopulmonary support in a patient suffering from CS. Placement of ECMO requires a high level of expertise and a lot of work. Therefore it's currently limited to only specific medical centers. ECMO can be used as a bridge therapy to cardiac transplant, to other more long-term mechanical cardiac support measure or to emergent reperfusion therapy. The most common problems encountered with these machines are the limited support time, rise in afterload, lack of direct left-ventricular unloading and frequent need of perfusionist. The large cannula sizes can also cause lower limb ischaemia and bleeding. A meta-analysis of 1866 CS patients listed some of the frequencies of important complications in following manner: major bleeding (40,8%), significant infection (30,4%), lower limb ischaemia (16,9%), stroke (5,9%) and

amputation (4,7%). A single-center, non-randomized retrospective analysis from 2010 states that there is improvement in outcomes in CS patients due to MI who had PCI with ECMO assistance in comparison to historical control.[53]

In recent prospective report from 2013 it was found that in-hospital mortality of ECLS patients was as high as 63,2%. Also the patient groups with cardiopulmonary resuscitation and the patient group with age over 62 years had a mortality of 100%, raising a question on necessity of ELCS without patient selection.[54]

7.4.2 PERCUTANEOUS LEFT VENTRICULAR ASSIST DEVICES

The pVAD devices have become more accessible recent days as a temporary mechanical support measures used as a bridge to recovery, to transplant or to a durable MCS device. They have the potential to provide more robust circulatory support compared to the IABP's delivering the flow from 2.5 do 4 l/min. The available devices are TandemHeart™ (Cardiac Assist, Inc, Pittsburgh, USA), microaxial Impella® 2.5, 5.0 and CP systems (Abiomed Europe, Aachen, Germany) and the new paracorporeal pulsatile device iVAC 2L® (PulseCath BV, Netherlands). A meta-analysis, published 2009, consisting of results of three randomized trials compared percutaneous LVADs (two trials for TandemHeart and one trial for Impella 2.5) against IABP.[47] From the results it was found that patients treated with LVADs had higher CI, higher MAP and lower PCWP. However, there was no effect on 30-day mortality. Also patients treated with LVADs were more likely affected by bleeding or inflammatory complications. Observational studies have demonstrated beneficial results of Impella in CS. Patients upgraded from Impella 2.5 to Impella 5.0 had better survival at discharge according to a crossover evaluation published in 2011.[55] Also it was found (in USpella registry) that patients had a better survival at the hospital discharge when they were treated with Impella before PCI in CS in comparison against a group that was treated with Impella after PCI.[56]

The newest Meta-Analysis of Rios SA at colleges published in 2018 included 5 RCTs and 1 non-randomized comparing pVADs and IABP (Intra-Aortic Balloon Pump) during high-risk PCI or in CS. The investigators demonstrated no difference in short-term (6 months) (RR 1.09, 95% CI 0.79 to 1.52; p=0.59) or long-term (12

months) (RR 1.00, 95% CI 0.57 to 1.76; p=1.00) all-cause mortality. The use of pVAD was associated with more adverse events (acute kidney injury, limb ischemia, infection, major bleeding, and vascular injury) compared with IABP (RR 1.65, 95% CI 1.14 to 2.39; p=0.008) what explains the main result of no advantage of pVAD despite the better haemodynamic support. The other explanation was that a decreased cardiac output seen in CS is just a one component of this syndrome that involves several other molecular and hemodynamic mechanisms. One of these is systemic inflammatory response in patients with restored cardiac output that might abolish the beneficial hemodynamic effects of pVAD.[64]

7.4.3 INTRA-AORTIC BALLOON PUMPING

The IABP remains the most commonly used mechanical device in patients with CS. They decrease afterload and improve the diastolic coronary flow. They have no effect on MAP. They do not lead to any improvement in CI or CPI.[57]

There has been several major changes in the recommendations considering the use of IABP in CS. Both European and American guidelines were recommending the use of IABP with CS patients with a class I (1) recommendation before years 2012 and 2013. However these recommendations have been downgraded in ESC guidelines (2012) to IIb B and in American guidelines (2013) to IIa B due to results of a systematic meta-analysis.[58,59] In the results of the meta-analysis of randomized studies it was found that the results did not support the use of routine IABP in high-risk STEMI. The results of the meta-analysis challenged the current treatment recommendations. There were also no differences in any of the secondary endpoints such as serum lactate, renal function, catecholamine doses, or length of intensive care unit treatment.

The negative results of IABP-SHOCK II triggered some discussion related to the study. There was a higher mortality assumption on the control group and the sample size calculation was based on this. However, the mortality was lower than anticipated and marginally lower when compared to other previous trials in CS

despite similar baseline characteristics.[30,60] Also type II error cannot be definitely excluded, which naturally the case in all negative trials. Still, the lack of evidence of benefit for any of the investigated secondary study endpoints, the neutral results in all subgroup analyses, the lack of benefit in 12-month-follow up and in the as-treated analysis argue against any meaningful IABP benefit.[61]

Consequently this had an influence on the ESC revascularization guidelines. IABP downgraded to IIIA classification for the routine use in CS.[32] In case of mechanical complications IABP is recommended as a use of IIaC measure.[32]

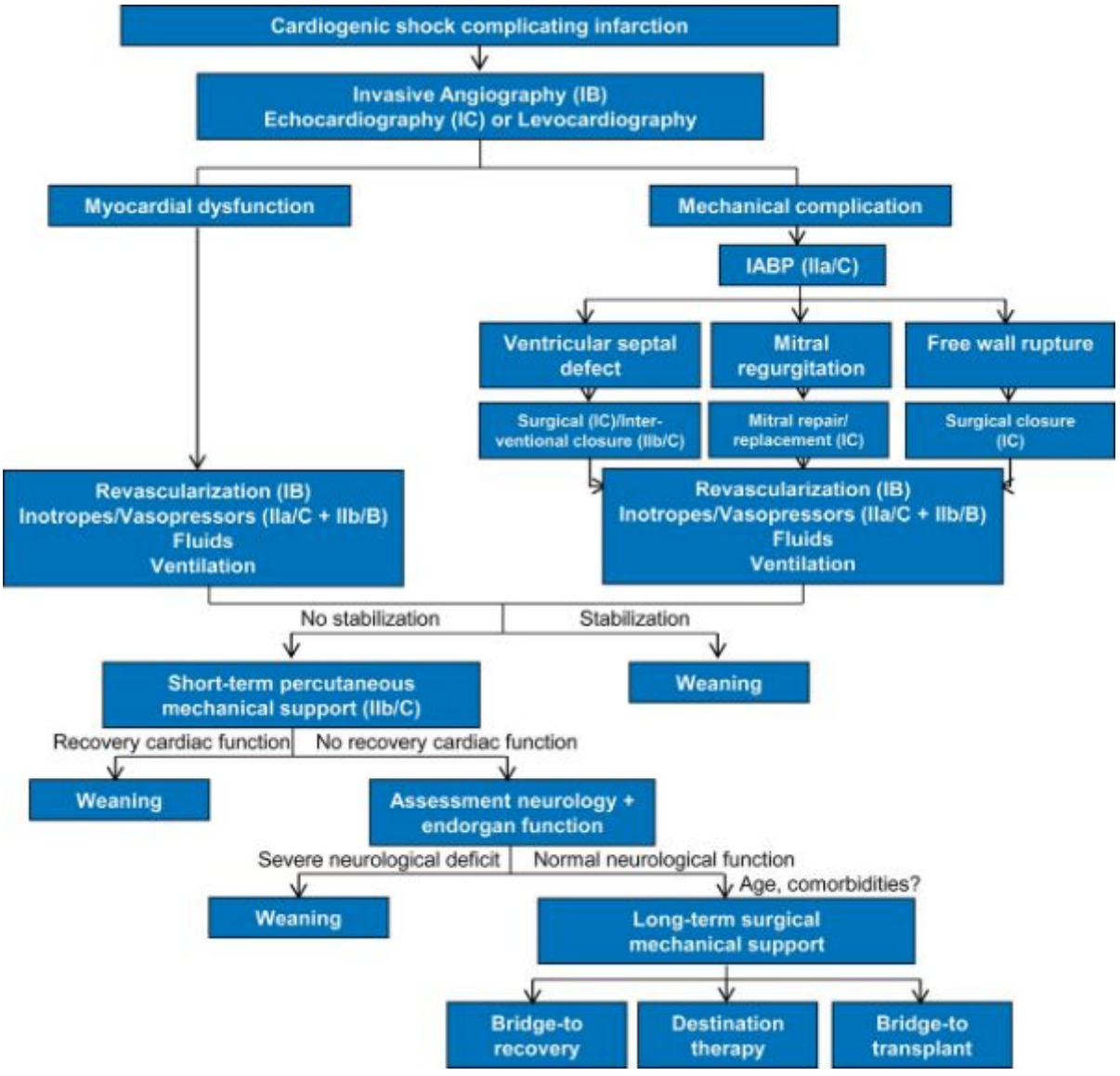

Figure 4. Treatment algorithm for patients with CS complicating MI.

8. DISCUSSION

Patients suffering from CS are typically critically ill and might decompensate quickly. Untreated and unrecognized tissue hypoperfusion can lead to a rapid organ dysfunction and death. The initial resuscitation of patients with CS is focused in restoring CO and tissue perfusion. This can be achieved by usage of inotropes and vasopressors, and intravenous fluids. Patients who don't respond to pharmacological therapy are indicated for mechanical circulatory support. These patients should undergo further therapy with either PCI or CABG.

The SHOCK trial was a definitely a milestone demonstrating improved outcomes in CS patients undergoing revascularization. The negative results from IABP-SHOCK trial shouldn't necessarily lead to the end of IABP therapy, it could be rather used as a foundation for future evidence based research. Cardiovascular research is currently researching very broadly different open topics and more research should be directed towards CS. Just the fact that certain treatment measures are used for decades shouldn't close these measures outside modern research and trials. There still exists multiple open questions in CS and these should be the focus of future research.

9. BIOGRAPHY

I was born in Espoo, Finland on October 13th, 1992. I went to primary school in School of Mankkaa, and I continued my education in the college of Pohjois-Tapiola. After completing my mandatory military service of 9 months in Finland I moved to Zagreb, Croatia, to pursue medical career in School of Medicine, University of Zagreb. In addition to studies included in the curriculum of our university, I also worked voluntarily as a student coordinator and as a class representative. On my 6th year of studies I traveled to United States to do a two-month clinical elective in the field of cardiovascular surgery and cardiology in

Texas Medical Center, Houston, Texas. Currently I am enrolled on my 6th year of studies. After completion of my studies I'm moving back to my home country Finland and I am planning to pursue my medical career in Internal Medicine.

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