

Cardioprotective shock management: monitoring and supportive therapies

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Cardiogenic shock is a highly lethal syndrome, leading to rapid death or secondary multiorgan damage, but current shock therapies, including mechanical support devices, also have a significant side effect profile. The overarching goal of shock therapy is ensuring long-term survival with good quality of life. This implies averting death, modifying the disease course by promoting heart recovery and avoiding additional cardiac damage, protecting other organs, and circumventing complications. Monitoring and supportive therapies are subordinate to these goals. Rather than merely following preconceived notions, the rapid evolution in mechanical support technology requires iterative and critical review of the benefits of current procedures, protocols and drugs in view of their overall contribution to the therapeutic goals. This article discusses various monitoring and supportive pharmaceutical modalities typically used in patients with cardiogenic shock requiring mechanical support.

Treatment goals: the paradigm of cardioprotective shock therapy

The overarching goal of shock therapy is ensuring long-term survival with good quality of life. This implies averting death, modifying the disease course, protecting organs, and circumventing complications, as shown in more detail in *Table 1*. In most fields of medicine, successful treatment of acute organ injury is treated by removing the causative factors, resting the organ and creating optimal conditions for organ recovery: stopping nephrotoxic drugs in kidney failure, resting strained muscles, immobilization of fractures, and protective ventilation in lung injury. For shock in myocardial infarction, this would imply revascularization

but avoiding reperfusion injury, resting the heart metabolically and mechanically and optimizing physiologic factors for recovery. Paradoxically, current cardiogenic shock therapy falls short in many of these aspects: myocardial energy demand and oxygen wasting, heart rate and wall stress are all increased by inotropes, and incomplete revascularization is currently preferred when circulation is not supported mechanically.¹

The paradigm of cardioprotective shock therapy implies

- removing the causative factors (myocardial energy depletion due to ischaemia and adrenergic stimulation, tachycardia; reperfusion injury; reducing wall tension),
- resting the heart metabolically and mechanically, and

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Table 1 Treatment goals in cardiogenic shock**Avert death**

- **Acute:** Arrhythmia, pump failure, mechanical infarct complications
- **Subacute:** Multiorgan failure due to hypoperfusion; systemic inflammatory syndrome
- **Late:** Chronic heart failure; sudden death

Modify disease course, facilitate myocardial recovery

- Progressive myocardial necrosis, ventricular dilation in AMI

Protect organs

- **Brain** damage due to circulatory arrest
- **Lung** damage due to cardiogenic pulmonary oedema, ventilator-associated complications
- **Kidney** damage due to cardiac arrest, protracted hypoperfusion, severe haemolysis

Circumvent complications

- Limb ischaemia
- Bleeding
- Embolism
- Haemolysis
- Infection

- creating optimal conditions for recovery (avoiding further loss of cardiomyocytes, avoiding ventricular overload and dilatation).

As the heart is mainly a mechanical pump delivering a few watts of mechanical energy, effective clinical implementation of the paradigm of cardioprotective shock therapy depends on the availability of a mechanical pump:

- is sufficiently effective haemodynamically to achieve ventricular unloading, peripheral organs, and coronary perfusion;
- has a low complication rate;
- is implanted early enough before organ damage is severe or cardiac arrest occurs;
- works for a sufficient time to allow cardiac recovery;
- minimizes the use of drugs that increase metabolic and mechanical cardiac burden; and
- allows early introduction of drugs that minimize metabolic and mechanical stress.

There has been significant progress in device technology that allows implementing the cardioprotective paradigm in shock therapy today. Intra-aortic balloon pumps are only marginally haemodynamically effective and provide no clinical benefit in acute myocardial infarction complicated by cardiogenic shock.² The TandemHeart is a short-term device (6 h) that provides significant haemodynamic support but is not easy to implant rapidly and has a high complication rate.³

Extracorporeal life support (ECLS) [venoarterial extracorporeal membrane oxygenation (ECMO)] is a widespread

tool of short-term mechanical circulatory support (MCS). It has a significant early complication rate, and as it provides retrograde aortic flow, it increases left ventricular afterload (*Table 2*).

Percutaneous cardiac pumps such as the Impella family, combined with suited pharmacology, may be the best option to implement the cardioprotective paradigm in shock therapy in theory. The percutaneous axial flow pump can be applied quickly in the catheterization laboratory (cath lab), thus reducing time to support but also ensuring sustained haemodynamic support. As an antegrade MCS device, it reduces myocardial preload and afterload, thus decreasing myocardial work and reducing infarct size.⁴

‘Permissive organ hypoperfusion’

The paradigm of cardioprotection in shock therapy and the ethical concept of ‘first, do not harm’ raise an additional question: If *long-term* patient benefit through optimal cardiac recovery is the main goal of therapy in cardiogenic shock, how much *acute* perfusion of other organs such as skin, muscles, kidney, intestines, and brain is actually needed to avoid long-term damage to these organs? We know from intensive care medicine that tolerating subnormal physiologic parameters when treating a severely diseased lung may actually be associated with an improved prognosis.⁵ Aiming for ‘normalization’ of organ perfusion rather than allowing a moderate reduction in target values may therefore induce an unnecessary therapeutic exacerbation that leads to ‘parameter cosmetics’ but potentially adds associated complications and may increase treatment costs.⁶ ‘Permissive organ hypoperfusion’, defined as permitting a moderate degree of organ hypoperfusion within a range where irreversible kidney failure, intestinal ischaemia, brain damage, and systemic inflammation are not triggered and limited to a period in which the heart is optimally unloaded and conditions for cardiac recovery are optimized, may minimize invasiveness, device size, device complication rate, and device cost. Such a concept awaits in-depth study.

Whenever dealing with acute decompensated heart failure patients and especially in cardiogenic shock patients, eliminating the immediate cause of cardiogenic compromise must be at the centre of all clinical attempts, particularly if such activity has been shown to provide prognostic benefit. Most of all, acute coronary syndrome (ACS) needs to be ruled out, as myocardial revascularization can profoundly change the prognosis of patients with acute myocardial infarction complicated by cardiogenic shock.⁷ Although myocardial revascularization is crucially important in these patients, the right timing for MCS should never be out of focus. There are observational data suggesting that early pre-percutaneous coronary intervention (PCI) and implantation of Impella are associated with improved outcomes.⁸ In addition, a pilot study raised the hypothesis that unloading the left ventricle with Impella prior to revascularization may reduce the infarct size.⁹ A large randomized clinical trial is therefore underway to confirm these preliminary data.¹⁰

Table 2 Abbreviations

ECLS	Extracorporeal life support	Cardio-pulmonary mechanical circulatory support (venoarterial ECMO)
ECMO	Extracorporeal membrane oxygenation	Pulmonary support which allow blood oxygenation and decarboxylation (veno-venous ECMO)
IABP	Intra-aortic ballon pump	Mechanical circulatory support by counterpulsation
Impella	Percutaneous ventricular assist device	Transaortic device providing left ventricular unloading and haemodynamic support in shock patients
PAC	Pulmonary artery catheter	Catheter within the pulmonary artery allowing pressure measurement within the pulmonary circulation and cardiac output measurement by thermodilution
PCWP	Pulmonary capillary wedge pressure	Pressure measured via PAC by inflation of a balloon in a small pulmonary artery—responds to left atrial pressure in patients with normal pulmonary circulation (8–12 mmHg)
PiCCO	Pulse contour cardiac output	Device to monitor haemodynamics by pulse contour analysis within a systemic artery
STEMI	ST-elevation myocardial infarction	Transmural myocardial infarction
SvO ₂	Mixed venous oxygen saturation	Oxygen saturation within the pulmonary artery measured by PAC—reflection oxygen supply and demand of patients (65 ± 5%)

Table 3 Shock phenotypes

		Fluid overload	
		Yes (wet)	No (dry)
Peripheral perfusion deficit	Yes (cold)	↓ CI	↓ CI
		↑ SVRi	↑ SVRi
	No (warm)	↑ PCWP	↔ PCWP
		↓ CI	↑ CI
		↔ SVRi	↓ SVRi
		↑ PCWP	↓ PCWP

Haemodynamic monitoring

Cardiogenic shock is a complex disease that encompasses various haemodynamic profiles. Cotter *et al.*¹¹ demonstrated that within cardiogenic shock, there is a broad spectrum of cardiac indices and systemic vascular resistance. This clinical scenario assessed haemodynamic parameters to guide therapy. Haemodynamic assessment is also critical to guide escalation/de-escalation of therapy. While invasive tools such as the pulmonary artery catheter (PAC) and pulse contour cardiac output (PiCCO) were considered the gold standard until recently, non-invasive evaluation is gaining interest.

Reliability of monitoring systems currently available

A rational cardiogenic shock therapy requires an understanding of both disease mechanisms and generic effects of therapies relative to the condition of the individual patient at specific time points during the course of the disease. During the acute phase, monitoring is usually performed by clinical assessment, vital sign and electrocardiogram

monitoring, urine output measurements, echo imaging and invasive monitoring (PAC; PiCCO catheter). There is a clear prognostic value of these parameters (e.g. low blood pressure, high heart rate, low ejection fraction, low cardiac output, ventricular arrhythmias), but deriving therapeutic targets that lead to patient benefit, e.g. from PAC, is difficult. Echocardiography is non-invasive and yields immediate information on pump position, a critical parameter in Impella therapy, and on right ventricular function, a neglected element in shock therapy. It should be performed repeatedly. Notably, monitoring may also lead physicians to therapeutic measures that are not helpful: monitoring-triggered antiarrhythmics historically led to excess mortality in myocardial infarction¹²; increasing blood pressure, myocardial contractility and 'normalizing' cardiac output parameters by inotropes remains of questionable value as discussed above, and reducing heart rate by certain drugs in unstable patients without mechanical support may be deleterious.¹³ The different haemodynamics induced by mechanical devices interact with current invasive monitoring: thermodilution (e.g. used by PAC and PiCCO systems) is known to have limited accuracy, in particular with tricuspid regurgitation or atrial fibrillation^{14,15} that is typically encountered in shock; pulse wave analysis used in PiCCO for continuous cardiac output determination is profoundly disturbed by devices that alter the waveform (e.g. intra-aortic ballon pump, ECMO, Impella) and is not reliable without recalibration if peripheral arterial resistance changes substantially, as typically seen in shock patients. Apart from routinely performed invasive blood pressure measurements, various arterial (e.g. cardiac power output) and venous (e.g. SvO₂) and metabolic (e.g. lactate) parameters can be assessed and are associated with prognosis⁸ in particular when combined, although their value as haemodynamic *targets* for guiding therapy has not been proven. *Trend measurements* of such parameters, e.g. failure to clear lactate,^{16,17} may help identify patients who do not satisfactorily respond to mechanical support, although the manifold causes of an increased

lactate level, in particular metabolic stimulation of glycolysis due to adrenergic stimulation, must be taken into account. In conclusion, invasive monitoring in Impella-supported patients, for example, by PAC, is desirable from the perspective of rational disease management and is supported by registry data,¹⁸ particularly for those patients who do not quickly stabilize clinically during support. It may help to detect right heart failure, acute valve regurgitation, or hypovolaemia, but at the same time, caution should be taken to avoid overinterpreting such data, which is of limited reliability and might lead to overtreatment without patient benefit.

Value of biomarkers

The availability of an easy and valid biomarker to screen patients with acute decompensated heart failure would be perfect to determine the risk of progression into cardiogenic shock. Furthermore, a biomarker showing the severity and risk of patients experiencing cardiogenic shock is warranted.

For the development of cardiogenic shock in patients with ST-elevation myocardial infarction, there are four upcoming biomarkers predicting late cardiogenic shock development.⁷ However, biomarkers that are widely available in cardiogenic shock patients, such as N-terminal pro-B-type natriuretic peptide and troponin, failed to predict outcomes.¹⁹ There is ongoing research to identify a predictive biomarker in cardiogenic shock, and there are some promising candidates.¹⁹

In patients treated with ECLS due to cardiogenic shock, the baseline lactate, as well as the lactate level at 24 h of ECLS therapy, is predictive for the mortality of these patients.^{20,21} As a consequence of the lack of significance of biomarkers alone on the severity and risk of cardiogenic shock, the Society for Cardiovascular Angiography and Intervention (SCAI) has defined five classifications of patients and their risk within cardiogenic shock depending on physical examination, biochemical markers and haemodynamics.¹¹ These classifications should be used whenever dealing with patients in or at risk for cardiogenic shock as it correlates with the clinical outcome.²²

In addition to biomarkers alone, combined risk scores involving clinical parameters can provide better prediction. As an example, the ORBI risk score, which was validated in two large French cohorts of ACS patients, turned out to be a good predictor of in-hospital mortality. It takes into account several clinical, angiographical, and biological markers available, such as age >70 years, prior stroke/transient ischaemic attack, cardiac arrest upon admission, anterior ST-elevation myocardial infarction, first medical contact-to-PCI delay >90 min, Killip class, heart rate >90/min, a combination of systolic blood pressure <125 mmHg and pulse pressure <45 mmHg, glycaemia >10 mmol/L, culprit lesion of the left main coronary artery, and post-PCI thrombolysis in myocardial infarction flow grade <3, that are available at the initiation of ACS management.²²

The National Cardiogenic Shock Initiative (NCSI) dataset provides similar risk stratification in cardiogenic shock patients. It takes into account the cardiac power output (>0.6 or <0.6 W) and lactate (>4 or <4 mg/dL) at 12-24 h after shock presentation. The risk score proved to be a good predictor of overall survival.⁸

Shock 'phenotypes'

Cardiogenic shock and the preceding acute decompensation of heart failure are divided into four different phenotypes with regard to volume status and peripheral perfusion.²³ These characteristics are described as wet vs. dry [definition: pulmonary capillary wedge pressure (PCWP) > vs. <18 mmHg] and cold vs. warm (definition cardiac index: < vs. >2.5 L/min/m²). Patients clinically defined as 'wet' can show signs of pulmonary congestion, peripheral oedema, jugular venous distention, hepatomegaly and, in some cases, ascites. 'Cold' patients typically show cold sweaty extremities, oliguria, skin mottling, and mental confusion (*Table 3*).

Most patients with acute decompensated heart failure will be classified in the 'wet' category and need to be divided into warm and cold patients.²³ Most patients within the 'wet and warm' category have high systemic resistance and can be recompensated using vasodilators together with diuretics or eventually ultrafiltration without proceeding to shock and need MCS.

Patients within the 'wet and cold' category have low cardiac output and low systemic vascular resistance and are at higher risk of proceeding to cardiogenic shock. One definition of shock is a systolic blood pressure below 90 mmHg. In these patients and in patients with severe signs of hypoperfusion (oliguria, mental confusion and often abdominal pain as warning signs), MCS should be evaluated closely within an intensive care unit (ICU) setting.

These clinical phenotypes are associated with various haemodynamic profiles, as stated above, and require further monitoring to accurately assess the cardiac index, systemic vascular resistance, and central venous pressure (CVP) to appropriately select the therapeutic strategy. Notably, randomized clinical trials evaluating the benefit of higher targets of MAP in cardiogenic shock following cardiac arrest failed to prove a clinical benefit.¹⁸

Patients with severe vasoplegia, often the day after shock presentation in the context of other evidence of cytokine release, typically need a vasoconstrictor, e.g. low-dose norepinephrine, as a complement to mechanical support. Inotropic therapy is valuable if potential damage to the myocardium due to the drug is less important than survival to the next therapeutic step, e.g. on the way to the cathlab in severe shock, or as a bridge in patients awaiting transplantation. Although no large studies comparing catecholamines vs. placebo document a prognostic benefit in shock after acute myocardial infarction,²⁴ some consider levosimendan as a superior inotrope compared to beta-adrenergic catecholamines or phosphodiesterase inhibitors such as milrinone or enoximone²⁵ due to their reduced metabolic demand

and possibly improved outcome. This is based on meta-analysis; otherwise, supporting data are weak.

Why do inotropes show little prognostic benefit in cardiogenic shock?

Historical treatment strategies aimed at reversal of some clinical parameters associated with shock, e.g. low blood pressure, tachycardia, low ejection fraction, low cardiac output, reduced diuresis or reduced oxygenation, in the hope that such numeric improvements would translate into patient benefit. cAMP-increasing inotropes (beta-adrenergic drugs, PDE3 inhibitors) actually increase cardiac output and ejection fraction, and vasoconstrictors typically increase blood pressure; such drugs have therefore been a mainstay of shock therapy in the past, although there is little evidence that they improve outcome.^{26,27}

Why does this discrepancy in inotrope effects on acute haemodynamics vs. prognosis? Catecholamines have well-known acute undesirable effects that include increases in heart rate, wall stress, myocardial oxygen consumption and arrhythmias and worsening of myocardial oxygen consumption. Myocardial akinesia seen in ischaemia (stunning, hibernation) is actually a protective mechanism of severely energy depleted cardiomyocytes that contributes to cell survival, but when it is overdriven by inotropes to restore contractility at substantial cost of energy, myocardial necrosis is induced,²⁸ an observation underscored by documentation of troponin release upon inotropic stimulation of ischaemic myocardium in dobutamine stress echo.²⁹ Dobutamine may increase cardiac output but also redistribute it to skeletal muscles at the expense of splanchnic circulation.^{30,31} The use of beta-adrenergic inotropes and vasoconstrictors in acute heart disease that otherwise largely benefits from beta blockers³² and vasodilators (even when hypotensive³³) thus raises unresolved questions with major implications for therapy. This is also one reason for the shifting paradigm and the tendency to favour early MCS in cardiogenic shock.

Algorithm for fluid administration/diuretic use according to different haemodynamic scenarios and filling pressures/SVR

Patients with cardiogenic shock who are treated with MCS can show different phenotypes of haemodynamic problems, which can be divided into four different phenotypes. Whenever the haemodynamic goals (MAP of 60-80 mmHg, CVP of 8-15 mmHg, and PCWP of less than 15 mmHg) are achieved, clinicians should try to identify the nature of the haemodynamic disorder based on the distribution of flow of the MCS device, CVP (or clinical signs of volume status, echo findings) and the mean arterial pressure (MAP) (Figure 1).

The principle of this flow chart works for biventricular MCS such as veno-arterial ECLS support and left ventricular support (Impella, TandemHeart, or durable left ventricular assist device) in a comparable manner. However, in patients with left ventricular support, the role of the right ventricle needs to be considered, especially in those patients with

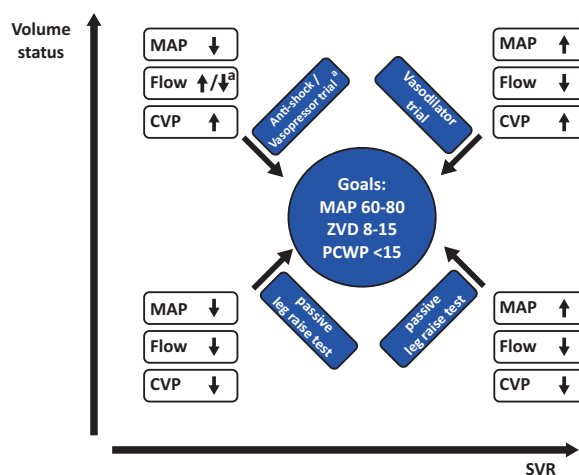


Figure 1 Phenotypes of haemodynamic problems of patients on mechanical circulatory support and suitable clinical tests to test treatment options. ^aDepending on right ventricular function (left ventricular support only) or setting of biventricular support.

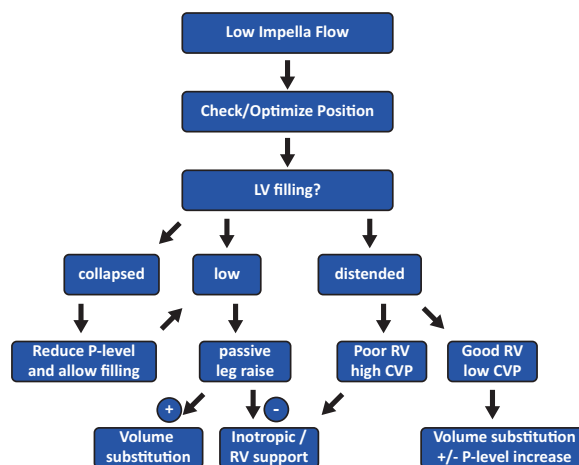


Figure 2 Troubleshooting for patients showing low Impella flow.

high volume status and low systemic vascular resistance (Figure 2).

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Whenever working with MCS patients, especially in patients with Impella support, all haemodynamic and pump-derived parameters should be monitored and documented closely.³⁴

When dealing with and interpreting these values, it is very important to continuously monitor the trends throughout hours and days rather than just check the absolute value. Therefore, values that are within the normal range can already help to foresee upcoming problems, and on the other hand, 'pathologic values' may be considered less problematic if the trend is either stable or leading into the right direction. Careful fluid administration should be considered in particular in patients under MCS and especially

Impella support since hypovolaemia is associated with haemolysis, suction and low output.

On the other hand, congestion could lead to cardiogenic shock aggravation and may require diuretics. IV continuous infusion is then preferred, while haemodialysis is considered in cases of acute renal injury.

Conclusion

In conclusion, rapid progress in mechanical support in cardiogenic shock elucidates how little we know about this highly lethal disease. While manifold monitoring methods exist and are in use in such critically ill patients, there is a large field of opportunity to improve knowledge on which parameters to monitor, which interpretations and conclusions to draw from monitoring and which supportive drugs to use if we want to achieve the overarching goal of our efforts, namely, long-term survival with good quality of life and preserved function of the organs, in particular the brain and the heart.

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