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The Heart in Sepsis: From Basic Mechanisms to Clinical Management

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Abstract: Septic shock is characterized by circulatory compromise, microcirculatory alterations and mitochondrial damage, which all reduce cellular energy production. In order to reduce the risk of major cell death and a diminished likelihood of recovery, adaptive changes appear to be activated. As a result, cells and organs may survive in a non-functioning hibernation-like condition. Sepsis-induced cardiac dysfunction may represent an example of such functional shutdown.

Sepsis-induced myocardial dysfunction is common, corresponds to the severity of sepsis, and is reversible in survivors. Its mechanisms include the attenuation of the adrenergic response at the cardiomyocyte level, alterations of intracellular calcium trafficking and blunted calcium sensitivity of contractile proteins. All these changes are mediated by cytokines.

Treatment includes preload optimization with sufficient fluids. However, excessive volume loading is harmful. The first line vasopressor recommended at present is norepinephrine, while vasopressin can be started as a salvage therapy for those not responding to catecholamines. During early sepsis, cardiac output can be increased by dobutamine. While early administration of catecholamines might be necessary to restore adequate organ perfusion, prolonged administration might be harmful.

Novel therapies for sepsis-induced cardiac dysfunction are discussed in this article. Cardiac inotropy can be increased by levosimendan, istaroxime or omecamtiv mecarbil without greatly increasing cellular oxygen demands. Heart rate reduction with ivabradine reduces myocardial oxygen expenditure and ameliorates diastolic filling. Beta-blockers additionally reduce local and systemic inflammation. Advances may also come from metabolic interventions such as pyruvate, succinate or high dose insulin substitutions. All these potentially advantageous concepts require rigorous testing before implementation in routine clinical practice.

Keywords: Adrenergic stimulation, beta blocker, early goal directed therapy, esmolol, inflammation, heart, levosimendan, sepsis.

INTRODUCTION

The aim of this article is to provide an overview on the underlying mechanisms of sepsis-induced cardiac dysfunction and its management. Particular attention will be paid to unraveling clinical paradoxes and to identify the hierarchy of mechanistic events, as the correct understanding of mechanisms is crucial for the clinical management of affected patients. Finally, novel and potentially interesting therapies of sepsis-induced cardiomyopathy will be discussed.

SEPSIS AND SEPTIC SHOCK

PAMPs and DAMPs

When microorganisms invade the host, pathogen associated molecular patterns (PAMPs) such as lipopolysaccharides (endotoxins) from Gram negative bacteria are recognized by immune cells [1]. The binding of PAMPs with particular receptors on the cell surface activates an intracellular cascade [2, 3]. This results in up- or down-regulation of specific genes encoding for a variety of proteins including cytokines and other inflammatory mediators and receptors [4]. The spread from local infection to sepsis depends on the severity of infection and the degree of inflammatory response [5]. In the most severe cases, shock develops as a result of decreased vascular tone, enhanced vascular permeability and sepsis-induced cardiomyopathy, leading to low stroke volume, low arterial blood pressure and, finally, impaired organ perfusion [6]. Tissue hypoperfusion is aggravated by microcirculatory disturbances [7-9]. If untreated, persistent shock causes cellular injury and the liberation of damage associated molecular patterns (DAMPs) such as mitochondrial proteins, adenosine or uric acid [10-12]. Like PAMPs, DAMPs have the potential to activate inflammation, creating a vicious spiral (Fig. **1**). If untreated, a point of no return is reached after which cell death pathways are activated, finally leading to the host's demise. This point is influenced by host characteristics such as age, gender [13], co-morbidities [14] and genetic background [15] as well as infection properties such as the site of infection and pathogen virulence [5]. We and others believe that the final outcome is already predetermined at

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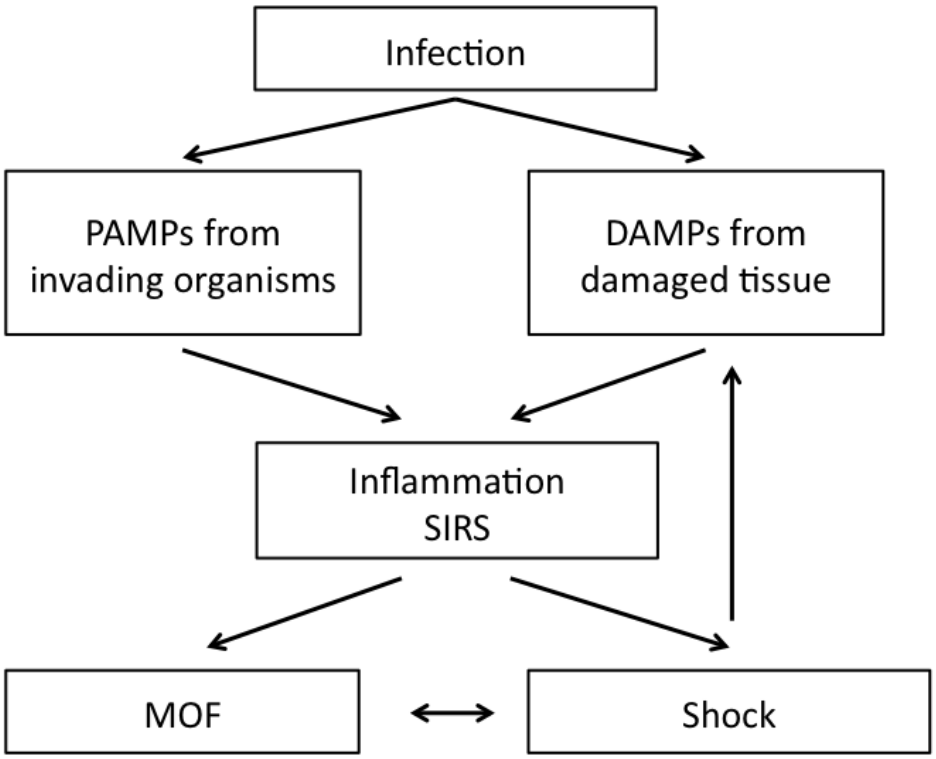

Fig. (1). Pathophysiological mechanisms of systemic inflammation, shock and organ failure in sepsis.
DAMP damage-associated molecular pattern; MOF multiple organ failure; PAMP pathogen-associated molecular pattern; SIRS systemic inflammatory response syndrome (for details see text).

an early stage of the disease process [16], resulting in three patient groups:. The first is a survivor group who will likely live, even without therapy. The key message for their management is "first do no harm" [17]. The second group consists of non-survivors whose fate is pre-determined, and where intensive care will only delay their demise. The intermediate group includes those patients who would die without treatment, but who can be saved by appropriate therapy.

Multiple Organ Dysfunction Syndrome

Sepsis impacts the entire organism in a time-dependent manner [18]. This syndrome can affect all organ systems including the cardiovascular system [19], autonomic nervous system [20-22], endocrine system [23], metabolism [24] and bioenergetics [25]. During septic shock, circulatory compromise and mitochondrial damage [26-28] reduce intra-cellular ATP production and place the cells at risk of bio-energetic failure and cell death. In order to reduce the risk of cell death, adaptive changes may be activated [29]. Cellular functions are reduced, perhaps in order to limit energy expenditure, thereby creating a new equilibrium between energy supply and consumption [30]. As a result, the organs may survive in a non-functioning hibernation-like condition. Consequently, extensive tissue necrosis is not a characteristic of sepsis-induced organ dysfunction [31-33]. When the inflammatory process is overcome, cellular energy generation can improve, leading to resumption of normal cell processes and functional recovery [34].

THE HEART IN SEPSIS

Clinical evidence of sepsis-induced cardiomyopathy

Cardiac dysfunction is a well-recognized organ manifestation during sepsis and septic shock [35]. The involvement of the heart varies according to the timing and severity of the sepsis syndrome. During the very early phase of the disease, an echo-derived left-ventricular (LV) ejection fraction (EF) >55% is indicative of sepsis, as demonstrated in a retrospective evaluation of shock patients in the emergency room [36]. This might be explained by increased cardiac contractility due to adrenergic stimulation. Importantly, despite this high LVEF, stroke volume at this timepoint is low because of insufficient cardiac preload due to a high vascular permeability and low vascular tone. The compensatory rise in heart rate is often insufficient to maintain adequate cardiac output during this very early phase of sepsis, as demonstrated by elevated lactate levels and a low central venous oxygen saturation (ScvO2) [6].

Jardin *et al.* assessed 90 septic shock patients (28-day mortality of 62 %) during the later phase of sepsis [37]. Non-survivors had higher severity scores (SAPS 68 vs 52) and were given more fluid (5.2 L/day vs 4.1 L/day) than survivors but, nevertheless, had lower end-diastolic volumes suggesting a persistent preload deficiency. After fluid loading LVEF was markedly decreased in all patients. However, by the time of discharge from the intensive care unit, LVEF had normalized in survivors. The pronounced systolic dysfunction in septic patients and the reversibility of the

phenomenon in sepsis survivors was published previously in a seminal paper by Parker *et al*. [38]. More recently, Vieillard-Baron and co-workers found that 40 of 67 (60%) septic shock patients developed a LVEF <45% during the first 3 days of haemodynamic support. It can be concluded that LV systolic dysfunction is common in septic patients and potentially reversible in survivors.

Several studies have provided evidence for diastolic dysfunction during sepsis [39-42]. Landsberg *et al*. investigated 262 patients with severe sepsis and septic shock (30 day mortality of 30%) by echocardiography [43]. Again, lower LV end-diastolic volumes and stroke volumes were seen in eventual non-survivors. In addition, diastolic dysfunction was common, and was associated with age, pre-existing hypertension and diabetes mellitus, and strongly correlated with an adverse outcome. Patients with systolic dysfunction (LVEF ≤50 %) and/or diastolic dysfunction had a higher mortality [43]. It can be concluded that the severity of sepsis corresponds to the degree of organ involvement in general, and cardiac impairment in particular.

Other clinical aspects of sepsis-induced cardiac dysfunction are tachyarrhythmias [44, 45], right heart failure [46, 47], elevated troponin [48, 49] and B-type natriuretic peptide levels [50-52].

While some studies suggest that the presence of cardiac dysfunction is a risk factor for adverse outcomes [43], other reported more cardiac depression in sepsis survivors compared to non-survivors [37, 38]. How can such conflicting results be explained? Clearly, the development of cardiac dysfunction requires some degree of inflammation. Hence, mild cardiac dysfunction might result from mild systemic inflammation, and therefore be a good prognostic sign. In very sick septic patients the presence of profound myocardial depression defined by a low LVEF may represent preload optimization and good adaptation, while a normal LVEF could be caused by persistent preload deficiency [37] and/or ongoing harmful adrenergic over-stimulation.

Underlying Mechanisms

Mechanisms of sepsis-induced cardiac dysfunction have been reviewed extensively [35, 53-59]. Early sepsis is characterized by high levels of circulating catecholamines [20, 60, 61] that derive from the autonomous nervous system, the gut [62], lymphocytes [63, 64] macrophages [65] and neutrophils [66, 67]. A major mechanism of sepsis-induced cardiac dysfunction is the attenuation of the adrenergic response at the cardiomyocyte level due to down-regulation of β-adrenergic receptors [68, 69] and depression of post-receptor signaling pathways [70-73]. These changes are mediated by cytokines [74, 75] and nitric oxide [76, 77]. Blunting of the adrenergic response is probably enhanced by neuronal apoptosis in the cardiovascular autonomic centres [78], and by inactivation of catecholamines by reactive oxygen species [79].

High levels of circulating catecholamines due to ongoing endogenous and pharmacological adrenergic stimulation may partially explain the discrepancy between maintained cardiac contractility *in vivo*, that clinicians observe at the bedside, and the profound decrease in cardiac contractility seen under laboratory conditions, for example in *ex vivo* models of cultured myocardial cells [80] and isolated perfused hearts [81]. Adrenergic downregulation, however, results in a reduced cardiac reserve that is unraveled by a reversible hyporesponsiveness to dobutamine in patients with septic shock [82]. Finally, preload optimization and catecholamine-driven tachycardia can generate a high cardiac output despite profound intrinsic myocardial depression [83]. In can be concluded that myocardial depression can be present despite a hyperdynamic state in resuscitated patients with established sepsis.

Sepsis-induced myocardial dysfunction is characterized by altered intracellular calcium trafficking. Suppression of L-type calcium currents [84-87], decreases in ryanodine receptor density and activity [88-90], and changes of calcium re-uptake into the sarcoplasmic reticulum [91, 92] have all been demonstrated in sepsis models. On a myofibrillar level, sepsis affects the calcium sensitivity of contractile proteins [93-95]. These changes will impair both systolic and diastolic function, but it remains to be determined how they relate to blunted β-adrenergic signaling and defective enzyme phosphorylation.

Severe infection leads to genetic reprogramming in myocardial cells. Using a fluid-resuscitated rat model of fecal peritonitis we identified 527 genes whose transcription was significantly down or up-regulated as early as 6h after the septic insult [96]. Dos Santos and coworkers demonstrated the expression of genes favoring fetal isoforms of contraction-related proteins in an iNOS-dependent manner [97]. Those findings confirm early gene activation and –suppression on an organ level during sepsis. Future research must investigate how novel interventions affect these mechanisms and influence outcomes.

PHARMACOLOGICAL SUPPORT OF THE SEPTIC HEART

Early Goal-directed Therapy

A critical determinant in patients with septic shock is time to shock resolution, as the severity and duration of shock correlates with the degree of inflammation, organ dysfunction and adverse outcomes. The use of a 6-hour protocol with the pre-defined haemodynamic goals listed below accelerated haemodynamic stabilization and significantly reduced mortality from 57% to 42% in patients with severe sepsis and septic shock [6]. Crystalloids were given as 500 ml boluses every 30 minutes to achieve a central venous pressure between 8-12 mmHg. Vasopressors or vasodilators were administered to maintain a mean arterial blood pressure between 65-90 mmHg. If the SvO_2 remained <70 %, oxygen delivery was increased by transfusion of red blood cells to a haematocrit ≥30 %. If SvO_2 still remained <70 %, dobutamine was added at a dose of 2.5-20 μg/kg body weight/min to increase cardiac contractility [6]. These measures were in addition to rapid diagnosis and treatment of the underlying infection by source control and antibiotic therapy [98]. This resuscitation care bundles is recommended at present in the Surviving Sepsis Campaign guidelines [99].

Fluids for Preload

While early and sufficient fluid administration is likely to be beneficial, excessive volume loading is harmful [100, 101]. The risk of pulmonary oedema formation is particularly elevated due to increased permeability of the pulmonary microcirculation and LV diastolic dysfunction [102]. Pulmonary oedema and concomitant hypoxaemia will cause vasoconstriction and increase pulmonary vascular resistance (= right ventricular afterload), potentially resulting in right ventricular deterioration with a fall in stroke volume and cardiac output. Depending on the fluids used, additional disadvantages include electrolyte disturbances with normal saline, the risk of renal failure with colloids [103-105], and high costs with albumin solutions [106].

Inotropes for Contractility

During early sepsis, a low SvO_2 value and hyperlactataemia indicate an imbalance between oxygen delivery and demand [107]. After optimization of oxygenation, volume status and haematocrit, cardiac output can be increased by inotropes. The combination of norepinephrine and dobutamine may allow a better modulation of vascular and cardiac effects than epinephrine alone. However, a multi-center study investigating 330 patients with septic shock revealed no differences regarding ICU length of stay and mortality between the two strategies [108]. Importantly, catecholamines and phosphodiesterase inhibitors (that also increase cAMP) have many adverse cardiac (arrhythmia, increased oxygen demands) and non-cardiac (hyperglycemia, muscle catabolism, stimulation of bacterial growth, immunosuppression) effects [109]. Accordingly, efforts to enhance cardiac index >4.5 l/min/m^2 or elevate mixed venous oxygen saturation ≥70% by dobutamine administration during established sepsis with organ failure is not beneficial and may be even harmful [110, 111]. This underlines the importance of timing and dosing of therapeutic interventions. While early administration of catecholamines might be necessary to reverse shock and restore adequate organ perfusion, prolonged administration, particularly at unnecessarily high doses, might be harmful [17, 109].

Milrinone and other phosphodiasterase III inhibitors have been used to stimulate the septic heart [112]. This approach might be useful if the patient is treated with β-blockers, as the adrenergic effect of milrinone does not come from β-receptor stimulation but via a decreased degradation of the second messenger cAMP. However, this group of agents also decreases vascular tone, consequently increasing the risks of arrhythmia and hypotension [113].

Vasopressors For Organ Perfusion Pressure

The most commonly used vasopressor in septic patients is norepinephrine, which is administered at doses up to 1.0 μg/kg/min. In a direct comparison with dopamine, noradrenaline caused less arrhythmia [45] and less skin ischaemia [114, 115]. While catecholamines are effective in counteracting haemodynamic instability [116], excessive use might be harmful. In a retrospective analysis, mean arterial pressures maintained >70 mmHg were not associated with improved survival though mortality was progressively higher in those given increasing doses of vasopressor to achieve this [117].

Vasopressin (or synthetic analogues such as terlipressin) is not recommended as a first line treatment, but can be considered as a salvage therapy [118, 119]. Vasopressin infusion rates up to 0.01-0.04 U/min are generally considered safe when norepinephrine infusion rate exceeds 0.5 μg/kg/min. Future studies are needed to identify the lowest acceptable mean arterial blood pressure in individual patients that is still compatible with adequate tissue perfusion pressures yet avoids unnecessary high vasopressor administration. More important than simply targeting arterial blood pressure, clinicians should try to assess the adequacy of organ perfusion in their sick patients and treat accordingly.

NOVEL THERAPIES FOR THE SEPTIC HEART

Novel Inotropes

The beneficial short-term effect of enhanced contractility by cAMP-elevating drugs (e.g. dobutamine, milrinone) is, at least partly, abolished by increased energy consumption at the cellular level [120]. This might explain the lack of favorable long-term outcomes with prolonged use of these drugs in critically ill patients [121]. Hence, novel inotropes are urgently needed.

Levosimendan is a calcium sensitizer that ameliorates contractility with relatively little rise in cellular oxygen demands [122-124]. It increases calcium affinity at the level of troponin C, thereby improving cross-bridge kinetics between actin and myosin [125]. Levosimendan improves contractility without compromising diastolic function. The drug has been successfully used in both preclinical sepsis models [126, 127] and in patients with septic shock [128]. As the molecule does not interact with β-adrenoreceptors, levosimendan might be particularly useful when β-blockers are administered (see below). Levosimendan also induces beneficial preconditioning via ATP-dependent potassium channels [129]. However, the same mechanism also causes vasodilation, which may limit its use in patients with septic shock [130].

Promising new intoropic drugs that have been developed for patients with heart failure are of potential interest for patients with sepsis-related myocardial depression [125]. Istaroxime represents a new class of Na^+/K^+-ATPase inhibitors and stimulates SERCA, thereby exhibiting inotropic and lusitropic effects [131, 132]. In animal models, this new drug exerts inotropic activity comparable with that of digitalis but produces less arrhythmia [133]. Initial clinical trials demonstrated a good safety profile, though future studies are needed before the drug can be considered for clinical use.

Omecamtiv mecarbil is a direct activator of the cardiac myosin-ATPase, thereby increasing the transition of myosin into the actin-bound force generating state [134]. Importantly, improvements in cardiac contractility were not associated with increased intracellular calcium transients nor with increased myocardial oxygen consumption [125]. First clinical studies demonstrated a dose-related increase in cardiac contractile function without clinically relevant changes in diastolic function [135, 136]. However, as omecamtiv

mecarbil increases contractility by prolonging systolic ejection time, cardiac filling might be impaired at higher heart rates (as usually observed in septic patients).

Beta-blockers in Sepsis

As adrenergic over-stimulation may contribute to the clinical deterioration and poor outcome of septic patients [61, 66, 137], several groups have tested β-blockers in septic animals and patients (see [30, 138-140] for reviews). In septic animals, β-blockers reduced heart rate though stroke volume was preserved [81, 141]. The longer duration of diastole may perhaps allow better diastolic filling. In a pig model of endotoxic shock, the infusion of the short-acting β_1 antagonist esmolol even improved stroke volume over time compared to control animals [142]. Despite reducing heart rate by approximately 20%, no septic animal suffered from cardiovascular collapse during the esmolol infusion period [142]. Initial preliminary studies in humans demonstrate that intravenous esmolol administration is feasible in patients with septic shock [143]. Beta-blockers also reduced plasma levels of pro-inflammatory cytokines such as TNF-α and IL-6 [81, 141, 144]. In rats with fecal peritonitis, an esmolol infusion reduced the local inflammatory response as well as bacterial translocation from the gut into mesenteric lymph nodes [145]. Survival times of septic animals have been prolonged in several animal studies [141, 145, 146]. Small clinical studies in septic patients revealed similar haemodynamic and inflammatory results with β-blockers [147-149]. Despite these promising results, more research is required to unravel clinically important questions before β-blockers can be recommended for routine use in septic patients. If patient selection, β-blocker dose and timing of administration are wrongly selected, harm might ensue, as has been observed in patients with acute myocardial infarction [150] or in patients undergoing non-cardiac surgery [151].

Heart rate reduction considerably lowers cardiac energy demands, thereby creating a better balance between myocardial energy generation and expenditure in conditions of impaired energy production [30]. Ivabradine, a funny channel blocker, can accomplish heart rate modulation without negative inotropism. This drug affects I_f –currents in myocardial cells producing a heart rate reduction during sinus rhythm. First results in patients with heart failure are promising [152, 153]. Currently, a clinical trial investigating the administration of ivabradine to patients with multiple organ dysfunction syndrome is being performed [154].

Metabolic Interventions

Sepsis causes profound metabolic changes and places vital organs at risk of energy failure [24]. Several strategies have been elucidated in order to reduce the cellular energy crisis. For example, pyruvate substitution has been evaluated as a cellular ATP provider. In aerobic conditions, pyruvate is efficiently metabolized in the Krebs cycle. Under anaerobic conditions, it is converted to lactate at a much lower ATP yield. Therapeutic pyruvate administration increased myocardial energy availability, particularly to the SERCA, resulting in improved intracellular calcium handling [155]. It should however be noted that pyruvate has separate immunomodulatory properties that may also play an important role.

Sepsis causes mitochondrial dysfunction, particularly affecting complex I of the respiratory chain [26, 156]. Succinate serves as a substrate for complex II and could potentially bypass a dysfunctional complex I, hence improving mitochondrial oxygen utilization and ATP production [157, 158]. Sepsis survival appears to require mitochondrial recovery by mitochondrial biogenesis [34]. This process depends, among other factors, on nitric oxide [159].

Elevated glucose levels are common in septic patients and represent an additional danger to cellular and mitochondrial integrity [160]. Hence, maintenance of normoglycaemia with insulin substitution improved outcomes in critically ill patients [161, 162]. A more liberal strategy aiming at blood glucose levels between 4.5-10.0 mmol/l was shown to be safer than a tighter control because of a lower incidence of hypoglycaemic episodes [163].

Insulin fuels glucose transport into the cardiomyocytes and intensifies cardiac inotropy [164]. Although glucose-insulin-potassium infusion (with insulin doses <0.2 U/kg/h) did not provide additional benefit in patients with myocardial infarction [165, 166], this regimen might still be an interesting option in sepsis-induced myocardial dysfunction [167, 168]. In patients with β-blocker or calcium channel-blocker poisoning, very high doses of insulin (0.5-10 U/kg/ h) have been used successfully to stimulate cardiac contractility [164, 169, 170]. First experiments in endotoxemic pigs with such high insulin dosages are also promising [171]. However, more research is needed before this concept can be applied to septic patients.

CONCLUSIONS

Sepsis-induced cardiac dysfunction is caused by a functional shutdown in a situation where energy requirements do not meet energy demands. The phenomenon is common, corresponds to the severity of sepsis, and is reversible in survivors.

Current treatment recommendations aim at increasing oxygen delivery to peripheral tissues. While fluids, vasopressors and β_1-adrenergic agonists may be necessary to restore organ perfusion and pressures in the early phase of sepsis, the same options may be harmful later on.

Potentially useful therapies for sepsis-induced cardiac dysfunction include novel inotropes that increase contractility without a large effect on cellular oxygen demands. Heart rate reduction further reduces cardiac oxygen expenditure and improves diastolic filling. Beta-blockers additionally reduce local and systemic inflammation. Important advances may also come from other metabolic interventions. However, all these potentially advantageous concepts require rigorous preclinical and clinical testing before implementation in the clinical routine.

CONFLICT OF INTEREST

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ABBREVIATIONS

cAMP	=	Cyclic adenosine monophosphate
ATP	=	Adenosine triphosphate
EF	=	Ejection fraction
IL-6	=	Interleukin 6
LV	=	Left ventricle
TNF-α	=	Tumor necrosis factor alpha
SERCA	=	Sarco-endoplasmic reticulum calcium-ATPase
SvO_2	=	Central-venous oxygen saturation

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