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# Pathophysiology of cardiovascular dysfunction in sepsis

JR Greer MB BCH BAO DGM FRCA FFICM*

Consultant in Anaesthesia and Critical Care, Department of Anaesthesia, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK

*To whom correspondence should be addressed. Tel: +44 1612764551; Fax: +44 1612768027; E-mail: ruari.greer@cmft.nhs.uk



### Key points

- Cardiovascular dysfunction is a common complication of sepsis and severe sepsis.
- Left ventricular performance is compromised by poor contractility and this is worsened by the imposed challenge of systemic vasodilatation.
- Right ventricular performance can be compromised by pulmonary hypertension.
- Nitric oxide is an inflammatory mediator which disrupts intracellular calcium flux leading to myocyte dysfunction, peripheral vasodilatation, and disruption of compensatory reflexes.
- Arrhythmogenesis is a feature of cardiovascular dysfunction in sepsis.

Sepsis is a common condition with a high mortality, which can also lead to severe sepsis and shock. This review will look at the physiological disruption of the cardiovascular system and the reflexes which occur during sepsis.

## The products of the septic cascade as mediators of cardiovascular dysfunction

The host response to sepsis is controlled by inflammatory mediators, which transmit, amplify, and maintain the generation of the host response. A specific myocardial-depressant factor has been suggested for some time, but the concept of a single agent underestimates the complexity of the immune system in sepsis.[1]

### Toll-like receptors

These are intermediate signalling molecules, which respond to the inflammatory stimulus and lead to the release of tumour necrosis factor α (TNF-α). These receptors impair myocyte function *in vitro*.

### Cytokines

The major pro-inflammatory mediators in sepsis are TNF-α, interleukin (IL) 1β, IL-6, and IL-8. They are secreted from macrophages and monocytes and are responsible for amplification of the septic cascade and have been demonstrated to cause fever, hypotension, and myocardial suppression.

### Nitric oxide

Nitric oxide (NO) is secreted from the endothelium and is central to cardiovascular control in health. During sepsis, NO production is increased after activation of the endothelium by pro-inflammatory mediators, resulting in up-regulation of the enzyme inducible NO synthetase (iNOS). This inducible (pathological) NO is responsible for vasodilatation. It is also responsible for dysfunction of enzyme messenger systems associated with normal intracellular calcium homeostasis and the maintenance of reflexes.

### Oxidative stress

Oxidative stress is a term applied to cellular damage by oxygen and nitrogen free radicals, which are produced in excess in sepsis. Oxygen free radicals include peroxide and hydroxyl groups, while nitrogen free radicals include peroxynitrite. These affect cellular and subcellular function, including damaging DNA, structural proteins, and mitochondrial enzyme systems. They are also responsible for the cytopathic hypoxia associated with damage to the electron transport chain.

Table 1 Molecular mechanisms of myocyte dysfunction—*in vitro* evidence

| Immune modulator | Action | Pathophysiology |
|---|---|---|
| Lipopolysaccharide | Indirect | Release of TNF-α |
| Toll-like receptors | Indirect | Release of TNF-α and IL-1β |
| TNF-α | Direct | Defective cellular Ca traffic |
| IL-1β | Direct | Defective cellular Ca traffic |
| Nitric oxide | Direct | Defective cellular Ca traffic |
| | Direct | Defective β-adrenergic response |
| | Direct | Arrhythmogenesis |
| Peroxynitrite | Indirect | Enhanced cytokine toxicity |
| Macrophage migration inhibitory factor (MIF) | Indirect | Enhanced cytokine toxicity |
| | Direct | Cellular apoptosis |

*In vitro* evidence for myocardial dysfunction is summarized in Table 1.

## The systemic circulation in sepsis

### The left ventricle: decreased contractility

The left ventricle (LV) is a muscular contractile chamber which pumps blood into the systemic circulation to perfuse and oxygenate the vital organs. It contracts in a circumferential manner and it creates a mean arterial pressure of 90 mm Hg. The systemic circulation has a high resistance and a low capacitance. The stroke volume of the ventricle in systole is determined by preload, afterload, and contractility. During diastole, ventricular filling and coronary artery perfusion takes place. Determinants of diastolic function include myocardial relaxation and passive properties of the ventricle such as stiffness and geometry.

Excitation–contraction (E–C) coupling is the process by which an action potential is converted to muscle contraction. When a cardiac muscle action potential occurs, calcium enters the cell and this leads to the further release of calcium from the sarcoplasmic reticulum. This calcium-induced calcium release is mediated by the cardiac ryanodine receptor (RyR2). The calcium binds to troponin-C which then leads to conformational change and allows the binding of actin to myosin causing shortening of the myocyte and the onset of systole. Then, during diastole, calcium reuptake into the sarcoplasmic reticulum occurs by an ATP-dependent pump (SERCA—sarco-endoplasmic reticulum ATP-ase). A decrease in intracellular calcium concentration then occurs and prepares the myocardium for the next systolic event.[2]

The clinical picture of early sepsis is a patient with a low systemic vascular resistance (SVR) and a normal or increased cardiac output, although the heart is compromised by poor contractility. Although the stroke volume may be maintained, there is an increase in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) and very often a decrease in the ejection fraction (EF), with cardiac output maintained by an increase in heart rate. There is also diastolic dysfunction with decreased left ventricular compliance and a subsequent increase in left ventricular end-diastolic pressure (LVEDP) (Figs 1–3).

During sepsis, excessive NO is produced by iNOS.[3,4] The excess NO causes ventricular dysfunction by three methods; it decreases both calcium trafficking during systole (leading to decreased contractility) and calcium flux during diastole (which leads to abnormal cardiac filling). In these circumstances, cardiac force is compromised by the resulting abnormalities of fibre length. This diastolic dysfunction can be seen globally as

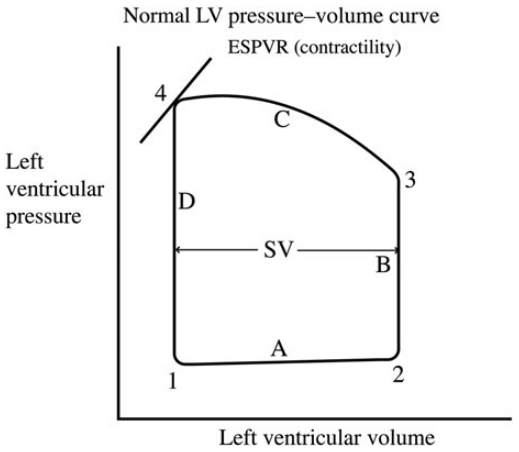


Fig 1 Pressure–volume curve for the normal LV. Phase A represents diastolic filling. B represents isovolumetric contraction. C represents ventricular ejection. D represents isovolumetric relaxation. Point 1 represents opening of the mitral valve. Point 2 represents closure of the mitral valve. Point 3 represents opening of the aortic valve. Stroke volume (SV) is demonstrated. The end-systolic pressure–volume relationship (ESPVR) can be extrapolated to form a line. The slope of this line represents the contractility of the heart.

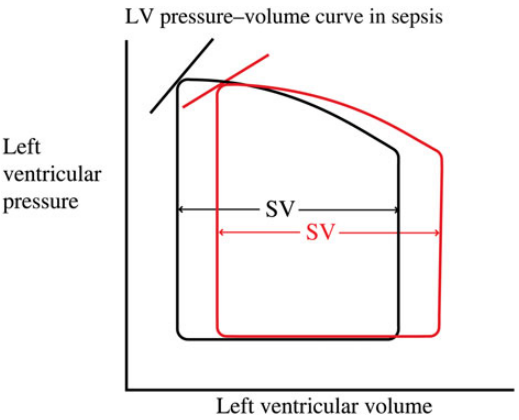


Fig 2 Pressure–volume curve for the LV during sepsis. During sepsis, LVESV and LVEDV are both increased. Stroke volume (SV) is maintained. The end-systolic pressure–volume relationship demonstrates decreased contractility.

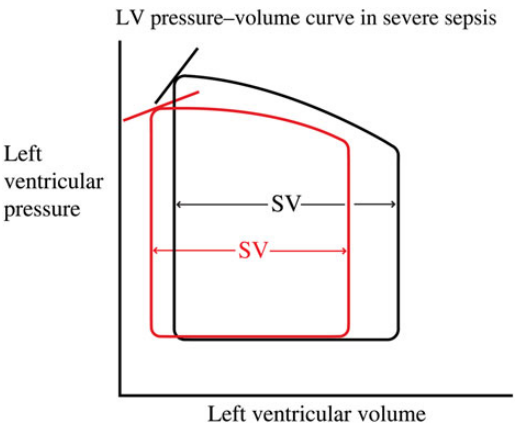


Fig 3 Pressure–volume curve for the LV during severe sepsis. During severe sepsis, there is a decrease in LVEDV and LVESP. There is hypotension.

increased LVEDP. Finally, NO decreases the sensitivity of the myocardium to endogenous adrenergic ligands by altering the response of second messenger systems. The protein kinase and cyclic GMP messenger systems are affected in this manner.

### The peripheral circulation: vasodilatation

Vasodilatation is the principal physiological abnormality in the cardiovascular response to sepsis. This leads to a low SVR and hypotension. One of the physiological functions of NO is to provide an intrinsic response to alterations in peripheral blood flow (myogenic control). When NO is formed in the endothelium, it diffuses into the vascular smooth muscle cells where it activates the enzyme guanylyl cyclase. This increases concentrations of cyclic GMP levels which lead to a reduction in intracellular calcium levels and activation of potassium channels. This leads to vascular smooth muscle relaxation.

Peripheral vascular dysfunction during sepsis is mediated by excessive production of NO by the enzyme iNOS. Increased NO concentration leads to hyperpolarization of potassium channels and persistent relaxation of smooth muscle.

In addition to vasodilatation, there is a failure of the cardiovascular reflexes, which normally control arterial pressure. The sympathetic and neuroendocrine responses to shock cause vasoconstriction, which is mediated by G-proteins and second messenger systems, in turn activating intracellular pathways. These responses to sympathetic activity and angiotensin II are decreased due to the increased production of NO, which decreases the cellular activity of signal transduction mechanisms.

## The pulmonary circulation in sepsis

### The right ventricle: decreased contractility and ventricular dilatation

The right ventricle (RV) differs embryologically, structurally, and functionally from the LV. The principle function of the RV is to facilitate efficient gas exchange. It has a thin wall with a low muscle mass, ejecting into the pulmonary circulation, which has a low resistance and a high compliance. The pressures generated on the right side are low; mean pulmonary artery pressure is 15 mm Hg. The RV depolarizes and then contracts in a longitudinal manner from the inflow tract to the outflow tract and produces a wave which is peristaltic in manner. This contrasts with the circumferential *pressure generating* contraction of the left side of the heart.

Like the LV, the cardiac output of the RV is determined by changes in preload, afterload, and contractility. The changes in ventricular function in sepsis are similar to those on the left side. The function is compromised by changes in contractility and afterload. The free wall of the RV has a low muscle mass and can respond to increases in preload by dilating, but it responds poorly to afterload because of its relative inefficiency as a muscle pump.

The onset of sepsis leads to a change in contractility due to effects of circulating inflammatory mediators which are the same as those outlined above. There is an increase in RVEDV and RVESV (stroke volume is maintained). There is a decrease in RVEF similar to that in the systemic circulation. The stresses imposed by sepsis on the RV muscle mass and the changes in afterload can ultimately lead to right ventricular failure.[5]

### The pulmonary circulation: pulmonary hypertension

The pulmonary circulation is a low-pressure system, which can respond to an increased cardiac output during exercise or after a physiological stress. The ability of the pulmonary circulation to respond to a large cardiac output without a major change in pressure ensures that effective gas exchange can take place.

It is important to consider the concept of *blood flow* in addition to generated pressure when considering the physiology of the pulmonary circulation. The right-sided circulation responds to changes in cardiac output by recruitment of pulmonary vessels which have low perfusion during stable conditions. In addition to recruitment, distension of these vessels allows an increase in blood flow which will support the need for improved gas exchange. These processes occur without vasomotor control.

The major stress imposed on the RV during sepsis is an increase in the afterload due to pulmonary hypertension. Hypoxic pulmonary vasoconstriction (HPV) is a response of the small arterioles of the pulmonary circulation to a decrease in alveolar or mixed venous oxygen content. The greater influence is from alveolar hypoxia. The function of this response is to divert blood from the hypoxic areas of the lungs to those which are ventilated, thus attempting to maintain optimum ventilation and perfusion ratios and ensure efficient gas exchange. It is a rapid response and occurs within seconds of induced hypoxia. The reflex occurs in the isolated lung and is independent of neural connections. The precise mechanism has not been proven, but NO is implicated. During sepsis, unregulated NO production in the systemic circulation leads to vasodilatation. In the presence of hypoxia, NO production decreases in the pulmonary circulation and local vasoconstriction occurs. It is also thought that local release of the potent vasoconstrictor endothelin occurs due to hypoxia.

There is evidence that the *active control* of the pulmonary circulation is influenced by ligands of systemic origin which lead to receptor activation. There are both cholinergic and adrenergic receptors in the pulmonary vascular tree, which allow changes in pulmonary vascular tone and resistance. Sympathetic stimulation can cause pulmonary vasoconstriction by α-1 receptor activity while they can cause vasodilatation by β-adrenergic stimulation. The predominant response is vasoconstriction. Cholinergic parasympathetic nerves cause vasodilatation by stimulation of muscarinic (M3) receptors, with NO acting as a mediator for cholinergic transmission. Other circulating humoral factors can induce a local vasoconstrictor response, including endothelin, angiotensin, and histamine.[6]

Pulmonary hypertension is thus a multifactorial consequence of sepsis and is probably due to inhibition of NO production due to hypoxia and also an enhanced vasoconstriction due to acidosis, increased adrenergic stimulation, and local mediators such as endothelin (Table 2).

## Ventricular interdependence: septal dysfunction

Ventricular interdependence is defined as the forces that are transmitted from one ventricle to the other ventricle through the myocardium and pericardium, independent of neural, humoral, or circulatory effects. Ventricular interdependence is a result of the close anatomical correlation of the ventricular cavities within the pericardium.[7,8] The round cavity of the LV approximates the interventricular septum during systole, while the less muscular RV contracts along its long axis to expel blood through the pulmonary valve. The ventricles can be considered in series. Stroke volume of systolic contraction of one cavity creates the preload of the next (Fig. 4).

The RV becomes impaired by increased afterload due to HPV. LVEDP increases in sepsis and this can impair RV function by

Table 2 The mediators involved in the active control of the pulmonary circulation[6]

| | Physiological change | Mediator agonist | Pulmonary vascular response | Receptor |
|---|---|---|---|---|
| Neural control | Sympathetic stimulation | Norepinephrine | Vasoconstriction | α1 adrenoceptor |
| | Sympathetic stimulation | Norepinephrine | Vasodilatation | β2 adrenoceptor |
| | Parasympathetic | Acetyl-choline | Vasodilatation | M3 muscarinic |
| | NANC | Unknown | Vasodilatation | NO-mediated |
| Receptor-mediated | Adrenergic response | Epinephrine | Vasoconstriction | α1 adrenoceptor |
| | Adrenergic response | Epinephrine | Vasodilatation | β2 adrenoceptor |
| | Histamine release | Histamine | Variable | H1 |
| | Histamine release | Histamine | Vasodilatation | H2 |
| | Angiotensin release | Angiotensin | Vasoconstriction | AT |
| | Endothelin release | Endothelin | Vasoconstriction | ET-A |
| | Endothelin release | Endothelin | Vasodilatation | ET-B |
| | Pain and stress | Substance P | Vasoconstriction | Neurokinin-1 |
| | Pain and inflammation | Neurokinin A | Vasoconstriction | Neurokinin-2 |

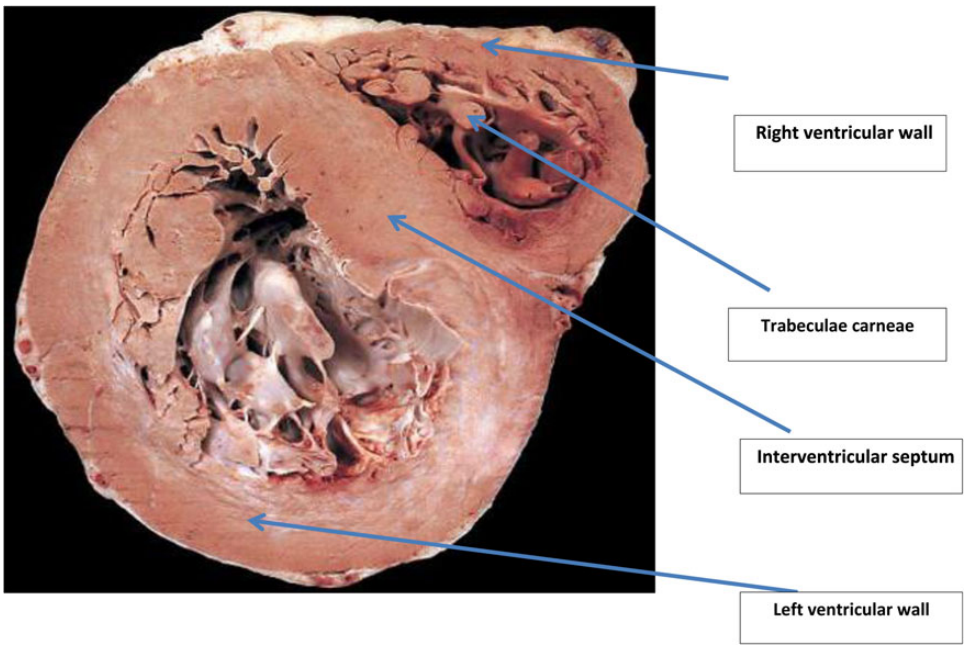


Fig 4 This is an oblique transverse section of the heart taken through the mid-cavity. It demonstrates the thick walled LV and the thinner wall of the RV. It demonstrates the crescentic shape of the RV in comparison with the round ventricular cavity on the left. The septum is noted. © 2008 by Mosby, an imprint of Elsevier, Ltd.[9]

increasing RV afterload further. This can lead to increased RVEDP and subsequently RVEDV increases as the ventricle dilates. The failing RV can impede left-sided performance by decreasing LV preload.

The failing RV has an increased RVEDV. Normally, LVEDP exceeds RVEDP and concentric contraction will maintain normal chamber shape during systole and diastole. However, in the presence of severe RV overload, the septum can shift towards the LV in end-diastole if the pressure gradient is reversed and RVEDP exceeds LVEDP. This severe RV diastolic dysfunction can be seen in sepsis (Fig. 5).

The pericardium normally allows free movement of the ventricular cavities even in the presence of a dilated heart; however, this may itself be compromised by pericardial disease during sepsis or high intrathoracic pressures caused by mechanical ventilation.

## Electrophysiology: increased arrhythmogenesis

Supraventricular tachyarrhythmias are commonly found in patients with sepsis, especially atrial fibrillation. It has been demonstrated that 32% of patients in intensive care who developed supraventricular tachyarrhythmias had sepsis and that septic shock was an independent predictor of their occurrence.

The voltage-dependent L-channels which are responsible for calcium flux in phase 2 of the cardiac action potential have a specific heteromeric structure. This calcium channel has five subunits (α1, α2, β, γ, and δ). The α1 subunit spans the cell membrane and forms the conduction pore, the voltage sensor, and the gating apparatus. It is a known site of channel regulation by second messenger systems. Animal studies have demonstrated that during sepsis, NO decreases the influx of calcium by

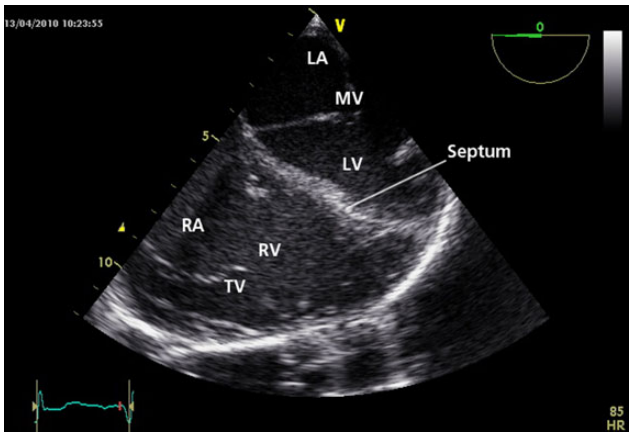


Fig 5 This is a four-chamber view of the heart observed with transoesophageal echocardiography. It is taken during end-diastole. The atrioventricular (TV and MV) valves are open. There is volume overload of the RV which has moved the septum towards the left side of the heart.

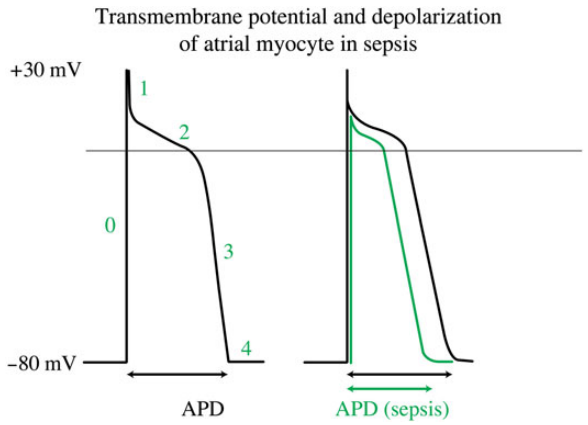


Fig 6 The phases of the action potential are shown. Phase 0, depolarization; phase 1, partial repolarization; phase 2, plateau phase; phase 3, repolarization. During phase 4, the negative potential is maintained at −80 mV. The APD is 300 ms in the ventricle and 200 ms in the atrium. The green line demonstrates how sepsis alters phase 2 and leads to a decrease in APD. This is due to a direct effect on the calcium channels and predisposes to atrial fibrillation.

alteration of the activity of this channel during phase 2 of repolarization. The potassium channel is also affected during sepsis and an increased influx of potassium occurs in myocytes during repolarization. These two mechanisms are responsible for the timing of repolarization. Action potential duration (APD) is decreased during sepsis in atrial myocytes. There is no change in resting membrane potential. A decrease in influx of calcium during phase 2 of repolarization is one of the electrophysiological changes associated with the genesis of tachyarrhythmias in sepsis (Fig. 6).[10]

## The coronary circulation

There is no evidence that global ischaemia leads to myocardial dysfunction in sepsis, with no alteration in coronary artery perfusion. There is a change in the metabolic activity of the heart during sepsis, as it develops an increased capacity to metabolize lactate as a substrate in preference to glucose and free fatty acids. High energy phosphate levels are maintained in the presence of normal arterial oxygen tension.[11]

If a patient has pre-existing coronary artery disease then the increased work of the heart can lead to myocardial ischaemia. The oxygen demand is increased by the tachycardia and the supply may be limited by decreased subendocardial perfusion due to increased end-diastolic pressure. It is important to consider sepsis as a risk factor in patients with diagnosed coronary atheroma. The increased work of the RV in the presence of pulmonary hypertension and systemic hypotension can alter the supply–demand ratio of the RV. This may worsen RV failure due to increased oxygen demand in the presence of impaired coronary artery perfusion.

## Cardiovascular reflexes and the neuroendocrine response in sepsis

The reflex response to shock is the activation of the sympathetic system. Hypotension stimulates high-pressure receptors in the aortic arch and the carotid bodies to transmit impulses to the medulla oblongata, which also co-ordinates the efferent responses. Norepinephrine is secreted locally and activates cellular activity via G-protein-coupled adrenergic receptors. This leads to increased heart rate, increased cardiac contractility, and peripheral vasoconstriction. In sepsis, the action of NO at the second messenger systems obtunds these reflex responses both at the heart and in the peripheral vascular system. These abnormal reflexes compromise the cardiovascular system in the presence of worsening disease.

The parasympathetic system is also affected in sepsis. Respiratory sinus arrhythmia is a primitive reflex which is present in mammals. It is seen as an increase in heart rate during inspiration and this is commonly measured as a decrease in the R–R interval witnessed on an ECG (heart rate variation). The function of this reflex is to maximize gas exchange at rest by matching alveolar ventilation and capillary perfusion during respiration. Heart rate variation (HRV) is widely used as an index of vagal function and easily becomes impaired during physiological stress or disease. The loss of HRV is an early indicator of sepsis.[12]

The parasympathetic nervous system interacts closely with the inflammatory system during sepsis. There is evidence to suggest that inflammatory products released during sepsis activate afferent signals to the nucleus tractus solitarius. This leads to inhibition of cytokine synthesis through the cholinergic anti-inflammatory pathway. This is termed 'The inflammatory reflex' and is mediated by the vagus nerve.[13]

The neuroendocrine response to shock comprises secretion of hormones from the hypophyseal–pituitary–adrenal axis and the activation of the renin–angiotensin aldosterone pathway. Vasopressin and angiotensin are normally potent vasoconstrictors. The pro-inflammatory mediators decrease the secretion of vasopressin from the posterior pituitary gland and nitric oxide obtunds the effects of angiotensin at peripheral receptors.

Cytokines decrease the secretion of glucocorticoids and the sensitivity of receptors to glucocorticoids. Glucocorticoids have an important role in the maintenance and sensitivity of the adrenergic receptor population. Relative adrenocortical insufficiency has been implicated in refractory shock and steroid replacement is associated with improved haemodynamic stability and earlier resolution of shock.

In the early stages of sepsis, the sympathetic responses maintain cardiac output but as the disease evolves, the compensatory neuroendocrine responses become overwhelmed. This is due to progressive insensitivity of the peripheral circulation to circulating vasoconstrictors such as vasopressin and angiotensin II. This leads from sepsis to severe sepsis and septic shock when the hypotension becomes refractory to treatment.

### Future trends

Improved technology has given us access to direct cardiac visualization by echocardiography. The current definition of myocardial dysfunction in sepsis is based upon an LVEF of <50% in the absence of cardiac disease that demonstrates reversibility on remission.

A recent transthoracic echocardiographic study has applied contemporary technology to a series of septic patients. This study was done during standardized fluid resuscitation in sepsis and demonstrated the frequency of myocardial dysfunction in patients with severe sepsis or septic shock to be 64%. The incidence of LV diastolic dysfunction was 37%, LV systolic dysfunction 31%, and RV dysfunction also 31%. There was significant overlap between all groups. There was no difference in 30 day or 1 yr mortality rates between septic patients who had cardiac dysfunction and those who did not. Moreover, not all patients with cardiac dysfunction due to sepsis demonstrated complete reversibility of function.[14] This study demonstrates that cardiac dysfunction during sepsis cannot be defined by a measurement based solely on LVE, but rather as a spectrum of functional changes throughout the cardiac cycle. Moreover, it is impossible to allow for differing host responses and individual differences in cardiorespiratory interaction and it is difficult to argue that a *snapshot* of activity in a complex and dynamic disease state is representative of the differing phases of sepsis, treatment, or resolution. It also suggests that echocardiographic techniques may be useful in sepsis.

Improved knowledge of cellular dysfunction has led to the development of new therapeutic agents which are designed to improve calcium trafficking during sepsis. Levosimendan increases calcium sensitization within the cardiac myocyte and in higher doses, it acts as a vasodilator and a phosphodiesterase inhibitor. Clinical trials in heart failure have demonstrated that it can improve cardiac output and stroke volume. Trials of this drug in sepsis are ongoing.

A number of other novel agents increase the activation of SERCA and may improve the cellular reuptake of calcium which is abnormal during sepsis. These include istaroxime, nitroxyl donor, and CXL-1020. SERCA activation is also considered to be treatable by gene transfer. Actin myosin cross-bridge activation is improved by omecamtiv mecarbil. These therapeutic strategies are currently undergoing trials.[15]

Cardiovascular dysfunction is a common sequel of sepsis. It is caused by the mediators of sepsis causing abnormalities of the normal cardiac physiology and additional disruption to the normal homeostatic and reflex responses. This review demonstrates that this process is widespread throughout all parts of the cardiovascular system.

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## Declaration of interest

None declared.

## MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at www.access.oxfordjournals.org by subscribers to *BJA Education*.

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REVIEW Open Access

# A review of sepsis-induced cardiomyopathy

Ryota Sato* and Michitaka Nasu

## Abstract

Sepsis-induced cardiomyopathy is a reversible myocardial dysfunction that typically resolves in 7–10 days. It is characterized by left ventricular dilatation and depressed ejection fraction. However, many uncertainties exist regarding the mechanisms, characteristics, and treatments of this condition. Therefore, this review attempts to summarize our current knowledge of sepsis-induced cardiomyopathy.

**Keywords:** Sepsis-induced cardiomyopathy, Septic cardiomyopathy, Cardiac depression in sepsis

## Introduction

Sepsis is a dysregulated systemic inflammation caused by infections involving various organs. Sepsis-induced cardiomyopathy is a complication of severe sepsis and septic shock first described by Parker et al. in 1984 as a reversible myocardial depression that occurs in patients with septic shock [1]. In sepsis-induced cardiomyopathy, the myocardium is functionally and structurally injured by inflammatory cytokines and mitochondrial dysfunction. However, our understanding regarding this condition remains incomplete. Recently, the development of tools, including echocardiography, has made it possible to visualize the hemodynamics of sepsis-induced cardiomyopathy. Sepsis-induced cardiomyopathy has three characteristics: left ventricular dilatation, depressed ejection fraction, and recovery in 7–10 days. Also, advances in molecular biology have made understanding the mechanisms of sepsis-induced cardiomyopathy possible (Fig. 1). Chemical mediators, including endotoxins, cytokines, and nitric oxide, appear to be the main mediators of sepsis-induced cardiomyopathy. The treatment strategy of sepsis-induced cardiomyopathy is the same with the adequate treatment of sepsis without cardiomyopathy. Although dobutamine is recommended in current guidance, recent trials have demonstrated that in patients with sepsis, it does not improve the prognosis and may have adverse effects. Here, we discuss the mechanisms, characteristics, and treatments of sepsis-induced cardiomyopathy.

* Correspondence: st051035@gmail.com
Department of Emergency and Critical Care Medicine, Urasoe General Hospital, 4-16-1, Iso, Urasoe, Okinawa, Japan

## Review

### Characteristics of sepsis-induced cardiomyopathy

In 1984, Parker et al. reported decreased ejection fraction and increased end-diastolic volume in septic shock survivors. These changes in left ventricular function were of rapid onset and reversed over 7–10 days in survivors; however, they were less profound in those who died [1, 2]. Moreover, Vieillard et al. demonstrated the mortality rate among patients in a hyperkinetic state to be significantly higher than that among patients in either a hypokinetic or normal-output state (100 vs 43 and 24 %) [3]. Conversely, a recent meta-analysis suggested that ventricular dysfunction or dilatation in patients with sepsis was not associated with lower mortality [4]. It suggested that mortality does not depend on whether the patients have sepsis-induced cardiomyopathy or not; however, it depends on whether the patient's heart is hyperkinetic or not. Because patients with sepsis-induced cardiomyopathy tend to be either hypokinetic or normokinetic but not hyperkinetic, in patients with sepsis-induced cardiomyopathy, the outcomes may be better than in patients without sepsis-induced cardiomyopathy. Larger studies are needed to clarify whether sepsis-induced cardiomyopathy is associated with improved outcomes.

Sepsis also triggers takotsubo cardiomyopathy, also known as stress cardiomyopathy, apical ballooning syndrome, or broken-heart syndrome, which is different from sepsis-induced cardiomyopathy. Takotsubo cardiomyopathy typically occurs when the contractile function of the mid-to-apical segments of the left ventricle is depressed and there is hyperkinesis of basal walls, producing a balloon-like appearance of the distal ventricle. Several studies have reported that this syndrome is induced by increased

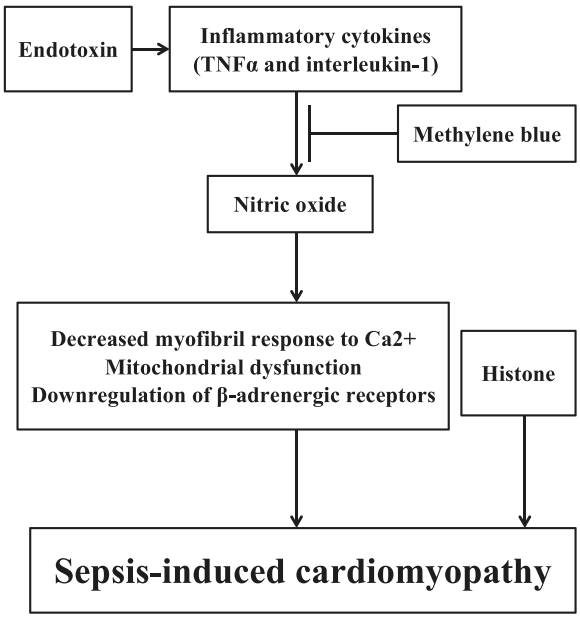


**Fig. 1** Mechanisms of sepsis-induced cardiomyopathy. Endotoxins cause depressed cardiac contractility, which is mediated by enhanced nitric oxide (NO) production. Tumor necrosis factor and interleukin-1β also contribute to NO overproduction. NO is believed to act in the heart by decreasing myofibril response to calcium, inducing mitochondrial dysfunction, and downregulating β-adrenergic receptors. These reactions lead to sepsis-induced cardiomyopathy. Methylene blue, an inhibitor of the NO pathway, counteracts the myocardial depression. Histones occur inside the nucleus and can be released into circulation because of extensive inflammation and cellular death during sepsis. Since cardiac dysfunction can be ameliorated by anti-histone antibodies in a septic mouse model, histones may be implicated in the pathophysiology of sepsis-induced cardiomyopathy

catecholamine levels. In takotsubo cardiomyopathy, the left ventricular function usually returns to normal within a few weeks. At a cellular level, changes were shown to be reversible with normalization of the left ventricular ejection fraction, including the cytoskeletal protein derangements, increase in extracellular matrix proteins, and accumulation of intracellular glycogen [5]. Although sepsis and septic shock can trigger takotsubo cardiomyopathy, the etiology and myocardial alterations appear to be different from those of sepsis-induced cardiomyopathy. In sepsis-induced cardiomyopathy, there is global ventricular dysfunction and dilated left ventricle without regional dysfunction. In takotsubo cardiomyopathy, there is typically regional dysfunction, especially characterized by apical ballooning mimicking acute coronary syndrome. Therefore, the accurate diagnosis of takotsubo cardiomyopathy requires coronary angiography to rule out acute coronary syndrome. In addition, many reports on takotsubo cardiomyopathy have mentioned various underlying diseases; this suggests that the pathophysiology of takotsubo cardiomyopathy is not specific to one particular disease. For these reasons, sepsis-induced cardiomyopathy and takotsubo cardiomyopathy are two different entities.

Despite the lack of diagnostic criteria for sepsis-induced cardiomyopathy to date, it is known to have three characteristics. The first is left ventricular dilatation with normal or low filling pressure. This probably occurs due to an increase in the left ventricular compliance, which was first described in patients with septic shock in 1984 [1]. Later, another study of the left ventricle response to volume loading showed that there was an abnormal increase in left ventricular end-diastolic volume in sepsis survivors, implying increased ventricular compliance [6]. The second characteristic is depressed ejection fraction. Parker et al. reported that end-diastolic and systolic ventricular volumes were increased but with normal or elevated stroke volume and cardiac index in septic shock survivors. In this study, although the number of patients is less, these results suggest that decreased ejection fraction may be caused by ventricular dilatation and not by decreased stroke volume. Because ejection fraction is defined as the stroke volume divided by the end-diastolic ventricular volume, the denominator increases as the ejection fraction decreases [7]. Vincent et al. demonstrated that the left and right ventricular ejection fractions are depressed in patients with septic shock [8]. Other studies support this result and have shown the development of right ventricular dilatation [6, 9, 10]. The third characteristic of sepsis-induced cardiomyopathy is that it should normalize within 7–10 days [1, 11, 12]. In sepsis-induced cardiomyopathy diagnosis, the first and second characteristics are particularly important and easy to detect using echocardiography. Thus, echocardiography in sepsis management is the most important thing for diagnosing sepsis-induced cardiomyopathy.

B-type natriuretic peptide (BNP), a diuretic hormone, is released from ventricular myocardium in response to cardiac wall stretch. Recent observational study demonstrated that sepsis-induced cardiomyopathy is associated with BNP rise, although not independently, whereas left ventricular filling pressures do not correlate with the BNP levels [13]. In this study, the author concluded that the severity of critical illness, rather than sepsis-induced cardiomyopathy, is probably the main determinant of BNP rise in critical patients with sepsis. For this reason, BNP should not be used as a predictive marker of sepsis-induced cardiomyopathy.

Troponin is a very sensitive and specific protein of myocardial damage and often used for the diagnosis of acute coronary syndrome (ACS). Troponin elevation is common in septic shock patients, and it was estimated that 43–85 % of patients with sepsis showed cardiac troponin I elevation [14–16]. Bessiere et al. performed a meta-analysis and reported that troponin elevation is associated with a higher risk of death among patients with

sepsis [17]. However, the use of troponin to diagnose sepsis-induced cardiomyopathy is limited because there are many causes such as ACS and low renal function that affect troponin levels.

### The mechanisms of sepsis-induced cardiomyopathy

Two possible causative mechanisms have been proposed to explain sepsis-induced cardiomyopathy. First, myocardial ischemia resulting from inadequate coronary blood flow has been proposed on the basis of a study in animals [18]. Second, there are strong arguments that chemical mediators, such as endotoxins, cytokines, and nitric oxide, are causative. To determine whether myocardial depression in humans with septic shock was associated with reduced coronary flow, a study was conducted that used coronary sinus thermodilution catheters to measure coronary flow and myocardial metabolism in seven patients [19]. Myocardial depression was observed in four of the seven patients who had coronary flow similar to or higher than that of controls and similar to that of other three patients. Therefore, reduced coronary flow may not contribute to the pathogenesis of sepsis-induced cardiomyopathy.

Concerning the role of chemical mediators, there are stronger arguments to support their role in sepsis-induced cardiomyopathy. Anthony et al. demonstrated that endotoxin administration to controls caused the left ventricular function to become depressed [20], with left ventricular end- and end-systolic volume indexes increasing by 18 and 24 %, respectively. Flesch et al. also demonstrated that exposure of the myocardium to endotoxins caused depressed cardiac contractility, which was mediated by enhanced inducible nitric oxide synthase activity and nitric oxide release [21]. In 1985, Parriio et al. demonstrated in vitro that myocardial cell shortening was reduced by exposure to the serum of patients with sepsis [22]. The same team later showed that this response was caused by tumor necrosis factor alpha (TNF-α) [23], which was confirmed when Vincent et al. demonstrated that anti-TNF antibody administration improved ventricular function without changing the cardiac filling pressure [24]. In a more recent study, interleukin-1β has also been implicated [25], further supporting cytokine's role in sepsis-induced cardiomyopathy.

Kumar et al. have suggested that cytokine's effect on cardiac myocytes results from an increase in both intracellular cyclic guanosine monophosphate and nitric oxide [26]. Because the half-lives of TNF and interleukin-1β are less than 6 h, nitric oxide appears to have an important contributory role in the pathogenesis of sepsis-induced cardiomyopathy. Nitric oxide is thought to act in the heart by decreasing myofibril response to calcium [27], inducing mitochondrial dysfunction [28], and downregulating β-adrenergic receptors [28, 29]. Some studies reported that the severity of cardiac dysfunction and mortality can be related to nitric oxide overproduction and mitochondrial dysfunction [30–32]. Larche et al. demonstrated that mitochondrial dysfunction in sepsis is causative rather than epiphenomenal and relevant in terms of myocardial dysfunction in sepsis [33]. In 2001, Kirov et al. evaluated the effects of continuous infusion of methylene blue, an inhibitor of the nitric oxide pathway, on the hemodynamics and organ function of patients with septic shock. They reported that continuous infusion of methylene blue counteracted the myocardial depression, maintained oxygen transport, and reduced the need for concurrent adrenergic support [34]. Later, in a systematic review, Kwok et al. reported that methylene blue administration during sepsis increased the mean arterial pressure and systemic vascular resistance while decreasing the vasopressor requirement [35].

A recent study demonstrated that high-circulating histone levels were significantly associated with new-onset left ventricular dysfunction and arrhythmias in patients with sepsis with no previous cardiac dysfunction [36]. However, because histones occur inside the nucleus and can be released into circulation because of extensive inflammation and cellular death during sepsis, it is unclear whether the circulating histones are the cause or the result of sepsis-induced cardiomyopathy. Further research is warranted to decide the role of circulating histones in the pathogenesis of sepsis-induced cardiomyopathy.

Although the reason why sepsis-induced cardiomyopathy resolves within 7–10 days is poorly understood, the mechanisms proposed in this section appear to be critical. In particular, chemical mediators, such as endotoxins and cytokines, are currently regarded as the most likely cause of sepsis-induced cardiomyopathy. However, the mechanism of myocardial recovery in sepsis-induced cardiomyopathy is poorly understood, and further research is clearly needed.

### Treatments for sepsis-induced cardiomyopathy

In 2001, Rivers et al. reported that early goal-directed therapy was effective for severe sepsis management. Although this strategy has become a standard therapy worldwide, the original study was only a small single-center study [37]. The ProCESS [38] and ARISE [39] trials (in 2014) and the ProMiSe trial [40] (in 2015) have since demonstrated that early goal-directed therapy did not improve outcomes compared with usual care. There is a widespread agreement that standard treatment for sepsis should focus on infection control and optimization of hemodynamic parameters by fluid resuscitation and vasopressor therapy. This strategy is also recognized as the standard therapy for sepsis-induced cardiomyopathy. Noradrenaline is recommended as a first-line vasopressor; however, some studies reported that vasopressin also may be effective for septic shock. Russell et al. suggested that

low-dose vasopressin may reduce the mortality of patients with less severe septic shock, although there was no significant difference between vasopressin and noradrenaline in the 28- and 90-day mortality of all patients with septic shock [41]. From this finding, current guidance describes that low-dose vasopressin can be added to noradrenaline with the intent of either raising mean arterial pressure or decreasing noradrenaline dosage; however, low-dose vasopressin is not recommended as a single vasopressor [42]. Mehta et al. reported that troponin, CK, and ECG are not different in patients with septic shock who are treated with noradrenaline and vasopressin [43]. This finding suggests that vasopressin also may be effective for the management of sepsis-induced cardiomyopathy. However, further study is warranted to confirm the effectiveness of vasopressin.

Current guidance recommends using dobutamine [42] to increase the cardiac index [44]. However, Gattinoni et al. reported that hemodynamic therapy with dobutamine and dopamine to achieve supranormal values for the cardiac index failed to reduce morbidity or mortality among critically ill patients [45]. Michelle et al. also demonstrated that the use of dobutamine to boost the cardiac index did not improve the outcome of critically ill patients [46]. Furthermore, Wilkman et al. reported that the use of dobutamine was associated with increased 90-day mortality from septic shock [47], while Hernandez et al. demonstrated that dobutamine did not improve sublingual microcirculatory, metabolic, hepatosplanchnic, or peripheral perfusion parameters in patients with septic shock [48].

Lyte et al. suggested that the ability of inotropic catecholamines to stimulate bacterial proliferation and biofilm formation might be an etiological factor in the development of intravascular catheter colonization and catheter-related infection [49]. This effect of inotropic catecholamines does not seem to be limited to only coagulase-negative *Staphylococcus* but also other gram-negative bacteria. The growth of these bacteria and production of virulence are associated with inotropic catecholamines [49]. Thus, inotropic catecholamines, such as dobutamine, may have adverse effects in patients with septic shock, and the decrease in β-adrenergic response in patients with sepsis-induced cardiomyopathy may be a protective mechanism to these effects. Morelli et al. suggest that β-blockade could be associated with reductions in the heart rate without adverse effects and that this could help to improve survival [50]. Although the mortality in the control group of their study was high, the study provided interesting preliminary data suggesting that β-blockade may be effective in septic shock treatment. For these reasons, despite the beneficial effects of dobutamine, it appears that excessive increases in sympathetic tone during sepsis can create adverse effects.

Levosimendan can increase contractile myofilament sensitivity to calcium and is a positive inotropic drug. Levosimendan sensitizes troponin C to calcium in a calcium concentration-dependent manner; this increases the effects of calcium on myofilaments during systole. This sensitization is diminished by decreasing calcium concentration level during diastole, and thus, diastolic relaxation remains largely unaffected. In contrast to other inotropic agents, levosimendan does not cause arrhythmias or increase the oxygen consumption. It also opens the ATP-sensitive potassium channels causing smooth muscle membrane hyperpolarization which leads to vasodilation. A meta-analysis evaluated the use of levosimendan in septic shock [51] and reported that it was associated with reduced mortality when compared with standard inotropic therapy. Although levosimendan is also an inotropic agent, it does not stimulate β-adrenergic receptor. This may be the reason why levosimendan can be effective to the patients with septic shock, despite dobutamine seems to create adverse effect in the patients with septic shock. To confirm this finding, a larger multicenter randomized trial is needed to assess the effectiveness of levosimendan in sepsis-induced cardiomyopathy.

Intra-aortic balloon pumping (IABP) is expected to increase the cardiac output and reduce the dosage of a vasopressor. Solomon et al. demonstrated that in a canine model of severe septic shock with a low cardiac index, IABP prolongs survival time and lowers vasopressor requirements [52]. Nakamura et al. reported two cases of severe sepsis-induced cardiomyopathy with refractory shock [53]. To our knowledge, this is the only report in which polymyxin B-immobilized fiber column-direct hemoperfusion (PMX-DHP) and IABP were used for the management of sepsis-induced cardiomyopathy. Although the authors suggested their use in sepsis-induced cardiomyopathy, their effectiveness and safety are not yet developed and their use in the management of septic shock are currently at an experimental stage. For example, a recent multicenter randomized controlled trial demonstrated a non-significant increase in mortality and no improvement in organ failure with PMX-DHP compared to the conventional treatment in patients with septic shock due to peritonitis [54]. There are some case reports of the successful use of veno-arterial extracorporeal membrane oxygenation (ECMO) as the last rescue therapy to unresponsive severe cardiogenic shock in patients with sepsis-induced cardiomyopathy. We searched PubMed (January 1990 to September 2015) for English language articles for sepsis-induced cardiomyopathy treated with veno-arterial ECMO. The keywords “sepsis” OR “septic shock” AND “extracorporeal membrane oxygenation” were used and we carefully reviewed the articles found. The adult patients with sepsis-induced cardiomyopathy who received veno-arterial ECMO support are listed in Table 1 [55–63]. This

**Table 1** Reported cases of the patients with sepsis-induced cardiomyopathy who received veno-arterial extracorporeal membrane oxygenation support

| Article | Age | Sex | Infection | Survival |
|---|---|---|---|---|
| Pořízka M et al. 2015 [55] | 31 | M | Necrotizing fasciitis | + |
| Fujisaki N et al.2014 [56] | 27 | F | CA pneumonia | + |
| Endo A et al. 2014 [57] | 41 | M | Purpura fulminans | – |
| Bréchot N et al. 2013 [58] | 33 | M | CA pneumonia | + |
| Bréchot N et al. 2013 [58] | 62 | M | CA pneumonia | + |
| Bréchot N et al. 2013 [58] | 31 | F | Acute cholecystitis | + |
| Bréchot N et al. 2013 [58] | 33 | F | Aspiration pneumonia | + |
| Bréchot N et al. 2013 [58] | 48 | F | CA pneumonia | – |
| Bréchot N et al. 2013 [58] | 66 | M | Peritonitis after liver transplant | – |
| Bréchot N et al. 2013 [58] | 59 | M | CA pneumonia | + |
| Bréchot N et al. 2013 [58] | 52 | M | CA pneumonia | – |
| Bréchot N et al. 2013 [58] | 28 | F | CA pneumonia | + |
| Bréchot N et al. 2013 [58] | 35 | M | Aspiration pneumonia | + |
| Bréchot N et al. 2013 [58] | 28 | F | Aspiration pneumonia | + |
| Bréchot N et al. 2013 [58] | 52 | F | Nosocomial pneumonia | + |
| Bréchot N et al. 2013 [58] | 57 | F | Pharyngitis | + |
| Bréchot N et al. 2013 [58] | 48 | M | CA pneumonia | – |
| Hagiwara et al. 2013 [59] | 69 | M | Klebsiella bacteremia | + |
| Firstenberg MS et al. 2010 [60] | 18 | M | Necrotizing fasciitis | + |
| Firstenberg MS et al. 2010 [60] | 39 | F | Necrotizing fasciitis | + |
| MacLaren G et al. 2010 [61] | 29 | F | H1N1 influenza | + |
| Vohra HA et al. 2009 [62] | 18 | M | Mediastinitis after Ravitch procedure | + |
| McLauren G et al. 2004 [63] | 22 | M | Vertebral osteomyelitis | + |

*CA* community acquired, *M* male, *F* female

strategy may provide time for antibiotics to work effectively. If both septic and cardiogenic factors contribute to the pathophysiology of shock, veno-arterial ECMO may improve the mortality of the most severe group. However, the experience of the use of ECMO in patients with septic shock is very limited. Moreover, the management of patients who need ECMO is very complex; thus, a well-experienced team should use it in a specialized center [64]. For these reasons, to date, mechanical support with IABP or ECMO seems not to be a standard therapy, although it may be the last option for unresponsive severe cardiogenic shock due to sepsis-induced cardiomyopathy.

## Summary of our current knowledge

Sepsis-induced cardiomyopathy is characterized by left ventricular dilatation and depressed ejection fraction that typically normalize within 7–10 days. Our current understanding is that sepsis-induced cardiomyopathy is induced by endotoxins and cytokines and that the initial management should be the same as for septic shock without cardiomyopathy. However, the lack of quality evidence that dobutamine improves survival and the concerning reports that it may adversely affect outcomes in patients with sepsis imply that the routine use of dobutamine should no longer be recommended. In the near future, levosimendan or mechanical support with ECMO may be developed as a therapeutic option, but further study is needed to confirm whether it is truly effective in sepsis-induced cardiomyopathy.

### Abbreviations

ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pumping; PMX-DHP: polymyxin B-immobilized fiber column-direct hemoperfusion; TNF: tumor necrosis factor.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

MN and RS helped in the draft of the manuscript. Both authors read and approved the final manuscript.

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