REVIEW

Sepsis-induced myocardial dysfunction

Keith R. Walley

Purpose of review
Sepsis leads to a complex intramyocardial inflammatory response that results in sepsis-induced myocardial dysfunction. Here, recent findings are reviewed in a physiologic context.

Recent findings
Decreased systolic contractility during sepsis limits ventricular ejection and stroke volume. Initially, this effect is compensated for by increased diastolic filling during volume resuscitation. Reduced afterload due to arterial vasodilation also compensates so that cardiac output can be maintained or increased. Recent results recognize the importance of diastolic dysfunction, reduced ventricular diastolic compliance that impedes ventricular filling. Diastolic dysfunction becomes increasingly important as severity of septic shock increases. When impaired ventricular ejection is coupled with limited diastolic filling, stroke volume must decrease. Accordingly, diastolic dysfunction is more closely related to mortality than systolic dysfunction. Recent trials of beta-adrenergic agonists and levosimendan have been disappointing, while approaches to modulating the intramyocardial inflammatory response show promise.

Summary
Sepsis-induced myocardial dysfunction is increasingly recognized as a major contributor to outcome of septic shock. Significant strides have been made in understanding the intramyocardial inflammatory response that causes myocardial dysfunction. A number of novel approaches show promise by modulating the intramyocardial inflammatory response.

Keywords
contractility, diastolic dysfunction, intramyocardial inflammation, myocardial dysfunction, septic shock

INTRODUCTION

Five of the top 10 WHO causes of death fulfil the definition of sepsis (http://www.who.int) making sepsis the number one killer worldwide. More deaths are due to sepsis and septic shock than myocardial infarction, even in the western world [1]. Severe infection triggers a systemic inflammatory response that can lead to septic shock. Septic shock is, fundamentally, failure of the cardiovascular system to maintain adequate tissue oxygenation, leading to organ dysfunction and resulting fairly rapidly in death [2]. A key component of the cardiovascular failure of septic shock is sepsis-induced myocardial dysfunction. In view of the importance of this issue, we review the clinical features, mechanism, diagnostic approaches and treatments of sepsis-induced myocardial dysfunction with particular attention to recent discoveries.

Myocardial dysfunction is a key component of cardiovascular failure of sepsis

Cardiovascular failure due to sepsis involves peripheral vascular dysfunction and myocardial dysfunction. Peripheral vascular dysfunction includes venodilation, arterial vasodilation, impaired regulation of the distribution of arteriolar blood flow, heterogeneity of capillary microcirculatory flow, inflammation involving the endothelium and microcirculation, and increased permeability of vessels leading to tissue oedema and intravascular hypovolemia. In this setting, myocardial dysfunction becomes particularly important because peripheral vascular dysfunction places much greater demand on the heart.

Unfortunately, significant myocardial dysfunction occurs in septic shock patients [3]. Early nuclear medicine measurements demonstrated that left ventricular ejection fraction is decreased in septic shock patients but resolves over 7–10 days in survivors [3].

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KEY POINTS

- Sepsis-induced myocardial dysfunction is extremely common and contributes to adverse clinical outcomes.
- Diastolic compliance initially increases and partially compensates for decreased systolic contractility of sepsis. However, more severe sepsis is associated with the development of decreased diastolic compliance (diastolic stiffness), which is strongly correlated with adverse clinical outcomes.
- A wide array of inflammatory pathways contribute to the intramyocardial inflammatory response of sepsis-induced myocardial dysfunction.

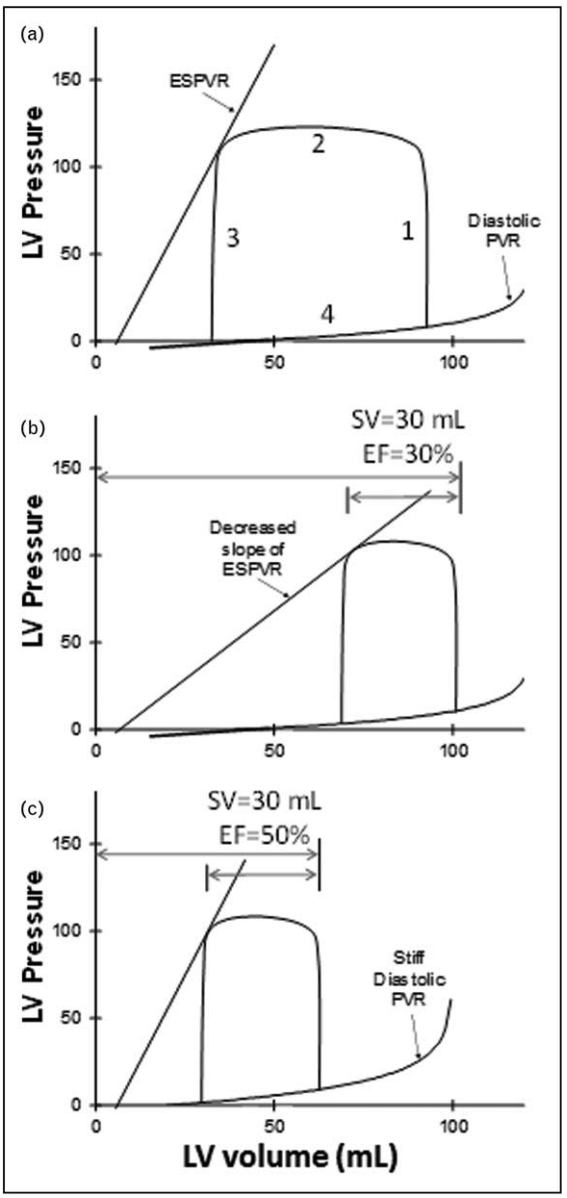

FIGURE 1. (a) A normal cardiac cycle is shown on a left ventricular (LV) pressure-volume diagram. Contraction starts at the end of diastole [1]. When ventricular pressure exceeds aortic pressure, the aortic valve opens and the ventricle ejects [2] until end-systolic volume and pressure approach the end-systolic pressure volume relationship (ESPVR). The slope of the ESPVR is a load-independent measure of ventricular contractility. Then, pressure in the ventricle falls exponentially during the isovolumic relaxation phase [3]. Diastolic filling occurs at low pressures along a compliant diastolic pressure volume relationship (Diastolic PVR) [4]. (b) During sepsis, systolic contractility decreases as indicated by a decrease in slope of the ESPVR. This initially results in a decrease in stroke volume (SV) before volume resuscitation occurs. The low stroke volume (short arrow) relative to the long arrow (end-diastolic volume) is ejection fraction (EF), which decreases is early sepsis-induced myocardial dysfunction. (c) When septic myocardial dysfunction is severe, diastolic dysfunction (decreased diastolic compliance) can occur as represented by a stiff diastolic pressure-volume relationship. This results in a decrease in end-diastolic volume (long arrow). Even though stroke volume is decreased by impaired diastolic filling, ejection fraction is not decreased that much because end-diastolic volume is also decreased.

Both systolic and diastolic dysfunction are observed [4]. Decreased systolic contractility limits the ability of the ventricle to eject to low end-systolic volumes so stroke volume is decreased (Fig. 1). This decrease in stroke volume can be compensated for by an increase in end-diastolic volume due to adequate fluid resuscitation and by decreased afterload due to septic arterial vasodilation (Fig. 2). These compensatory mechanisms can generate high stroke volume hyperdynamic septic shock even in the face of decreased systolic contractility. But in severe septic shock, diastolic dysfunction (decreased diastolic compliance) can also occur, impairing the ability of the diastolic ventricle to fill (Fig. 1c). The combination of impaired ability to eject and impaired ability to fill leads to low stroke volume, hypodynamic, fatal septic shock.

Sepsis-induced myocardial dysfunction occurs in one quarter to one half of all adult septic shock patients [4] and occurs in a similarly high fraction of children [5▪]. Much of the focus has been on left ventricular dysfunction, but right ventricular dysfunction is equally prevalent in critically ill septic patients [6]. Although left ventricular afterload is typically reduced during septic shock, right ventricular afterload is often increased, further impeding right ventricular function.

CLINICAL FEATURES OF SEPSIS-INDUCED MYOCARDIAL DYSFUNCTION

Decreased systolic contractility

The observation that ejection fraction is decreased in septic shock patients was surprising [3], as arterial

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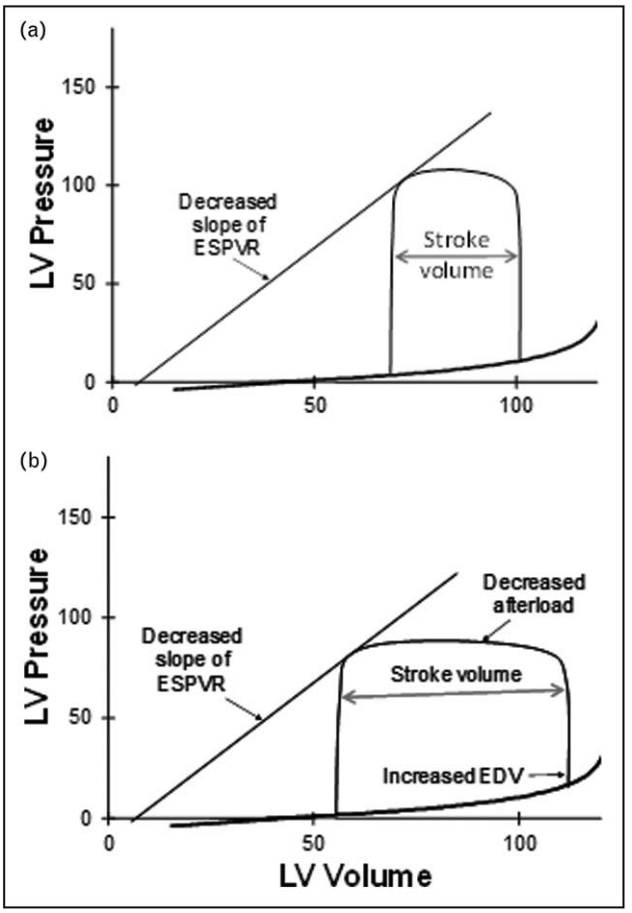

FIGURE 2. (a) Sepsis-induced myocardial dysfunction is initially manifested as decreased contractility, as indicated by the low slope of the ESPVR, which initially results in a low stroke volume. (b) However, several compensatory mechanisms help to restore stroke volume and result in hyperdynamic septic shock with an elevated stroke volume. Decreased afterload allows further ejection to a smaller end-systolic volume. Increased end-diastolic volume (EDV) occurs due to volume resuscitation and can also occur as a result of increased diastolic compliance (a shift of the end-diastolic pressure volume relationship down and to the right). Finally, infused catecholamines may increase contractility, which is a shift up and to the left of the ESPVR.

pressure afterload was decreased, which should have resulted in increased ejection fraction. Furthermore, many patients are treated with adrenergic agonists (norepinephrine, epinephrine, dopamine), which should have increased ventricular contractility. Thus, the observation of decreased ejection fraction [3] suggests that myocardial dysfunction was severe. Using more sensitive cardiac ultrasound measurements, septic myocardial dysfunction can be identified in more than half of patients with septic shock [4]. Decreased systolic contractility can be heterogeneous with evidence of regional wall motion abnormalities. True myocardial tissue damage is indicated by increased troponin and creatine kinase-muscle/brain (CKMB) concentrations in the blood [5▪,7].

Impaired diastolic function

Early studies also identified diastolic dysfunction, although this is more complicated. In survivors, the diastolic ventricle typically increased in volume, similar to diastolic compensation for decreased systolic contractility in other ventricular disease states. However, in nonsurvivors, the diastolic ventricle did not dilate. Echocardiographic measurements demonstrate that impaired early diastolic filling, indicating decreased diastolic compliance, is common in patients with septic shock [4,8▪▪]. The cause of decreased diastolic compliance in those septic patients who do not develop a dilated diastolic ventricle, has not been fully elucidated. Increased myocardial oedema is one possibility [9]. Indeed, resuscitation with colloid solutions to prevent myocardial oedema results in improved ventricular function in animal models of sepsis [10,11]. Contraction band necrosis contributes to decreased diastolic compliance during hypovolemic shock [12] and may also contribute during septic shock. Impaired diastolic relaxation may also contribute. It is also important to consider the contribution from structures outside of the heart, including lungs inflated with positive pressures and intra-abdominal pressure, because contributions from these factors can potentially be reduced by appropriate ventilator, and other, management.

A meta-analysis of echocardiographic assessments of diastolic dysfunction during sepsis show an association between echocardiographic indices of impaired diastolic function and mortality [8▪▪].

Survivors versus nonsurvivors

An interesting feature of sepsis-induced myocardial dysfunction is that ejection fraction is decreased less in nonsurvivors than survivors of sepsis [3,13]. At least part of the explanation for this is that left-ventricular afterload is decreased (decreased systemic arterial pressure due to decreased systemic vascular resistance) more in nonsurvivors than survivors. A greater decrease in left ventricular afterload facilitates systolic ejection and preserves ejection fraction more in nonsurvivors. A second possible contributor is diastolic dysfunction. Impaired diastolic filling due to decreased diastolic compliance decreases stroke volume but does not decrease ejection fraction as much as decreased systolic contractility does (Fig. 1b, c). A related observation is that left ventricular dilation is associated with lower mortality [13]. When the ventricle does not fully

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eject, the normal compensatory response is increased filling volume of the diastolic ventricle, which requires a highly compliant, relatively normal, diastolic ventricle (Fig. 2).

Thus, septic myocardial dysfunction initially is predominantly characterized by decreased systolic contractility associated with a compensatory diastolic ventricular dilation, necessary for survival. When sepsis and septic myocardial dysfunction is more severe then diastolic dysfunction – decreased diastolic compliance – results and mortality increases [4]. A degree of diastolic dysfunction means that the ventricle does not dilate and may remain a normal size on echocardiographic examination, which can mask the presence of fairly severe septic myocardial dysfunction for all but the most skilled observers.

Demand ischemia

It is also possible for true myocardial ischemia to contribute to myocardial dysfunction during sepsis. Increased myocardial oxygen demand is driven by sepsis-induced tachycardia and increased cardiac output and the ability of the myocardium to extract oxygen is diminished [14]. It is often challenging to distinguish myocardial demand ischemia from sepsis-induced myocardial dysfunction because both can result in elevated cardiac enzymes, ECG changes and echocardiographic changes [7]. True ST elevation myocardial infarction events due to coronary occlusion are typically more clearly separable from septic myocardial dysfunction. Takotsubo cardiomyopathy can also occur during sepsis and may be aggravated by the use of infused catecholamines to manage hypotension [15].

Cardiac rhythm

The intramyocardial septic inflammatory response can also influence cardiac rhythm. Sinus tachycardia is the most common rhythm abnormality, but atrial fibrillation and flutter are surprisingly common and are associated with adverse outcome. In a large study of vasopressor treatment of septic shock, patients treated with dopamine had an incidence of atrial fibrillation of 22%, which was reduced to 11% in patients treated with norepinephrine [16]. New atrial fibrillation has approximately the same impact on mortality as full organ failure in septic shock patients.

MOLECULAR MECHANISMS

Innate immune receptors

Myocardial dysfunction is due to intramyocardial inflammation involving many parallel pathways of the septic inflammatory response. Pathogen-associated molecular patterns (PAMPs) expressed by bacteria and other pathogens initially activate a septic inflammatory response via toll-like receptors (TLRs) and other innate immune receptors. Cardiomyocytes express TLRs [17] and can therefore respond directly to PAMPs and also to endogenous damage-associated molecular patterns (DAMPs) [18] that arise from concurrent tissue damage. Ventricular function improves when TLR4 is eliminated on cardiomyocytes in a mouse model of sepsis [19]. Other innate immune receptors activate the NLRP3 inflammasome, which results in interleukin (IL)-1β maturation and signalling. This pathway can be modulated by a low concentration of carbon monoxide, which then ameliorates sepsis-induced myocardial dysfunction [20].

Intracellular signalling

TLRs signal via several intracellular signalling pathways, including nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), to increase inflammatory cytokine and interferon inducible gene production. Modulation of these pathways impacts sepsis-induced myocardial dysfunction [21–25]. Complement C5a activates MAPKs and Akt in the heart, which was reduced by a p38 MAPK inhibitor [21]. p38 MAPK inhibition also decreased sepsis-induced myocardial dysfunction [21]. Statins inhibit signalling via p38 MAPK and NF-κB, which attenuates cardiac dysfunction [23,24]. Calpain activation, as part of the intramyocardial inflammatory response, results in disruption of structural and contractile proteins with activation of proteasome-dependent proteolysis and inhibition of mechanistic target of rapamycin [26].

Cytokine response

Activation of TLRs on monocytes and macrophage cell lines results in increased circulating levels of inflammatory cytokines, which amplify activation of the intramyocardial inflammatory response. For example, IL18 contributes to sepsis-induced myocardial dysfunction via phospholamban and Akt phosphorylation [27▪]. Cardiomyocytes also directly release inflammatory cytokines and express cell adhesion molecules such as ICAM-1 [28,29]. Chemotactic cytokines then draw leukocytes from coronary microvessels into the myocardium [30]. Binding of cardiomyocyte ICAM-1 by molecules such as fibrinogen [31] and even intramyocardial leukocytes [28] alters the cardiomyocyte actin cytoskeleton with an impact on the coordination of depolarization of cardiomyocytes and subsequent

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sarcoplasmic calcium release [29]. This leads to decreased cardiomyocyte contractility.

Nitric oxide, mitochondria and apoptosis

Activated coronary endothelium increases production of nitric oxide that contributes to impaired systolic contractility [32]. Activated endothelium slows and retains transiting leukocytes in the coronary circulation [33]. These leukocytes contribute to myocardial dysfunction [30] by releasing reactive oxygen species [30,34,35], which damage intracellular organelles including mitochondria. Mitochondrial cAMP/protein kinase A signalling, which impairs mitochondrial function, contributes to sepsis-induced myocardial dysfunction [36]. Dysfunctional mitochondria generate excessive reactive oxygen species, which, when combined with increased nitric oxide, form peroxynitrite and contribute to oxidative and nitrosative stress and myocardial dysfunction [37]. Damaged mitochondria trigger apoptotic pathways [38]. Although apoptosis progresses to cell death in only a small fraction of cardiomyocytes, activation of apoptotic pathways may contribute to myocardial dysfunction [39]. Inhibition of apoptosis using miR-155 reduces lipopolysaccharide (LPS)-induced myocardial dysfunction [40]. Autophagy also plays a role and can be modulated via opioid receptor activation [41].

Myocardial metabolism

Myocardial metabolism during sepsis shifts from normal fatty acid and glucose oxidation to involve a greater contribution from glycolysis and lactate metabolism [42]. The shift away from normal myocardial fatty acid oxidation during sepsis [43] is attenuated by PPAR-alpha [44]. Efficiency of oxygen extraction from coronary arterial blood is also diminished [14,45] so that evidence of anaerobic metabolism may appear [42], further inducing myocardial expression of hypoxia-inducible genes [46].

DIAGNOSTIC TESTS/BIOMARKERS

Echocardiography

Bedside goal-directed echocardiographic assessment of the septic patient often provides the first evidence of septic myocardial dysfunction [47]. The goal of this bedside assessment is to identify or exclude significant contributions from Septic, Hypovolemic, Obstructive, Cardiogenic and other Kinds of SHOCK (mneumonic). Echocardiography stress/strain measures may be a sensitive approach to identifying early sepsis-induced myocardial dysfunction [48,49], which correlates with disease severity [50], but can be challenging to measure in the clinical setting [51▪].

Biomarkers

Troponin and CKMB levels are elevated in patients who have septic myocardial dysfunction [52]. In patients with septic shock, one quarter to one-third have significantly elevated troponin. In sepsis, elevated cardiac troponin I is associated with decreased ejection fraction, increased vasopressor use and increased mortality [7]. Brain natriuretic peptide (BNP) levels are also elevated in patients who have septic myocardial dysfunction [53,54]. Higher BNP levels are associated with decreased ejection fraction and higher central venous pressure (CVP). Cardiomyocyte calcium handling is regulated in part by secretoneurin. Secretoneurin levels are associated with 90-day mortality from septic shock so this new biomarker may relate to septic myocardial dysfunction [55]. Neutrophil gelatinase-associated lipocaline (NGAL) is another biomarker associated with sepsis-induced myocardial dysfunction [56].

TREATMENT

Current management

After antibiotic administration, the first component of management of septic myocardial dysfunction is optimizing ventricular preload using fluid resuscitation. Capillary leak and venodilation components of cardiovascular dysfunction of sepsis typically result in a decrease in effective intravascular volume and therefore a decrease in ventricular preload. Because the diastolic ventricular pressure-volume relationship is relatively flat at low ventricular diastolic volumes, the initial 1–2 l of fluid resuscitation typically have the greatest effect on increasing ventricular end-diastolic volume and, hence, stroke volume. Thereafter, the ventricular diastolic pressure-volume relationship becomes steeper meaning that further fluid resuscitation will have less impact on increasing diastolic volume and stroke volume, but have a greater impact on increasing ventricular diastolic pressures and associated right and left atrial pressures that lead to tissue oedema. It follows that the goal of fluid resuscitation is to achieve an acceptable increase in cardiac output to increase oxygen delivery to tissues without causing excessive tissue oedema, which impairs tissue oxygen extraction capacity.

A variety of bedside measures suggest that further fluid resuscitation may not be helpful. A CVP more than 12 mmHg is associated with increased mortality [57]. Indeed, if tissue oxygen delivery appears to be adequate at 8 mmHg or less, then these lower CVP values are associated with further decreases in mortality [57]. Loss of pulse pressure variation with respiratory efforts or mechanical ventilation suggests that further fluid

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resuscitation is unlikely to increase cardiac output much further.

Inotropes

The surviving sepsis campaign guidelines [58▪] suggest that dobutamine may be used to treat septic myocardial dysfunction. However, solid evidence of benefit is lacking. An important consideration is that dobutamine will increase contractility if systolic dysfunction is present; however, these patients are more likely to survive even without dobutamine treatment. Patients with decreased diastolic compliance are unlikely to benefit from dobutamine, but these patients are more likely to die and therefore more in need of therapeutic intervention. A number of studies suggest that the use of dobutamine is associated with increased mortality [59,60] and an open hypothesis is that beta-blocker therapy may be helpful [61]. It is important to note that choosing infused vasopressor/inotrope combination therapy that has a high beta-adrenergic component is associated with worse outcome, including a substantial increase in atrial fibrillation [16]. These observations have led to recent calls for re-evaluation of the use of dobutamine for sepsis-induced myocardial dysfunction [62].

The calcium sensitizer levosimendan, as an alternative to beta-adrenergic agents, has been proposed as a treatment for septic myocardial dysfunction because it is suggested to increase systolic ventricular contractility without further impairing diastolic relaxation. This appeared to be a promising therapy in early clinical studies [63]. However, an adequately powered phase 3 randomized controlled trial demonstrated no benefit of levosimendan and a trend towards increased 28-day mortality and greater incidence of supraventricular tachyarrhythmia [64▪▪]. A meta-analysis demonstrated no benefit of levosimendan over dobutamine [65]. Another alternative to beta-adrenergic agents is infusion of glucose-insulin-potassium (GIK), which results in short term hemodynamic improvement in patients with sepsis-induced myocardial dysfunction [66]. No evidence for improvement in clinical outcomes is available for this relatively old therapy.

Novel therapeutics: animal studies

A number of novel approaches to treating sepsis-induced myocardial dysfunction have recently been proposed. The free-radical scavenger quercetin reduces production of inflammatory cytokines and ameliorated LPS-induced myocardial dysfunction in a murine model [67]. Myricetin [68] and puerarin [69] are plant derivatives that have similar beneficial effects [68]. Thioredoxin 1 in the heart reduces mitochondrial damage and improves ventricular function in a cecal ligation and puncture model of murine sepsis [70,71]. Attenuation of nitric oxide using brain-derived neurotrophic factor improves myocardial dysfunction [72]. Signalling via the apelinergic pathway is another novel approach to increasing ventricular contractility during sepsis [73]. In a murine model of sepsis, apelin-13 compared with dobutamine resulted in better clinically relevant measures of response including increased urine output and survival [74▪].

CONCLUSION

Sepsis-induced myocardial dysfunction is increasingly recognized as a major contributor to outcome of septic shock. Recently, significant strides have been made in understanding the intramyocardial inflammatory response that causes myocardial dysfunction. Although recent trials of beta-adrenergic agonists and levosimendan have been disappointing, a number of novel approaches show promise by modulating the intramyocardial inflammatory response.

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Conflicts of interest

The author has no conflicts of interest with respect to this manuscript.

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- ▪ of special interest
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References [66–73,74■] provide recent evidence that targeting signalling pathways that contribute to the genesis of sepsis-induced myocardial dysfunction may be helpful.

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