Myocardial dysfunction in sepsis: mechanisms and therapeutic implications

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Introduction

Sepsis and its related syndromes represent potentially devastating illnesses, estimated to account for 1% of all hospital admissions and for 100,000 deaths per annum in the U.S.A. alone[1]. Although sepsis is defined as the systemic response to infection, an infective organism is found in fewer than 50% of cases[2]. It is therefore increasingly recognised that sepsis represents only one example of a systemic inflammatory response that can be triggered not only by infection, but also by non-infectious disorders such as trauma and pancreatitis. The clinical features of these conditions are thought to be attributable to the triggering of a cascade of inflammatory mediators, the overproduction of which result in organ dysfunction. This spectrum of diseases shares a common, overlapping clinical end-point, termed the systemic inflammatory response syndrome[3]. The definitions of sepsis, the systemic inflammatory response syndrome and related syndromes are shown in Table 1[4]. The systemic inflammatory response syndrome is associated with considerable morbidity and is the leading cause of death in the intensive care unit, attributable to refractory hypotension, cardiac dysfunction and multi-organ failure[5]. In the 40% of patients with sepsis who develop cardiovascular impairment, mortality rises from 20% to 70–90%, a figure that has changed little in recent years, despite considerable advances in supportive techniques[5].

This review describes the changes in cardiac function in sepsis, outlines the underlying mechanisms by which they are thought to occur, and discusses the current strategies available for the treatment of sepsis and its related disorders.

Characterization of cardiac function in septic shock

The classical cardiovascular response to septic shock is peripheral vasodilatation manifest as systemic hypotension, hyporesponsive to pressor agents. Although it has been recognised for many years that intrinsic myocardial dysfunction also occurs, this is commonly masked by the concomitant elevation in cardiac index. It was not until the mid-1980s that the first formal studies employing pulmonary artery catheterization and radionucleotide techniques were performed in such patients, delineating the changes in cardiac function[6]. Survivors of septic shock were found to have decreased systolic function to an ejection fraction of about 33% and an increase in left ventricular end-diastolic diameter. These changes in left ventricular function were of rapid onset and reversible in survivors within 7 to 10 days. Paradoxically the changes seen were less profound in those who died, who were subdivided in subsequent studies into two groups: those with increased end-diastolic volume and stroke volume, but no increase in heart rate and ejection fraction[7]. Further studies of the response of the left ventricle to volume loading showed an abnormal increase in left ventricular end-diastolic diameter in the survivors of sepsis, implying increased ventricular compliance[8]. Studies of right ventricular function have shown a similar pattern in septic shock, with decreased ejection fraction, and increased end-diastolic volume, occurring independently of the changes in pulmonary artery pressure. The theoretical left ventricular pressure–volume curves for normal patients, survivors and non-survivors of septic shock are shown in Fig. 1[9].
Mechanisms of myocardial dysfunction in sepsis

Coronary perfusion and metabolism

Early theories of myocardial depression in sepsis were based upon a hypothesis that involved global myocardial ischaemia. Under normal conditions, coronary arterial blood flow is precisely regulated over a wide range of cardiac activity. In contrast to patients with shock attributable to other causes, those with sepsis have high coronary blood flow and diminished coronary artery–coronary sinus oxygen difference, analogous to the changes seen in the peripheral circulation. These changes may be due to a disturbance in the normal autoregulatory mechanisms of flow, and/or a disturbance in oxygen utilization. Indeed, there is evidence to show that both mechanisms occur in sepsis. Studies sampling coronary sinus blood in patients with septic shock have also provided insight into associated alterations in cardiac

Table 1 Definitions of sepsis-related syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
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<tr>
<td>SIRS</td>
<td>The systemic inflammatory response to a variety of severe clinical insults manifested by two or more of the following: Temperature &gt;38 °C or &lt;36 °C, Heart rate &gt;90 beats min⁻¹, Respiratory rate &gt;20 breaths min⁻¹ or PaCO₂ &lt;4·3 kPa, Leukocyte count &gt;120 000 mm⁻³ or &gt;10% immature (band) forms</td>
</tr>
<tr>
<td>Sepsis</td>
<td>The systemic response to infection, manifested by two or more of the above</td>
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<tr>
<td>Severe sepsis</td>
<td>Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria or an acute alteration in mental state</td>
</tr>
<tr>
<td>Sepsis-induced hypotension</td>
<td>A systolic blood pressure of &lt;90 mmHg or a reduction by 40 mmHg from baseline values in the absence of other causes of hypotension, e.g. hypovolaemia</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Sepsis-induced hypotension despite adequate fluid resuscitation, in the presence of perfusion abnormalities that may include, but are not limited to lactic acidemia, oliguria or an acute alteration in mental status. Patients who are on inotropic or vasopressor support may not be hypotensive at the time that the perfusion abnormalities are measured</td>
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Figure 1 Theoretical pressure–volume loops in normal controls, survivors and non-survivors of septic shock. In non-survivors, failure to increase ventricular compliance results in inability to maintain stroke volume and hence cardiac output. Similar changes are seen in both right and left ventricles.
metabolism. Increased lactate extraction, decreased myocardial free fatty acid extraction and decreased myocardial glucose uptake (lower in non-survivors) has been demonstrated when compared with normal controls\[14\]. There is therefore no evidence that global ischaemia is seen in patients with septic shock, a contention further supported by nuclear magnetic resonance studies showing that normal myocardial high energy phosphate levels are present\[15,16\].

**Free radicals and myocardial dysfunction**

Under physiological condition, cells exist in a delicate state of redox balance between the generation of free radical species and their removal by anti-oxidant mechanisms. Studies in models of myocardial ischaemia-reperfusion have shown that reactive oxygen species increase left ventricular end-diastolic diameter, decrease left ventricular contractility and impair mitochondrial function. Animal models of sepsis and humans with septic shock have also demonstrated increased markers of oxidant stress\[17,18\]. This is unsurprising as reactive oxygen species are generated by many of the humoral factors known to be increased in sepsis. Moreover, the combination of reactive oxygen species and nitric oxide (see section on nitric oxide) may lead to the formation of highly reactive peroxynitrite which can cause cell membrane damage and enzymatic dysfunction and potently suppresses mitochondrial function\[19,20\]. Free radicals have been implicated in the myocardial dysfunction of hypothyroidism, hyperthyroidism and severe burns. However, their role in the modulation of myocardial dysfunction of sepsis has yet to be elucidated.

**The role of circulating factors**

**Lipopolysaccharide and cytokines**

A circulating myocardial depressant factor in septic shock was first proposed over 50 years ago\[21\], but it was not until the late 1980s that myocardial dysfunction was quantitatively linked with the effects of a serum factor\[22\]. Thus, when serum from patients with sepsis-induced myocardial depression was applied to isolated rat cardiac myocytes, a decrease in the extent and velocity of myocyte shortening was observed, which was correlated to the degree of depression of systolic function seen clinically. The effects were not seen when applying serum from convalescent patients whose cardiac function had returned to normal, or in other critically ill, non-septic patients. Subsequent haemofiltration studies have shown this factor to be a >10 kDa, heat-labile, water-soluble substance, consistent with a protein or polypeptide\[23,24\]. Candidate substances for myocardial depressant factor are shown in Table 2, together with the evidence for and against each. Lipopolysaccharide (an obligatory component of Gram-negative bacterial cell wall) mimics the haemo-

dynamic effects of septic shock when infused into both animals and humans\[25\], and levels of endotoxin correlate well with the degree of myocardial depression seen. However, not all patients with septic shock have detectable endotoxaemia, and the chemical characteristics and prolonged time course of myocardial depression seen are not consistent with lipopolysaccharide as the sole substance responsible for the myocardial depression seen in sepsis\[22,23\]. There is evidence that in sepsis, polymorphonuclear leukocytes are retained in the coronary circulation and contribute to the early generation of myocardial depression, possibly through the release of cytokines (i.e. tumour necrosis factor-alpha/interleukin-beta) or reactive oxygen species\[26\]. Cytokines fit the chemical characteristics of the myocardial depressant factor from filtration studies and simulate septic shock with myocardial depression within 1 h of injection. Recent isolated cardiac myocyte studies have indicated that activation of both polymorphonuclear and the cardiac myocyte are important in decreasing myocardial contractility\[27\]. In humans, application of anti-tumour necrosis factor-alpha antibodies improve left ventricular function in patients with septic shock\[28\]. Although cytokines certainly play a key role in the early decrease in contractility, they do not explain the time course of the clinical disorder, unless they result in the induction or release of additional factors that in turn alter myocardial function, such as prostanoids and/or nitric oxide\[29\].

**Prostanoids**

The prostanoids are a large family of lipid mediators with diverse physiological and pathological properties, produced from arachidonic acid via the cyclo-oxygenase enzyme, of which there are two recognised isoforms; cyclo-oxygenase enzyme-1 (constitutively expressed) and cyclo-oxygenase enzyme-2, the expression of which is induced in response to numerous stimuli, including lipopolysaccharide and cytokines\[30\]. Humans with sepsis have elevated prostacyclin and thromboxane levels, associated with increased mortality\[31\]. The increase in prostanoid levels is coupled with a rise in cyclo-oxygenase enzyme-2 enzyme expression in the endothelial, endocardial and vascular smooth muscle cells. Although their direct role in the control of cardiac function is unclear, the potential for indirect effects via alterations in coronary autoregulation, intracoronary leukocyte activation and endothelial function is considerable. Recently, cyclo-oxygenase enzyme-2 has been shown to be induced by the action of lipopolysaccharides in vascular smooth muscle cells over a 10-day period, with consequent implications for a role in the myocardial depression of sepsis\[32\]. Evidence implicating the prostanoids as potential myocardial depressant substances is shown in Table 2.

**Nitric oxide**

Nitric oxide is a ubiquitous free radical synthesized as a result of the action of the membrane-bound nitric oxide
synthase from the semi-essential amino acid L-arginine in the presence of various co-factors (Fig. 2). Three distinct nitric oxide synthase isoforms have been identified, which are divided into two main groups; the calcium-calmodulin-dependent constitutive and neuronal forms (cNOS and nNOS)\([33,34]\) and the calcium-independent, cytokine-inducible form (iNOS)\([35,36]\). The role of nitric oxide in modulating vascular tone is well established (for review\([37]\)).

Under physiological conditions nitric oxide is thought to modulate both systolic and diastolic cardiac function. Animal experiments have shown nitric oxide to decrease contractility in isolated cardiac myocytes, in isolated papillary muscle preparations and in the isolated working heart\([38-40]\). Nitric oxide is thought to act in the heart by three main mechanisms, shown in Fig. 3: (a) via alterations in protein kinase activity and thence the L-type calcium channel\([41]\) (b) via a decrease in the myofibril response to calcium\([42,43]\), and (c) through decreased cAMP via phosphodiesterase\([44]\).

After exposure to lipopolysaccharide and cytokines in vitro or in clinical sepsis, increased expression of iNOS is observed in endothelial cells, vascular smooth muscle cells, the endocardium and macrophages\([30]\], resulting in the release of large amounts of nitric oxide. In sepsis, the large amounts of nitric oxide released by the induction of iNOS and massive production of nitric oxide are not accounted for early myocardial depression.

### Table 2 Potential myocardial depressant factors (MDS)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Factors for MDS</th>
<th>Factors against MDS</th>
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<tbody>
<tr>
<td>LPS (lipopolysaccharide)</td>
<td>Mimics septic shock in humans and animals([2,25])</td>
<td>Not all patients have elevated levels</td>
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<td></td>
<td>Levels correlate with degree of myocardial depression</td>
<td>Does not correlate with chemical characteristics of MDS([22,23])</td>
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<td></td>
<td></td>
<td>Does not consistently inhibit myocardial function in vitro (need co-culture with activated macrophages)([82])</td>
</tr>
<tr>
<td>Cytokines (tumour necrosis factor-alpha interleukin-beta)</td>
<td>Injection simulates septic shock with myocardial depression within 1 h([27])</td>
<td>Do not account for 7–10 day time-course of myocardial depression in sepsis</td>
</tr>
<tr>
<td>Prostanoids</td>
<td>Increased levels in sepsis([31]) coupled with induction of cyclo-oxygenase enzyme-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclo-oxygenase enzyme-2 induced by LPS and cytokines([60])</td>
<td></td>
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<tr>
<td></td>
<td>Knockout mice for cyclo-oxygenase enzyme-2 have protection against the haemodynamic effects of LPS</td>
<td></td>
</tr>
<tr>
<td>NO (nitric oxide)</td>
<td>Removal of endocardium decreases contractility([43])</td>
<td>Equivocal evidence for direct myocardial depressant activity</td>
</tr>
<tr>
<td></td>
<td>NO alters left ventricular and right ventricular function([40,83])</td>
<td>Production relies on enzyme induction — does not account for early myocardial depression</td>
</tr>
<tr>
<td></td>
<td>NO alters coronary vascular tone</td>
<td></td>
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<tr>
<td></td>
<td>Injection of LPS causes induction of iNOS and massive production of nitric oxide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At post mortem, increased iNOS is seen in hearts of patients succumbing to sepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clear mechanisms for depression of cardiac function exist (see text)</td>
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</table>

**Figure 2** Synthesis of nitric oxide and co-factor requirements of nitric oxide synthase. Unlike eNOS and nNOS, iNOS activity does not depend upon calcium or calmodulin. Ca++ = calcium; NADPH = nicotinamide adenine dinucleotide phosphate; O_2 = oxygen.

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Figure 3  The potential mechanisms of action of nitric oxide in modulation of cardiac function under physiological conditions and in septic shock. NO=nitric oxide; iNOS=inducible nitric oxide synthase; ROS=reactive oxygen species; Ca++=calcium; GC=guanylyl cyclase; cGMP=cyclic GMP; LCa=L-type calcium channel; PDE=phosphodiesterase; cAMP=cyclic AMP; ONOO-=peroxynitrite.
formation of peroxynitrite (ONOO-) and causing further cellular damage. The potential mechanisms whereby nitric oxide may modulate myocardial contractility are shown in Fig. 4, and the characteristics that support nitric oxide as the myocardial depressant substance are shown in Table 2.

The role of the endothelium

Early evidence that the endothelial endocardial cells could influence myocardial function showed that selective damage of the endocardium caused immediate and irreversible abbreviation of the isometric twitch in isolated cardiac myocytes. The endocardium has been found to produce a number of substances that alter myocyte contractility. In addition, in vitro studies have shown that the endothelial endocardial cells can alter myocyte contractility in response to numerous factors, including acetylcholine, vasopressin, endothelin and phenylephrine. Coronary vascular endothelial cells are similar anatomically and physiologically to those of the endocardium, and influence the contractile performance of adjacent cardiac myocytes in a manner similar to that of the endocardial endothelium. Considering no cardiac myocyte is more than 3–5 μm from an endothelial endocardial cells/vascular endothelial cells, the potential capacity of these endothelial cells to modulate cardiac function is enormous. In sepsis, both the endothelial endocardial cells and vascular endothelial cells can therefore produce substances likely to alter vascular tone, to cause hyporeactivity to pressor agents and to depress myocyte contractility. Other substances are produced that result in margination of neutrophils and further activation of local inflammatory responses, the generation of reactive oxygen species, and subsequently damage of the endocardium itself. Subsequently, the actions of inducible enzymes such as cyclooxygenase enzyme-2 and iNOS result in a more prolonged production of modulators of vascular tone and myocyte contractility.

### Treatment strategies in the systemic inflammatory response syndrome

#### General

In addition to treating the underlying cause and ensuring adequate fluid resuscitation, management of cardiovascular dysfunction in septic shock/the systemic inflammatory response syndromes was previously aimed at correcting hypotension and maintaining end-organ perfusion, as indicated by simple indices such as urine output. It was subsequently thought that correcting both haemodynamic and metabolic abnormalities might favourably influence outcome in patients with septic shock, employing supranormal goals for cardiac index (>4.5 l.min⁻¹m⁻²), oxygen delivery (DO₂ >550 ml.min⁻¹m⁻²) and oxygen uptake (VO₂ >150 ml.min⁻¹m⁻²). It is becoming increasingly clear that it is not enough to treat the numerical values of cardiac and peripheral circulatory function. Indeed, many patients have normal or high cardiac index within hours of their death.

A common concern is whether it is necessary to strive to correct the marked peripheral dilatation seen in septic shock, which might be considered an appropriate compensatory response to the decrease in cardiac contractility. However, the vasoplegia seen in septic shock causes normal vascular autoregulation to be disrupted, such that blood flow becomes linearly correlated to the organ perfusion pressure. It is therefore necessary to restore adequate organ perfusion pressure to match O₂ supply and demand, although this has potential detrimental effects, such as excessive constriction in some vascular beds, and increased cardiac afterload.

Management is therefore directed towards simultaneously correcting haemodynamic and metabolic abnormalities, usually by using single or combination inotropic and vasopressor agents, in order to maintain cardiac output and therefore organ perfusion (for review, see[60]). To date there has not been an adequate study delineating the best therapeutic strategy in patients with septic shock, as trials have included heterogeneous groups of patients or compared outcomes against patients with a surprisingly low overall mortality, resulting in either decreased, unchanged, or even increased mortality.

#### Specific

Advances in the understanding of the pathophysiology of sepsis and septic shock have led to a number of attempts to modify clinical outcome by altering the host immune response. Although many investigations have been directed at determining factors that alter mortality, few have studied the effects of such immunomodulatory maneuvers on cardiac function. The major studies outlining the specific strategies used in septic shock are shown in Table 3. Initial experiments in animal models showed that pre-treatment with antibodies directed against the core lipopolysaccharide moieties protect against the haemodynamic effects of sepsis[61,62]. In human experiments, however, no decrease in hypotension is observed, and mortality remains unchanged[63,64].

The use of inhibitors of prostanoid synthesis has also long been considered a potentially useful strategy and indeed, at one time high-dose corticosteroids were used routinely in the management of septic shock. Controversial early studies using steroids in controlled randomized trials supported this strategy, with improved haemodynamic parameters[65]. These findings have not been supported with later studies[60,61], although a recent study using corticosteroids in the treatment of refractory septic shock showed potential benefit in patients who remained on inotropic support[66]. Non steroidal anti-inflammatory drugs in the treatment of sepsis and septic shock have been similarly disappointing, with only one
study specifically looking at the effects on cardiac function, and showing improvement\[67\]. However, once again these findings (with non-selective cyclo-oxygenase enzyme inhibitors) have not been supported in subsequent human studies\[68\]. The potential use of selective cyclo-oxygenase-2 inhibitors in the treatment of sepsis and the systemic inflammatory response syndrome has not been evaluated to date. The use of non-specific nitric oxide synthase inhibitors has been investigated more extensively. The theoretical advantage of nitric oxide synthase inhibition, with reversal of vasoplegia and potential for a decrease in vasopressor requirements has been supported in animal experiments\[69–73\], together with preliminary studies in humans\[74–76\]. The attractiveness of nitric oxide synthase inhibition in sepsis is further supported by the evidence of its involvement in the pathophysiology of the myocardial dysfunction in sepsis and septic shock. Indeed, early experiments with methylene blue (a non-specific inhibitor of guanylyl cyclase) in patients with septic shock revealed increased systemic vascular resistance, mean arterial pressure and left ventricular stroke work index\[77\]. It seems likely, however, that the potential benefits will be limited as a result of a detrimental increase in cardiac afterload, especially in the face of impaired cardiac function\[78\]. Moreover, if the cardiac dilatation in the survivors of septic shock is mediated either all or in part by nitric oxide, then inhibition could be envisaged to prevent the cardiac dilatation necessary to maintain cardiac output in the presence of a dilating ventricle.

Recently, much more attention has been focused on the role of pro-inflammatory cytokines in the development of sepsis and septic shock. Tumour necrosis factor-alpha has long been considered a key component in the development of sepsis and the related syndromes. Initial animal experiments using anti-tumour necrosis factor-alpha antibodies or fusion proteins showed improved cardiovascular parameters and decreased mortality\[78,79\]. Early clinical trials seemed to support these findings\[28\], but more recent large trials have been uniformly disappointing, with no improvement in 28 day mortality\[80,81\]. It is becoming increasingly apparent that the response of a patient depends not on the absolute pro-inflammatory cytokine level (i.e. tumour necrosis factor-alpha) but more on the resulting balance of pro- and anti-inflammatory cytokines — the response of which may be genetically predetermined.

The complex array of mediators released in sepsis and septic shock suggests that trials enrolling heterogeneous groups of patients at differing time course in many different disease states and using single agent therapy are unlikely to show improvement in mortality. The effects on cardiac function of these agents have yet to be determined, but cardiac dysfunction in sepsis clearly is an important determinant in the eventual outcome in such patients. Specific strategies to alter the course of this have been directed at correction of vasoplegia and systolic depression, and the promising results from animal models clearly warrant further investigation. Determination of the factor(s) responsible for the increase in ventricular compliance seen in the survivors of sepsis may lead to a future therapeutic target.

In addition to investigating the generalized pathophysiology of sepsis and septic shock, further research is needed to determine the immunological and molecular basis of the cardiac dysfunction seen in these disorders, and the time point at which each is predominant (either detrimental or, indeed beneficial). This information,
together with an assessment and understanding of the immune profile of the patient will allow more specific treatment strategies to be used in the treatment of such patients, with more chance of a significant improvement in outcome.

References


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