Sepsis and the heart

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Sepsis is the leading cause of death in critically ill patients. The yearly incidence of severe sepsis is increasing and has recently been reported as 132 per 100 000 population, with a mortality approaching 50%. The incidence of sepsis is disproportionately increased in the elderly, and age is an independent predictor of survival.

Sepsis is a complex disease and is the manifestation of the immune and inflammatory response to infection. Severe sepsis is defined as sepsis with organ dysfunction, while septic shock is sepsis with hypotension that persists despite resuscitation with i.v. fluids. Recent definitions recognize the importance of myocardial depression and include a low cardiac index (CI) or echocardiographic evidence of cardiac dysfunction as one of the criteria for diagnosis of severe sepsis (Table 1).

Before the introduction of invasive cardiovascular monitoring, it was widely thought that there were two distinct phases to septic shock. It was noted that patients with septic shock initially went through a hyperdynamic phase ('warm shock') characterized by a bounding pulse and warm hands, despite concomitant hypotension followed by 'cold shock', with poor peripheral perfusion, a thready pulse, cool extremities, which lead ultimately to death. Studies at that time demonstrating an association between a high CI and survival reinforced this view. Others reported that patients with septic shock who were not hypovolaemic demonstrated a hyperdynamic circulation with a normal or elevated cardiac output (CO) and a low systemic vascular resistance (SVR). However, it was not until the introduction of the pulmonary artery catheter with its ability to accurately measure CO and estimate left ventricular (LV) filling pressures that it was shown that patients with septic shock who were resuscitated adequately with fluids consistently demonstrated a hyperdynamic circulation with a high CO and a low SVR. This led to the realization that the haemodynamic profile of those with ‘cold shock’ was due to inadequate resuscitation and relative hypovolaemia.

Adequately resuscitated patients with severe sepsis display a hyperdynamic circulation with warm peripheries, low SVR, and high CO. However, despite the increase in CO and maintenance of a normal stroke volume, many also suffer from intrinsic myocardial dysfunction. This is manifest as a reduction in ejection fraction (EF), which is a clinically useful quantitative measurement of ventricular performance. Although EF is dependent on afterload and preload, assessment of the myocardium in patients with sepsis using load-independent techniques also reveal significant myocardial dysfunction.

Myocardial depression

Left ventricular function

Myocardial depression in patients with septic shock was first reported in a study using radionuclide-gated blood
and myocardial depression may confer a protective effect.

Notably, non-survivors had higher EFs and lower end-systolic volumes with preserved stroke volumes. In the survivors, serial scans showed a gradual return towards a normal EF and ventricular volume by 10 days, but the non-survivors had initially normal EFs and ventricular volumes that did not change during serial studies.

The myocardial response to volume infusion was examined in septic patients using data obtained from right heart catheterization and radionuclide cineangiography. This study found that patients with sepsis had significantly impaired ventricular performance, as measured by LV stroke work index (LVSWI), compared with controls who received similar volumes of fluid. Another study of 35 patients with culture-positive septic shock examined LV performance and confirmed that LVSWI was depressed in the majority (94%) of patients.

More recent studies have predominantly used echocardiography to assess myocardial function. Transeosophageal echocardiographic (TOE) recordings obtained on 67 mechanically ventilated patients with no previous history of heart disease admitted to a French intensive care unit with septic shock revealed global ventricular hypokinesia in 26 of the 67 patients on admission. In addition, a further 14 patients requiring vasopressor support with norepinephrine for 24–48 h developed LV dysfunction leading to an overall hypokinesia rate of 60%. Another study of 90 consecutive patients with septic shock requiring mechanical ventilation who underwent serial two-dimensional bedside echocardiography demonstrated that although LV diastolic volume was within the normal range in all patients, there was a universal reduction in LV diastolic filling volume resulting in a severe reduction in the LV stroke volume. Interestingly, like the initial observations, LV dysfunction was mostly marked in those who survived. A prospective observational echocardiographic study of 34 consecutive patients with...
severe sepsis or septic shock reported severely impaired myocardial performance as measured by fractional area contraction in 44% of patients. In a series of 183 patients with septic shock, 35% of patients had a low CI (<3 litre min\(^{-1}\) m\(^{-2}\)) on admission. Echocardiographic assessment of myocardial function in these patients revealed a markedly hypokinetic LV [mean LVEF: 38 (sd 17)%].

Although other echocardiographic studies consistently report a reduced EF in septic shock, only one supported the ventricular dilatation reported in earlier studies.

Severe sepsis and septic shock may also be associated with diastolic dysfunction. Pressure/volume tracings in anaesthetized rabbits rendered endotoxaemic suggest a reduction in LV compliance leading to an increase in end-diastolic pressure.

Human studies confirm the existence of diastolic dysfunction. Diastolic filling was determined using pulsed Doppler trans-mitral spectral tracings in 13 patients with septic shock, 10 patients with sepsis without shock, and 33 normal controls. All the septic patients had an abnormal pattern of diastolic filling compared with controls. In a study of patients with septic shock using invasive haemodynamic monitoring and two-dimensional TOE and Doppler echocardiography, it was found that cardiac dysfunction in septic shock showed a continuum from isolated diastolic dysfunction to both diastolic and systolic ventricular failure.

Few studies have examined LV relaxation in septic shock. Prospective assessment of LV function in 54 patients with septic shock using TOE demonstrated that isolated and reversible impairment of LV relaxation was present in 20% of patients. This impairment was associated with significant increases in cardiac troponin I (cTnI), tumour-necrosis factor-α (TNF-α), interleukin (IL)-8, and IL-10.

**Right ventricular function**

The performance of the right ventricle is also altered by sepsis. Right heart catheterization and radionuclide ventriculography were used to examine the role of the right ventricle in patients with septic shock. Of the 25 patients studied, a depressed right ventricular EF (<0.38) was observed in 13. Although right ventricular afterload is commonly elevated in the critically ill as a result of mechanical ventilation and acute lung injury, no correlation was found between abnormal right ventricular afterload and depressed right ventricular EF. Serial haemodynamic and radionuclide angiographic studies in 39 patients with septic shock demonstrated that both ventricles displayed a similar pattern of myocardial dysfunction.

Right ventricular diastolic function may also be altered by sepsis, although few studies specifically address this issue.

**Myocardial dysfunction and prognosis**

Although earlier studies reported that septic patients with impaired LVEF and LV dilatation had a good prognosis, more recent studies using echocardiography to assess LV performance show that an impaired LVEF is associated with a poor prognosis. This discrepancy may be because the EF is influenced not only by cardiac contractility, but also by preload and afterload and therefore does not fully quantify the complex haemodynamic profile in the critically ill septic patient.

Vasodilatation occurs in severe sepsis, and SVR may be significantly reduced. Retrospective examination of the haemodynamic profile of 42 patients with documented septic shock revealed that those who died had a significantly lower SVR. Other groups have reported similar findings.

Analysis of the haemodynamic data obtained from right heart catheterization in 48 patients with septic shock found that an initial heart rate of <106 beats min\(^{-1}\) at presentation significantly predicted survival, as did a heart rate of <95 beats min\(^{-1}\) and an SVR index of >1529 dyne s cm\(^{-5}\) m\(^{-2}\) at 24 h. As quantification of myocardial performance in the septic patient requires specialist equipment and expertise, there is increasing interest in the measurement of cardiac biomarkers such as troponin to detect myocardial dysfunction.

**Aetiology of myocardial depression**

**Myocardial ischaemia and microvascular dysfunction**

Early investigators postulated that the myocardial dysfunction observed in sepsis was due to myocardial ischaemia. However, subsequent work has excluded global myocardial ischaemia as a cause. Studies using thermodilution catheters placed in the coronary sinus in patients with septic shock allow measurement of coronary flow and myocardial metabolism. These studies report preservation of myocardial blood flow, net myocardial lactate extraction, and diminished coronary artery—coronary sinus oxygen difference compared with controls. Others have also reported marked coronary vasodilatation in septic patients and no elevation in myocardial lactate production. In a canine model of sepsis, no impairment of high-energy phosphate metabolism could be demonstrated using magnetic resonance spectroscopy.

The microcirculation undergoes profound changes during sepsis, with endothelial disruption and maldistribution of blood flow. Microvascular blood flow to the heart may also be altered in sepsis causing regional ischaemia, although investigations are still at an early stage.

**Myocardial depressant substance**

The concept of a circulating myocardial depressant factor in sepsis was first proposed in the 1970s. In 1985, it was shown that serum obtained from patients with septic shock caused a significant depression in an in vitro model.
of mammalian myocardial cell performance. This study concluded that a circulating myocardial depressant substance was a cause of the myocardial depression frequently accompanying human septic shock.

It is unlikely that a single factor is responsible for myocardial depression. In a study of neonatal rat cardiac myocyte cultures exposed to an ultrafiltrate obtained from either healthy volunteers or those with severe sepsis, the ultrafiltrate from septic patients caused significant toxic effects, while the serum from the control group had no effect. Analysis of the ultrafiltrate from the septic patients revealed significantly higher amounts of IL-1, IL-8, and complement component 3a when compared with controls, suggesting that a number of circulating factors are involved in sepsis-induced myocardial depression.

**Endotoxin**

Endotoxin is released by lysis of gram-negative bacteria. To evaluate the cardiovascular effects of endotoxaemia in humans, nine healthy volunteers were injected with a bolus dose of endotoxin. Three hours after the injection of endotoxin, the typical haemodynamic pattern of severe sepsis developed, with an increase in heart rate, an increase in CI, and a reduction in SVR. After volume loading, there was a reduction in LVEF and LV performance. However, it is unlikely that it is the endotoxin per se that is directly causing myocardial depression as only a minority of septic patients have detectable levels of endotoxin. The delay in onset of myocardial depression after endotoxin administration suggests that endotoxin causes the release of other mediators such as cytokines with myocardial depressant properties. It is likely that Toll-like receptor-4 plays a pivotal role in endotoxin-induced myocyte dysfunction. These receptors provide critical links between immune stimulants produced by micro-organisms and the initiation of host defences. Activation causes the release of various cytokines and propagation of the inflammatory response. In vitro experiments suggest that the presence of Toll-like receptor-4 on macrophages and neutrophils is necessary to cause myocardial dysfunction, probably via the release of TNF-α.

**Cytokines**

The inflammatory cytokines, TNF-α and IL-1, play a pivotal role in sepsis-induced myocardial dysfunction. Infusion of TNF-α in dogs reproduces the haemodynamic profile of septic shock with an associated reduction in EF. Other in vitro experiments using rabbit ventricular myocytes demonstrate that direct exposure of myocytes to TNF-α reduces contractility by decreasing myofilament responsiveness. The infusion of murine monoclonal anti-TNF antibody into 10 patients with septic shock caused a transient increase in LVSWI, indicating an improvement in cardiac performance. The mechanism(s) responsible for TNF-α-induced cardiac dysfunction are not known, but probably involve alterations in calcium homeostasis and the production of nitric oxide (NO).

The addition of IL-1 to an in vitro myocardial cell assay caused significant concentration-dependent depression of maximum extent and peak velocity of myocyte shortening.

**Nitric oxide**

Nitric oxide can be considered a ‘double-edged sword’ as it has both beneficial and detrimental effects on cardiac function. NO is produced from virtually all cell types composing the myocardium and has multiple physiological roles in cardiovascular homeostasis. Cardiac function is regulated through both vascular-dependent and -independent effects. In addition to regulating coronary vessel tone and thrombogenicity, NO also has a direct effect on cardiac contractility.

Nitric oxide synthases are the enzymes responsible for NO production. Three distinct forms have been identified: neuronal NO synthase (NOS1), inducible NOS (NOS2), and endothelial NOS (NOS3). NOS2 expression is rapidly induced in the myocardium on exposure to many of the pro-inflammatory cytokines involved in sepsis leading to increased NO levels. Although low doses of NO may increase LV function, the induction of NOS2 and the overproduction of NO adversely affects myocardial contractile function. In vitro experiments using freshly isolated ventricular myocytes from adult rat hearts incubated in medium conditioned by endotoxin (LPS)-activated rat alveolar macrophages demonstrate a reduced myocardial response to inotropic stimulation which can be fully reversed by NOS inhibition. Guinea pig cardiac myocytes directly superfused in NO containing solution demonstrated significantly reduced contractility.

Echocardiographic examination of the cardiac function of wild-type and NOS2-deficient mice after infusion of endotoxin demonstrated preserved myocardial performance in the NOS2-deficient group. Further in vitro work has demonstrated that sepsis-induced myocardial depression can be prevented by administration of NO synthase and guanylate cyclase inhibitors such as N-methyl-l-arginine and methylene blue. NO has also been shown to depress myocardial energy production.

Myocardial NOS3 may have an important protective role against sepsis-induced myocardial dysfunction. Experiments using mice with cardiomyocyte-specific NOS3 overexpression are protected from myocardial dysfunction and death associated with endotoxaemia. Increased myocardial NO levels were shown to attenuate endotoxin-induced reactive oxygen species production and increase total sarcoplasmic reticulum Ca2+ load and myofilament sensitivity to Ca2+.

Many of the adverse effects of NO on myocardial performance may be secondary to the generation of the powerful oxidant peroxynitrite produced from the
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diffusion-controlled reaction between NO and another free radical, the superoxide anion. Peroxynitrite interacts with lipids, DNA, and proteins and can be highly cytotoxic.\textsuperscript{69} In \textit{vitro} studies of cytokine-induced myocardial depression demonstrate an improvement in myocardial performance on removal of peroxynitrite.\textsuperscript{26} High concentrations of NO also caused apoptosis of cardiomyocytes.\textsuperscript{45}

\textbf{Other mechanisms}

Severe sepsis and septic shock are also associated with alterations in intracellular calcium trafficking, with a reduction in systolic intracellular calcium concentration and reduced myocyte contraction.\textsuperscript{85} The contractile apparatus may also be damaged in septic shock. Histological examination of heart tissue obtained from patients who had died of severe sepsis showed disruption of the actin/myosin contractile apparatus.\textsuperscript{85} Septic shock is associated with a down-regulation of the \textit{β}-adrenergic response to catecholamines. It is likely that several mechanisms may be responsible for this phenomenon. Endotoxin administration to rats results in a reduction in \textit{β}-adrenergic receptor density.\textsuperscript{89} Cytokines have also been shown to inhibit intracellular cyclic adenosine monophosphate (cAMP) accumulation in response to catecholamines.\textsuperscript{18} Sepsis may also cause an increase in inhibitory G-proteins which results in decreased activity of adenylate cyclase and subsequently cAMP.\textsuperscript{12}

There is some evidence to suggest that myocardial dysfunction associated with sepsis is due to myocardial hibernation and is an adaptive response to maintain myocardial viability and the potential for full recovery.\textsuperscript{30} Myocardial hibernation allows preservation of cardiac myocytes by down-regulation of oxygen consumption, energy requirements, and ATP demands in response to ischaemia and hypoxia. Experiments with septic mice using clinically relevant technology such as magnetic resonance imaging, positron emission tomography, and single photon emission computed tomography imaging have demonstrated diminished cardiac performance along with many of the features commonly observed during hibernation after ischaemia and hypoxia.\textsuperscript{56} The observed reduction in energy expenditure may prevent activation of cell death pathways and aid full recovery.\textsuperscript{86,92}

\textbf{Cardiac troponins}

Cardiac troponins are regulatory proteins of the thin actin filaments of the cardiac muscle.\textsuperscript{4} cTnI and cardiac troponin T (cTnT) are released as a result of myocardial cell injury, and are highly sensitive and specific markers of myocardial damage.\textsuperscript{108} Serial measurement of these biomarkers is routinely used for the diagnosis and risk stratification of patients with acute coronary syndrome. Several studies have demonstrated that the presence of elevated troponin levels in critically ill septic patients predict the presence of myocardial dysfunction and an increased mortality rate.\textsuperscript{2,7} In a study of 37 consecutive patients with septic shock,\textsuperscript{53} the 16 (43%) patients with an elevated serum cTnI had a significantly lower EF and a significantly higher mortality than the other patients studied. A significant correlation between the serum level of cTnI and the reduction in EF was also observed.\textsuperscript{63} In another study of 46 patients with septic shock, increased plasma concentrations of cTnI and cTnT were found in 50% and 36% of patients, respectively. LV functional assessment by two-dimensional TOE revealed that both cTnI and cTnT were exclusively associated with LV dysfunction \textit{(P<0.0001)}.\textsuperscript{100} However, the usefulness of elevated troponin levels in identifying septic patients with myocardial dysfunction is limited as many other conditions commonly observed within the intensive care unit such as acute coronary syndrome, acute kidney injury, and pulmonary embolism are also associated with an increase in troponin levels.\textsuperscript{108} As such, there is no evidence to support the use of inotropes in patients with elevated troponin levels in an effort to enhance myocardial performance. Indeed, this approach may be harmful.\textsuperscript{101} Nevertheless, an elevated troponin level in the critically ill is associated with an adverse prognosis irrespective of the underlying cause.\textsuperscript{3,34,48,49}

\textbf{Management of sepsis-induced myocardial dysfunction}

Until the cellular mechanisms underlying sepsis-induced myocardial dysfunction are fully understood, the management of the resulting circulatory compromise remains supportive. Fluid resuscitation should be initiated promptly and guided by measurement of the central venous oxygen saturation and the haemodynamic response.\textsuperscript{22,83} Vasopressors should be titrated to maintain an adequate perfusion pressure. Delayed capillary refill, oliguria, and impaired consciousness all suggest tissue hypoperfusion as does lactic acidosis with an elevated lactate/pyruvate ratio, signifying a decrease in the cytoplasmic and mitochondrial redox state.\textsuperscript{54} Interventions designed to achieve supraphysiological goals of CI are not beneficial,\textsuperscript{37} and may be detrimental.\textsuperscript{36} For those patients with a persistently low CO, despite adequate LV filling pressures, dobutamine remains the first-choice agent.\textsuperscript{22} This catecholamine with selective \textit{β}-effects increases stroke volume, heart rate, and CI in septic patients.\textsuperscript{44,104} However, sepsis-induced impaired \textit{β}-adrenergic receptor stimulation of cAMP may cause the myocardium to be less responsive to catecholamines.\textsuperscript{90} Inotropic agents that act independently of \textit{β}-adrenoceptors may therefore have a valuable role in treating sepsis-related myocardial dysfunction.

As sepsis-induced myocardial dysfunction may reflect cardiac hibernation and be an adaptive response, judicious use of catecholamines is recommended. Adrenergic stimulation leads to an increase in cardiac work and may damage cardiomyocytes.\textsuperscript{91} In addition, the use of
norepinephrine has been associated with myocardial depression. In a study of 67 patients with septic shock, global LV dysfunction developed in 34% of those patients with no previous evidence of myocardial depression after 24–48 h of continuous norepinephrine infusion.\(^1\)\(^{10}\)

Levosimendan may be a valuable adjunct to, or replacement for, conventional catecholamine therapy in the treatment of the myocardial dysfunction associated with sepsis.\(^2\)\(^{21}\) Levosimendan is an inodilatory agent used in the management of acute decompensated cardiac failure. Catecholamines enhance muscle contraction by increasing the level of cAMP and subsequently intracellular calcium concentration. Levosimendan exerts its inotropic effects by selectively binding to the N-domain of cardiac troponin C (cTnC) in a calcium-dependent manner thereby sensitizing cTnC to calcium.\(^3\)\(^{5}\)\(^{9}\)\(^4\) It also opens adenosine triphosphate (ATP)-dependent potassium channels (K\(_{\text{ATP}}\) channels) with resulting systemic and pulmonary vasodilatation.\(^7\)\(^0\)

Although there are a large number of animal studies reporting the beneficial haemodynamic effects of levsimendan in sepsis, the first report of its successful use in humans did not appear until 2005.\(^6\)\(^2\)\(^{7}\) A case series of seven patients with refractory septic shock also reported an improvement in cardiac function and tissue perfusion after the initiation of levsimendan.\(^7\)\(^8\) The only prospective randomized controlled trial examining the systemic and regional haemodynamics in septic myocardial depression studied 28 septic shock patients with LV dysfunction (LVEF <45%) persisting after 48 h of conventional treatment who were then randomized to receive a 24 h infusion of either levsimendan (0.2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) or dobutamine (5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)). Norepinephrine was used to maintain a mean arterial pressure of 70–80 mm Hg and volume therapy was guided by right heart catheterization. Although the dobutamine did not alter systemic or regional haemodynamic variables, levsimendan had beneficial effects on both cardiovascular performance and regional perfusion. In particular, the use of levsimendan was associated with a reduction in LV end-diastolic volume and a significant increase in stroke index, CI, oxygen delivery index, oxygen consumption index, and LVSWI. Levsimendan also resulted in increased gastric mucosal flow, creatinine clearance, and urinary output and decreased lactate concentrations.\(^6\)\(^4\)

Although levsimendan shows promise, its use remains experimental and large, prospective randomized controlled trials are required to clarify its role in the management of patients with septic shock.

**Conclusions**

Although CO is maintained or elevated during septic shock, intrinsic cardiac dysfunction is demonstrable in up to 40% of patients, and while the stroke volume is maintained, due to alterations in the peripheral circulation and possibly ventricular dilatation, LVEF is often depressed. The mechanisms underlying this myocardial depression have not been fully elucidated and there are still many unanswered questions.\(^2\)\(^7\) However, it is likely that cytokines and nitric oxide have pivotal roles in its pathogenesis. Although myocardial depression is maximal 48 h after the onset of sepsis, there is a gradual normalization of EF in survivors.

Elevation of cardiac troponin levels in patients with septic shock with no evidence of flow limiting coronary artery disease has been shown to be an indicator of LV dysfunction and is associated with a worse prognosis. Unfortunately, the usefulness of this biomarker to predict sepsis-induced myocardial dysfunction is limited by the large number of other conditions commonly encountered in the critically ill that are associated with raised cardiac troponin levels.

The management of sepsis-induced myocardial dysfunction remains supportive. Persistent myocardial dysfunction despite adequate volume loading requires inotropic support. Although dobutamine remains the inotrope of choice, there is increasing interest in the use of the calcium-sensitizing agent levsimendan.

**References**

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De BD, Taccone FS, Radermacher P, Levosimendan in septic shock: another piece in the puzzle, but many pieces are still missing. Intensive Care Med 2007; 33: 403–5


Fernandes CJ. Sepsis-induced myocardial depression: where is the missing link? Crit Care Med 2007; 35: 972–3


Kollef MH, Ladenson JH, Eisenberg PR. Clinically recognized cardiac dysfunction: an independent determinant of mortality
among critically ill patients. Is there a role for serial measurement of cardiac troponin I? Chest 1997; 111: 1340–7


71 Parker MM, McCarthy KE, Ognibene FP, Parrillo JE. Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression of septic shock in humans. Chest 1990; 97: 126–31


85 Rossi MA, Celes MR, Prado CM, Saggorio FP. Myocardial structural changes in long-term human severe sepsis/septic shock may be responsible for cardiac dysfunction. Shock 2007; 27: 10–8


Singer M. Powering up failed organs. Am J Respir Crit Care Med 2007; 176: 733–4


Zhong J, Hwang TC, Adams HR, Rubin LJ. Reduced L-type calcium current in ventricular myocytes from endotoxemic guinea pigs. Am J Physiol 1997; 273: H2312–24