

Review Article

Myocardial Depression in Sepsis and Septic Shock

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ABSTRACT

In the setting of severe sepsis and septic shock myocardial depression is common despite an apparent normal or increased cardiac output. Myocardial depression represents a spectrum of cardiac dysfunction present in varying degrees in virtually all cases of sepsis and septic shock. This myocardial depression persists throughout the course of the disorder and either improves with patient's recovery or accompanies them to their death. If patient does survive, myocardial function usually returns to baseline within 7-10 days. The pathogenesis of the myocardial dysfunction derives from a cascade of events triggered by the initial inciting infection. This cascade results in the production of a variety of endogenous

inflammatory cytokines (e. g., TNF , IL-1) and other factors (e.g., lysozyme, platelet activating factor, leukotrienes, prostaglandins) which cause severe cardiovascular derangement including myocardial depression. The exact sequence of events leading to myocardial depression have not been fully elucidated but likely involves, in part, nitric oxide dependent and independent pathways and early events of programmed myocardial cell death (apoptosis). This paper reviews the clinical aspects and molecular/cellular insights into the pathophysiology of sepsis-induced myocardial depression.

KEY WORDS: myocardial depression, sepsis, septic shock

INTRODUCTION

Despite advances in modern medical knowledge and treatment of sepsis and septic shock, its incidence and mortality continue to rise. Over the past 40 years, age adjusted mortality has increased from 0.5-7 per 100,000 episodes of sepsis and septic shock^[1]. The incidence of severe sepsis in the United States is 750,000 cases per year, with 215,000 deaths annually^[2]. The majority of these patients die of refractory hypotension and cardiovascular collapse.

Sepsis has been defined as the systemic inflammatory response to infection^[3]. The inciting focus of sepsis, either an organism, component of an organism, or product of the organism, causes local and systemic release of a wide variety of inflammatory mediators like tumor necrosis factor- (TNF-), interleukin-1b (IL-1)^[4], platelet activating factor (PAF)^[5,6], oxygen free radicals^[7], interferon gamma (IFN-)^[8] and arachidonic acid metabolites^[9] from monocytes/ macrophages and other cells^[4]. In order to maintain a homeostasis (and likely as part of a feedback mechanism), several anti-inflammatory mediators are also released as part of the cascade including interleukin-10 (IL-10), transforming growth factor- (TGF-) and interleukin-1 receptor antagonist (IL-1ra). If the

balance is sufficiently shifted in favor of the inflammatory component, cardiovascular stress may result. An inability to respond adequately to this challenge, either on the basis of excessive cardiovascular dysfunction or limited cardiovascular reserve, results in septic shock. One of the components of septic cardiovascular stress (whether overt shock is present or not) is myocardial depression.

This article reviews the following aspects of septic myocardial dysfunction - right and left ventricular failure, systolic and diastolic dysfunction and cardiovascular prognosticating factors. Potential pathophysiologic mechanisms of myocardial depression from organ to molecular/cellular level are also examined.

CLINICAL MANIFESTATIONS OF CARDIOVASCULAR DYSFUNCTION: HISTORICAL PERSPECTIVES

Prior to the introduction of new techniques such as the balloon-tipped pulmonary artery catheter (PAC) and echocardiography to assess cardiovascular performance, much of our understanding of septic hemodynamics was based on clinical findings. There were two distinct clinical presentations of septic shock: warm shock characterized with high cardiac output (CO), warm dry skin, bounding

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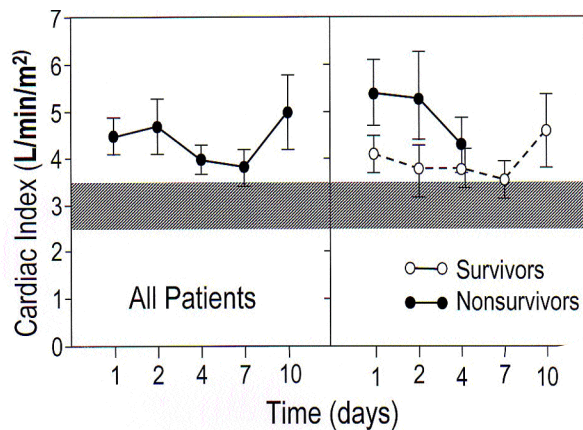


Fig. 1: The mean (\pm SEM) cardiac index plotted against time for all patients, survivors, and non-survivors. The hatched areas show the normal range.

Open circles = survivors; closed circles = non-survivors.

pulses and hypotension; and cold shock characterized with low CO, cold clammy skin and diminished pulses^[10]. Clowes *et al.*^[11] went on to describe a relationship between warm and cold shock as a continuum where either recovery or progression to death occurred. This notion was supported by other studies showing a correlation between survival and a high cardiac index (CI)^[10,12]. However all these studies used central venous pressure (CVP) as a reflection of left ventricular end-diastolic volume (LVEDV) and adequacy of resuscitation. The importance of adequate volume status and its relation to survival and CI was suggested in only a handful of studies^[13,14]. Based on evidence collected over the past four decades, we now know that CVP is a poor measure of preload in critically ill patients, particularly septic patients^[15].

In addition to allowing the routine measurement of cardiac output, the introduction of the PAC enabled the routine measurement of preload as pulmonary capillary wedge pressure (PCWP). Using the PAC, several studies have now shown that adequately resuscitated septic shock patients have a persistent hyperdynamic state, high CO and low SVR (systemic vascular resistance)^[16,17]. In non-survivors this hyperdynamic state usually persists until death (Fig. 1)^[18,19].

Since cardiac output is the product of heart rate (HR) and stroke volume (SV) septic patients can have a hyperdynamic circulation (high CO, low SVR) even in the setting of significant myocardial depression as manifested by decreased left ventricular stroke work index (LVSWI)^[20]. Myocardial dysfunction could be explained by a change in contractility and/or compliance. Radionuclide cineangiography (RNCA) and its application to critically ill patients have offered insight into the relative contribution of decreased contractility and compliance in myocardial depression.

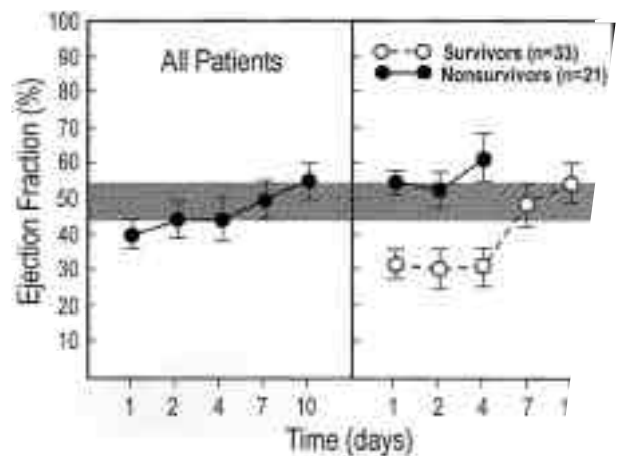


Fig. 2: The mean (\pm SEM) left ventricular ejection fraction (LVEF) plotted versus time for all patients, survivors, and non-survivors. The hatched area represents the normal range.

Open circles = survivors; closed circles = non-survivors.

Ventricular function

Elements of both right and left ventricular dysfunction exist in sepsis and septic shock; the relative contribution and importance of each to clinical manifestations are not clearly delineated. Similarly, there are elements of systolic and diastolic dysfunction in patients with septic myocardial depression; controversy regarding their relative roles in generating clinical manifestations has been argued. It is broadly accepted that in patients who survive their episode of septic shock, cardiac function returns to baseline within 7-10 days.

Left Ventricular Function

Systolic function has been shown to be impaired in septic patients in a number of studies. Parker *et al.*^[21] demonstrated that survivors had decreased left ventricular ejection fraction (LVEF) and acute left ventricular (LV) dilatation evidenced by increased LVEDV index (LVEDVI) (Fig. 2) using RNCA. These changes in survivors corrected to baseline in 7-10 days. Non-survivors sustained normal LVEF and LVEDVI until death. Despite systolic dysfunction, these patients maintained a high CO and low SVR as shown by the PAC. In a later study, Ognibene *et al.* compared left ventricular performance curves (plotting LVSWI vs LVEDVI) of septic and non-septic critically ill patients (Fig. 3). They showed a flattening of the curve in septic shock patients, with significantly smaller LVSWI increments in response to similar LVEDVI increments when compared to non-septic critically ill controls^[22]. In the years since these observations, other studies have confirmed the presence of significant left ventricular systolic dysfunction in septic patients^[23-26].

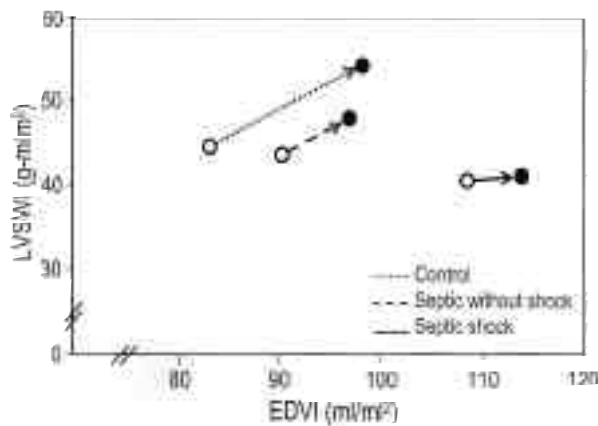


Fig. 3: Frank-Starling ventricular performance relationship for each of the three patient groups. Data points plotted represent the mean prevolume and postvolume infusion values of end-diastolic volume index (EDVI) and left ventricular stroke work index (LVSWI) for each patient group.

Diastolic dysfunction in septic patients is less clearly defined. The acute LV dilatation shown by Parker *et al*^[21] and a concordant relation between PAWP and LVEDV do not support the presence of significant diastolic dysfunction. However, more recent studies using echocardiography have shown impaired compliance as evidenced by slower left ventricular filling^[27], aberrant left ventricular relaxation^[28,29] and failure of ventricular dilatation^[25,26] in septic patients. The clinical impact and relative contribution of diastolic dysfunction to myocardial depression is yet to be elucidated.

Right ventricular Function

The peripheral vasodilatation seen in sepsis leads to decreased left ventricular afterload and eventually preload. The increase in cardiac output can be limited by decreased preload if patient is not adequately volume resuscitated. However, the right ventricular afterload is frequently elevated due to increased pulmonary vascular resistance (PVR) from acute lung injury^[30]. Because of the variability in RV afterload, it may not behave like the LV in septic patients. This is the reason for a number of studies looking into RV function in sepsis.

Systolic RV dysfunction has been shown by decreased RVEF and RV dilatation in volume resuscitated patients^[31-34]. Kimchi *et al*^[31] and Parker *et al*^[33] showed that RV dysfunction can occur even in the absence of increased pulmonary artery pressures and pulmonary vascular resistance suggesting that increased RV afterload may not be the sole explanation for RV dysfunction in septic shock. Parker *et al*^[33] also showed that RV and LV function paralleled each other in dysfunction and recovery (Fig. 4). In this study survivors showed RV dilatation and decreased RVEF and RWSWI

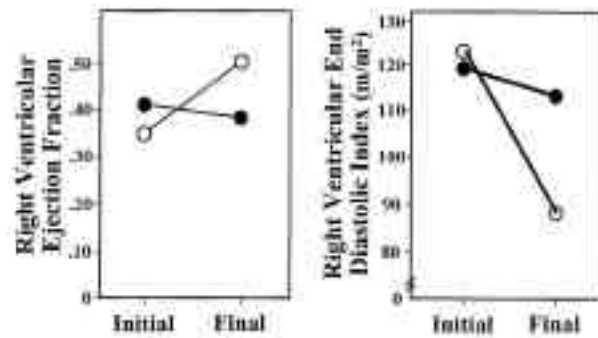


Fig. 4: Serial changes in right ventricular ejection fraction and end-diastolic volume index during septic shock in humans. (A) Mean initial and final right ventricular ejection fractions for survivors (closed circles, $p < 0.001$) and non-survivors (open circles, $p < 0.001$). (B) Mean initial and final right ventricular end-diastolic volume index for survivors (closed circles, $p < 0.05$) and non-survivors (open circles, $p = \text{not significant}$).

which normalized in 7-14 days. As with the LV, the RV was only moderately dilated and RVEF marginally decreased; both persisted through their course of sepsis.

Diastolic dysfunction of the RV has also been demonstrated in a number of studies. Kimchi *et al*^[31] noticed a lack of correlation between right atrial pressure and RVEDV, suggesting altered RV compliance. In another study, a subgroup of patients who were volume loaded demonstrated increase in CVP but not RVEDVI^[32]. As in the LV, the relative contribution of systolic and diastolic dysfunction in the RV is unknown.

CARDIOVASCULAR PROGNOSTIC FACTORS IN SEPTIC SHOCK

Cardiac index appears not to be a reliable predictor of mortality in septic shock. Despite early evidence suggesting low CI as a poor prognostic factor^[10-13], introduction of the PAC has shown that septic shock patients, when adequately fluid-resuscitated, have a high CI and low SVR amongst both survivors and non-survivors^[16,17]. Armed with the PAC, other hemodynamic parameters were investigated as prognostic indicators.

Baumgartner *et al*^[35] recognized that patients with extremely high CI (> 7.0 L/min/m²) and accordingly low SVR had poor outcomes. Groenveld *et al* also found non-survivors had lower SVR's than survivors after matching other characteristics concluding that there may be a link between outcome in septic shock and the degree of peripheral vasodilation^[36].

Parker *et al*^[18] reviewed hemodynamic data from septic shock patients on presentation and at 24 hours to identify prognostic value. On presentation, only heart rate < 106 beats/min suggested a favorable outcome. At 24 hours, heart rate < 95 beats/min, SVRI > 1529 dynes·sec·cm⁵/m², a

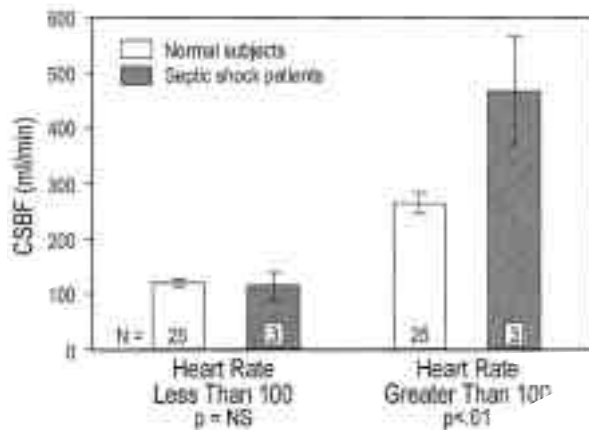


Fig. 5: Mean coronary sinus blood flow (CSBF) in seven patients with septic shock compared with normal subjects.

decrease in heart rate > 18 beats/min and a decrease in CI > 0.5 L/min/m² all predicted survival. In a subsequent study^[19], the same authors confirmed previous findings of decreased LVEF and increased LVEDVI in survivors of septic shock but not in non-survivors, a finding that has been confirmed by other groups^[25,26]. Although myocardial depression has been historically linked to increased mortality, this data may imply that depression, at least as manifested by decreased ejection fraction with ventricular dilatation may actually represent an adaptive response to stress rather than a maladaptive manifestation of injury.

From the studies of Parker and Parillo^[18,19], it is apparent that, despite not developing significant LV dilatation overall, non-survivors could be divided into two patterns: those with progressively declining LVEDVI and CI, and the others with incremental increases in LVEDVI while maintaining CI. Based on this, Parker *et al* described different hemodynamic collapse profiles leading to death in septic shock^[18,19]. First, some patients die from refractory hypotension secondary to distributive shock with preserved or elevated CI. The other pattern consists of cardiogenic form of septic shock with decreased CI and mixture of cardiogenic and distributive shock patterns. The explanation of the two patterns came from a study by Parker *et al*^[19]. It appears that patients who cannot dilate their LV (decreasing CI and LVEDVI) die from cardiogenic form of septic shock. The other fatal pattern consists of those patients who can dilate their LV and preserve CI (increase LVEDVI while maintaining CI), but eventually die of distributive shock.

The prognostic value of RV hemodynamic parameters has been debated. A number of studies^[31-34] have shown that RV dilatation and decrease RVEF, if persistent is associated with poor prognosis^[33,34]. However, Vincent *et al*^[34] suggested that high initial RVEF portends a good prognosis.

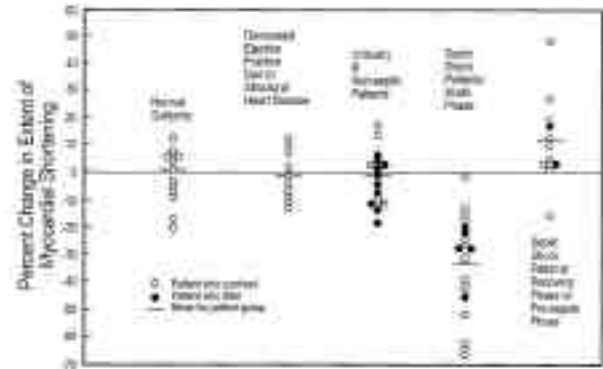


Fig. 6: The effect of serum from septic shock patients and control groups on the extent of myocardial cell shortening of spontaneously beating rat heart cells in vitro. Open circles, survivors; closed circles, non-survivors; horizontal line, mean for each group.

On the other hand, Parker *et al*^[33] found that the survivors had a lower RVEF. The answer to this question requires additional investigation.

The other prognostic parameter is response of hemodynamic parameters to dynamic challenges, namely dobutamine. Non-survivors of septic shock have a blunted response to dobutamine^[37-39] whereas survivors demonstrated increased SVI (stroke work index), increased mixed venous oxygen saturation, ventricular dilatation and a decrease in diastolic blood pressure after a dobutamine challenge. The above response to dobutamine predicts survival in patients with septic shock.

ETIOLOGY OF MYOCARDIAL DEPRESSION IN SEPSIS AND SEPTIC SHOCK

The exact sequence of events in the pathophysiology of septic myocardial depression has only begun to be elucidated in recent years. There are likely a multitude of mechanisms and factors that play a role. A number of potential pathogenic mechanisms have been proposed. The two major theories have been myocardial hypoperfusion or a circulating myocardial depressant substance.

Organ Level: Myocardial Hypoperfusion

The potential of myocardial hypoperfusion leading to myocardial depression via global ischemia has been largely dismissed by a number of studies. Cunnion *et al*^[40] inserted thermodilution catheters into the coronary sinus of septic patients and measured serial coronary flow and metabolism (Fig. 5). Normal or elevated coronary flow was present in septic patients in comparison to normal controls with comparable heart rates. There was also no difference in myocardial blood flow between septic patients, who did and did not develop myocardial dysfunction. There also was no net lactate production.

Dhainaut *et al*^[41] also confirmed these findings while employing similar methods. In addition to human studies, a canine model of sepsis study^[42] showed that myocardial high energy phosphates and oxygen utilization were preserved in septic shock. Both of these observations argue against, neither global myocardial ischemia nor hypoperfusion.

Perfusion aside, there is evidence for myocardial cell injury evidenced by increased troponin I levels in septic shock^[43]. A study by Elst *et al*^[44] examined levels of troponin I and T in patients with septic shock. A correlation between LV dysfunction and TnI (troponin I) positivity (78% vs 9% in cTnI negative patients $p < 0.001$) existed. They also found that older patients with underlying cardiovascular disease more often had both troponin positivity and LV dysfunction. However, whether the clinically inapparent myocardial cell injury contributes to or is a consequence of septic shock is yet to be determined^[44]. Although troponin is used as a marker of myocardial injury (particularly in the context of myocardial ischemia), it does not specifically suggest myocardial hypoperfusion in other contexts.

Myocardial depressant substances

The theory of a circulating myocardial depressant factor was put forth by Wiggers *et al*^[45] in 1947 in the context of hemorrhagic shock. The presence of such a factor was confirmed by Brand and Lefer^[46] in 1966. Lefer's work prompted further research into septic myocardial depressant substances^[46-54].

A number of endogenous substances have been implicated as potential causes of septic myocardial depression. These have included estrogenic compounds, histamine, eicosanoids/prostaglandins and several novel substances that could never be effectively isolated^[46-54] (for review^[55]). In the last decade, the dominant focus has been on inflammatory cytokines.

In one of the seminal studies in the field, Parillo *et al* in 1985^[56] showed a link between myocyte depression and septic serum from a patient with sepsis associated myocardial depression. The serum from patients demonstrated concentration-dependent depression of *in vitro* myocyte contractility (Fig. 6). Parillo *et al* were also able to correlate a temporal and qualitative relationship between *in vivo* myocardial depression (decrease LVEF) and *in vitro* cardiac myocyte depression induced by serum from corresponding patients.

In another study^[57], investigators noted that higher levels of myocardial depressant activity correlated with higher peak serum lactate increase

ventricular filling pressures, increased LVEDVI, and mortality (36% vs 10%), when compared with patients with lower or absent activity levels. Subsequent work focused on identifying the myocardial depressant substances and thereby investigating potential treatments.

Potential circulating myocardial depressant substances include arachidonic acid metabolites, platelet activating factor, histamine and endorphins. Filtration studies^[57] found that the substance was water soluble, heat labile and greater than 10 kilo Daltons. These characteristics pointed towards a protein or polypeptide consistent with cytokines such as TNF- and IL-1 .

TNF- likely has a role as a myocardial depressant substance for a number of reasons. TNF- shares the same biochemical profile as myocardial depressant substances^[56,58]. Clinically, TNF- is associated with fever, increased lactic acid, disseminated intravascular coagulation, acute lung injury and death. The hemodynamic effects of TNF- are similar to sepsis, in particular hypotension, increased cardiac output and low systemic vascular resistance^[59,60].

Healthy human volunteers given TNF- infusions have similar responses^[61,62]. Experimentally, TNF- given to *in vitro* and *ex vivo* animal and human myocardial tissue demonstrated a concentration dependent depression of contractility^[49,63]. Kumar *et al*^[64] showed that removal of TNF- from patients serum with septic shock decreased the myocardial depression. Also, Vincent *et al*^[65] in a pilot study showed improved LVSWI with administration of anti-TNF- monoclonal antibody even though there was no survival benefit.

IL-1 produces similar hemodynamic responses to TNF- . IL-1 levels are also elevated in sepsis and septic shock^[66]. *In vitro* and *ex vivo* myocardial contractility is depressed when cardiac tissue is exposed to IL-1^[63,67,68]. Removal of IL-1 via immunoabsorption from septic human serum attenuates the depression of cardiac myocytes^[64]. The effects of IL-1 antagonist on cardiac function and survival are unimpressive^[69-71] even though metabolic derangements are attenuated by IL-1 antagonist^[70,71].

It is likely that cytokines such as TNF and IL-1 , rather than working in isolation synergize to exert their depressant effects. In isolation, TNF- and IL-1 require very high concentration to induce *in vitro* rat myocyte depression^[64]. However, when combined, they act synergistically and require concentrations 50-100 times lower than those required individually^[64,72]. These concentrations are within the range of those found in septic shock patients.

Another recent series of studies by Pathan and colleagues have strongly implicated circulating IL-6 as an important myocardial depressant substance in human septic shock^[73-75]. These investigators have demonstrated that meningococcal sepsis is associated with induction of IL-6 expression in blood mononuclear cells and that the level of serum IL-6 corresponds with the degree of cardiac function in such patients. Further, they have recently shown that IL-6 depresses contractility of myocardial tissue in-vitro and that neutralization of IL-6 in serum from patients with meningococcal septic shock neutralizes this effect^[73].

Evidence for other potential myocardial depressant substances continue to be developed. Recently, Mink *et al* have implicated lysozyme C (consistent with that found in the spleen, leukocytes in the spleen or other organs) as a potential MDS^[47]. In the canine model of *E. coli* sepsis lysozyme C caused myocardial depression and attenuated response to beta-agonists^[47]. The potential mechanism proposed was lysozyme binding or hydrolyzing the membrane glycoprotein of cardiac myocytes, thereby affecting signal transduction (linking physiologic excitation with physiologic contraction). The levels of lysozyme C were found to be elevated in the heart and spleen, but not in lymphocytes when compared to pre-septic levels^[47]. Mink *et al* went on further to show that pretreatment with an inhibitor of lysozyme (N,N',N''-triacetylglucosamine) prevented myocardial depression in canine sepsis^[76]. However, the effect of this lysozyme inhibitor (TAC) was only seen in pretreatment and early treatment groups (1.5 hours after onset of septic shock) and not in late treatment groups (greater than 3.5 hours)^[76].

An important microbial factor that has recently been shown to potentially exert hemodynamic and myocardial depressant activity in sepsis and septic shock is bacterial nucleic acid. Several investigators have demonstrated that unique aspects of bacterial nucleic acid structure may allow bacterial DNA to generate a shock state similar to that produced by endotoxin when administered to animals^[77]. Extending these observations, we have recently demonstrated depression of rat myocyte contraction with bacterial DNA and RNA^[78]. This effect was more marked when DNA and RNA came from pathogenic strains of *S. aureus* and *E. coli*. These effects were not seen when the rat myocyte was pretreated with DNase and RNase.

Cellular Level

The sequence of mechanisms leading from a MDS to cellular dysfunction remains substantially opaque. There are several potential mechanisms that may play a role at the cellular level.

Overproduction of nitric oxide (NO) and derangements of calcium physiology in the myocardial cell are two potential cellular mechanisms.

In vitro, myocyte depression in response to inflammatory cytokines can be divided into early and late phases. Early depression of cardiac myocyte depression occurs within minutes of exposure to either TNF- α , IL-1 β , TNF- α and IL-1 β given together or septic serum^[64,79]. TNF- α also demonstrates the ability to cause rapid myocardial depression in dogs^[60,80]. Besides the early effects of TNF- α , IL-1 β and supernatants of activated macrophages also have a later, prolonged effect on in vitro myocardial tissue^[67,68,80,81]. This late phase establishes within hours and lasts for days. This suggests a different mechanism from early myocardial depression.

Production of nitric oxide (NO) may be a potential explanation for both early and late myocardial depression. NO is produced from conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS). NOS has two forms: one is constitutive (cNOS) and the other is inducible (iNOS). NO produced by cNOS appears to have a regulatory role in cardiac contractility^[82-84]. However, when cardiac myocytes are exposed to supra-physiologic levels of NO or NO donors (nitroprusside and SIN-1) there is a reduction in myocardial contractility^[85]. Paulus *et al*^[86] infused nitroprusside into coronary arteries which decreased intraventricular pressures and improved diastolic function.

Current evidence suggests that early myocyte dysfunction may occur through generation of NO and resultant cGMP via cNOS activation in cardiac myocytes and adjacent endothelium^[72,79,87]. Late myocardial depression may be secondary to induction of synthesis of iNOS NO^[68,79,88,89]. In addition, the generation of peroxynitrite via interaction of the free radical NO group and oxygen may also play a role in more prolonged effects^[90]. We have demonstrated that the early phase may involve both a NO dependent but β -adrenergic-independent mechanism and a NO-independent defect of β -adrenoreceptor signal transduction^[55,87,91,92]. Others have shown that IL-6 can cause both early and late NO-mediated myocardial depression in an avian myocardial cell model via sequential activation of cNOS followed by induction of iNOS, a finding that could explain recent human data implicating IL-6 in meningococcal septic myocardial dysfunction^[73,74,93-95]. This study suggests the role for sequential production of NO from cNOS and iNOS in the pathogenesis of myocardial depression from cytokines.

POTENTIAL THERAPIES

In the minority of cases where septic myocardial depression may be sufficiently expressed clinically to require treatment, options are available. Epinephrine, dobutamine, milrinone and digoxin have all been shown to improve cardiac function in low-output septic shock^[96-98]. However, these modalities are supportive in nature and do not specifically attempt to neutralize myocardial depressant pathways.

Research into the pathophysiology of sepsis induced myocardial depression naturally leads into potential specific therapies to reverse septic myocardial dysfunction. Several investigators have examined the use of various hemofiltration modalities in septic shock^[53,99-102]. However, results have been highly inconsistent. Mink *et al*^[99] demonstrated that continuous arteriovenous hemofiltration combined with systemic vasopressor therapy can reverse cardiac depression and hypotension in an endotoxemia-equivalent canine *E. coli* sepsis model. Freeman and colleagues, however, were unable to demonstrate such a benefit^[100].

Inflammatory cytokine antagonists are another area of research. As previously mentioned TNF-monoclonal antibodies have improved LV function when given to patients in septic shock^[65] despite failing to show a survival benefit. IL-1 antagonists have shown mixed results. Despite the absence of a survival benefit, attenuation of metabolic derangements in septic shock was noted^[70,71] although no hemodynamic benefit was apparent^[69].

Further down the sequence of pathogenesis in septic myocardial depression are the therapeutic potential of NO scavengers or NO inhibitors. Methylene blue (NO scavenger) has been shown to attenuate the hemodynamic alterations in a randomized open label pilot study of 20 patients with sepsis^[103]. This study was a randomized open label pilot on 20 patients. Suzuki *et al*^[104] used an inhibitor of iNOS (L-canavanine) in septic rats which showed prevention of myocardial contractility depression. However, L-canavanine itself depressed myocardial contractility via decreased coronary blood flow, an effect that was thought to be potentially responsible for the increased mortality in the only randomized double-blinded clinical study of a NOS inhibitor in clinical septic shock^[105,106].

CONCLUSION

Myocardial dysfunction is an important component in the hemodynamic collapse induced by sepsis and septic shock. A series of inflammatory cascades triggered by the inciting infection generate circulatory myocardial depressant

substances, including TNF- α , IL-1, PAF and lysozyme. Their effects are partly mediated through NO generation. How NO depresses cardiac contractility is largely unknown. The research into the pathophysiology of septic myocardial depression will hopefully yield potential therapies. Until then, volume resuscitation, inotropic and vasopressor support is the current standard of care to restore tissue perfusion.

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