Myocardial Dysfunction in Sepsis
Recent Insights

Shock secondary to sepsis has increased in incidence during the past five decades and is now the most common cause of death in ICUs in the United States.\(^1\) The sepsis syndrome results in marked metabolic abnormalities, cardiovascular derangements, and organ system dysfunction.\(^1\) In our judgment, the cardiovascular derangements are the usual cause of patient demise, and our studies have focused on these heart and vascular abnormalities (Fig 1).

There is widespread recognition that most patients with sepsis and septic shock develop significant derangements of myocardial function.\(^1,2\) These abnormalities, which include depression of left\(^3,4\) and right\(^5\) ventricular ejection fraction, ventricular dilatation,\(^3,4\) and altered Frank-Starling and diastolic pressure-volume relationships,\(^6\) usually are present from the first to fourth days after the onset of shock. In survivors, the abnormalities resolve in seven to ten days. The clinical appearance of such derangements may be subtle. Sepsis and septic shock patients, after adequately resuscitated with substantial volume administration, usually have cardiac outputs that are normal or increased relative to those of resting normal humans. Even preterminally, the cardiac output usually does not fall to subnormal levels.\(^7\) In the context of sepsis, however, a normal cardiac output, as conventionally defined, may be inadequate for the metabolic needs of the organs and cells. One can argue theoretically that, in a patient with severe sepsis-induced peripheral vascular abnormalities, a physiologically appropriate cardiac output might be very high, perhaps 30 L/min or more. Thus, the myocardial depression of sepsis, while perhaps allowing a “normal” cardiac output, may preclude a needed physiologically maximal cardiac output response.

Two different postulates have been offered to account for myocardial depression in sepsis. The first postulate, based on work in animal models, is that coronary hypoperfusion leads to ischemic myocardial dysfunction. However, we have measured coronary blood flow in human septic shock, utilizing coronary sinus thermodilution catheters, and demonstrated both preservation of myocardial blood flow and net myocardial lactate extraction, so that global ischemia cannot be the cause of myocardial depression.\(^8\) In this study the difference in oxygen content between arterial and coronary sinus blood was found to be narrowed, and the fractional extraction of arterial oxygen...
in the coronary circulation was demonstrated to be diminished. This pattern of abnormalities suggests that sepsis results in a deranged coronary flow analogous to the pattern of arteriovenous shunting characteristic of other organs and the entire systemic circulation in human septic shock.

The second postulate is the presence of a circulating myocardial depressant substance (MDS) or substances. Most early investigations of myocardial depressant activity employed animal models of endotoxic or hemorrhagic shock, disease entities whose hemodynamics differed substantially from human sepsis and hence were of dubious human relevance. Further, in these studies the isolated papillary muscle preparations used to assay for myocardial depressant activity were difficult to establish and reproduce. The search for MDSs in human sepsis was hindered by the need for a less cumbersome in vitro myocardial contractility assay that could be correlated with in vivo measurements of cardiac function.

Our bioassay for myocardial depressant activity in human serum, reported in 1985, utilized newborn rat myocytes in tissue culture, which exhibited spontaneous rhythmic contractions after growing for three to four days in physiologic medium and attaching to the bottom of a Petri dish. Videodensitometry permitted quantitative recording of the amplitude and velocity of the contractions of a single myocyte. When newborn rat myocytes were exposed in vitro to sera from patients during the acute phase of human septic shock, their extent and velocity of shortening were depressed significantly. This in vitro depression did not occur with sera from normal volunteers, critically ill nonseptic patients, or patients with reduced ejection fractions due to structural heart disease. Importantly, the quantity of depression of the in vitro myocyte correlated with the amount of decrease in the in vitro left ventricular ejection fraction. These findings were the first strong evidence that circulating MDS(s) played a pathophysiologic role in the myocardial dysfunction of human septic shock.

Subsequently, this assay system was modified by placing microscopic latex beads onto the cultured myocytes, allowing the use of a video displayed closed-loop tracking system to quantitate myocyte contractions with greater ease and accuracy. The experiments reported in this issue of Chest (see page 1072), which utilized the modified assay system, represent a step in the evolution of our understanding of circulating myocardial depressant activity in septic shock. Substantial depressant activity (>20 percent depression was considered a positive assay) was found in almost half of septic shock patients in a consecutive series, and, as in the 1985 study, in vitro depression of myocardial cell contractility correlated with in vitro depression of ejection fraction. Patients with circulating MDS activity (MDS-positive) had higher pulmonary artery wedge pressures and larger end-diastolic volume indices than those without such circulating activity. Further, these MDS-positive patients had higher mean peak lactate acid levels, suggesting either greater inadequacy of cardiac output relative to the body's metabolic needs or perhaps a direct peripheral vascular effect of MDS(s). Hence, high levels of myocardial depressant activity can be found in sera from a large proportion of septic shock patients, particularly those with the most severe cardiovascular derangements. Myocardial depressant activity was associated with increased mortality (36 percent mortality in MDS-positive vs 10 percent in MDS-negative patients) in this study; however, this association achieved only borderline statistical significance (0.05<p<0.10). This may result from the small number of deaths (n = 7) in the entire series. As more data are gathered, it seems likely that depressant activity will prove to be predictive of clinical outcome.

The structural and chemical nature of this myocardial depressant substance (or possibly substances) is currently unknown, but this represents an area of active investigation. Previous experiments have shown myocardial depressant substance (MDS) to have a number of specific characteristics. As the concentration of depressant serum placed onto the myocytes is increased from 0 percent to 5 percent, 10 percent, and 20 percent, there is a dose-dependent, stepwise decrease in both the extent and velocity of myocardial cell shortening. Thus, MDS produces a concentration-dependent decrease in myocyte function. Depressant activity is water soluble and will diffuse through a dialysis membrane. Molecular filtration experiments with Amicon filters have produced somewhat contradictory results: one group of experiments suggesting a molecular weight between 500 and 5,000 daltons, with other experiments suggesting activity at greater than 10,000 daltons. This discrepancy may result from either the active molecule's ability to bind to proteins or its ability to produce dimers, trimers, or other multimers of the native molecule. Such a characteristic has been described with other mediators, eg, tumor necrosis factor (TNF). We currently believe that MDS is a water-soluble molecule weighing 10,000 to 30,000 daltons. Due to the inherent technical difficulties involved in obtaining large volumes of human serum from critically ill patients, MDS has not yet been purified. However, isolation efforts are presently underway utilizing human and animal sources and employing cell cultures as another potential source of this important molecule.

In some very recent experiments, previously described putative mediators of physiologic processes were tested for direct myocardial depressant capability using the in vitro assay of rat myocardial cells...
described above. Highly purified preparations of endotoxin (lipopolysaccharide), interleukin-1, and interleukin-2 were added to the myocyte assay and produced no depression, even in concentrations higher than those occurring physiologically. However, TNF, a molecule known to be released during Gram-negative bacteremia and endotoxemia in animals and humans, produced significant depression of myocyte shortening (mean, −24 percent). These are preliminary experiments, and further confirmatory studies are needed. However, these findings suggest that TNF may play a key role in directly producing the myocardial depression characteristic of human septic shock.

The overall pathogenesis of human septic shock is extremely complex (Fig 1), and a wide variety of putative mediators have been implicated. In recent years there has been an explosion of knowledge, largely concerning the peripheral vascular and metabolic effects of the known mediators of sepsis, including endotoxin, TNF, interleukin-1, and interleukin-2. In Table 1 we summarize our observations of the hemodynamic effects of experimental administration of these mediators to humans and dogs. Definitive data remain sparse, though, regarding the direct effects of the known mediators of peripheral vascular dysfunction on the contractile state of the myocardium.

The recent development of an appropriate animal model by Natanson and coworkers has extended our knowledge of sepsis-associated myocardial abnormalities and provided invaluable insights into the relationships between some of these mediators and the cardiovascular manifestations of sepsis. This canine sepsis model, extensively validated and studied, simulates very closely the cardiovascular pattern of human septic shock. Live bacteria, contained in a fibrin clot, are implanted surgically into the peritoneal cavity as a nidus of infection, leading to sustained bacteremia in all animals. Serial hemodynamics are performed in conscious, unsedated animals both before and after fluid loading, using arterial and pulmonary artery catheters and simultaneous radionuclide cineangiography. These determinations permit analysis of both systolic and diastolic ventricular performance, ventricular volumes, and pressure/volume relationships without the confounding effects of anesthesia.

Using this canine model, an Escherichia coli nidus and subsequent bacteremia were demonstrated to produce cardiovascular dysfunction characterized by a decreased mean arterial pressure, an elevated cardiac output, and a reduced systemic vascular resistance. These "hyperdynamic" parameters were associated with a depressed left ventricular ejection fraction and a dilated ventricle (increased end-diastolic and end-systolic volumes). In addition to this systolic dysfunction, the pressure/volume relationship during diastole also was abnormal; ie, the ventricle was dilated with little change in filling pressure, reflecting an increase in ventricular compliance. This pattern of cardiovascular dysfunction was found with both Gram-positive and Gram-negative organisms.

In further studies the canine model demonstrated a relationship between the number of organisms placed into the nidus and the amount of decrease in ejection fraction: the higher the organism number, the greater the myocardial depression, until a lethal dose was reached. Staphylococcus aureus could be placed into the peritoneal clot at lower doses than E. coli and produce the same decrease in ejection fraction. This was probably due to the ability of S. aureus to multiply more quickly in vivo, resulting in a greater number of organisms. Thus, both the quantity of organisms and the organism type have direct associations with sepsis-induced cardiac dysfunction.

Natanson and coworkers recently investigated whether endotoxin alone could produce serial cardiovascular abnormalities in the canine model. Endotoxin, a mediator known to trigger the release of a large number of other mediators, was placed into a

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fibrin clot and implanted into the peritoneum. The subsequent pattern of cardiovascular changes, including those in the ejection fraction, was identical to that previously described for septic shock induced by live organisms (E coli or S aureus) in the canine model.24 In human experiments, Sufredini and coworkers22 found that administering IV endotoxin boluses to healthy volunteers produced decreases in left ventricular ejection fraction and increases in end-diastolic volume, as well as increased cardiac output, increased heart rate, decreased arterial pressure, and decreased systemic vascular resistance. Thus, endotoxin administration to dogs and to humans can produce a hyperdynamic cardiovascular state and a depressed myocardium. This suggests that endotoxin is probably an important mediator of myocardial dysfunction in Gram-negative sepsis, though endotoxin’s precise role remains to be defined. Endotoxin may cause the release of other mediators that produce direct myocardial effects, eg, MDS. Recently, Doerfler and coworkers26 demonstrated that the lipopolysaccharide moiety of endotoxin can potentiate the effects of other stimulants on neutrophil production of leukotriene B4, an eicosanoid that increases vascular permeability. Thus, complex interactions among WBCs, endotoxin, leukotrienes, and other potent mediators probably contribute to the final common pathogenetic mechanisms of septic shock (Fig 1).

Danner and coworkers27 measured serial endotoxin levels in 100 critically ill patients with clinical signs of sepsis. On average, patients with endotoxemia had lower left ventricular ejection fractions than patients without endotoxemia, as well as higher peak lactic acid levels and lower systemic vascular resistances. The findings of this study provide further evidence of an important pathogenetic role for endotoxin in human sepsis; however, such a phenomenologic association between endotoxemia and depression of ejection fraction does not provide data on whether endotoxin was actually the direct cause of the myocardial depression. In further endotoxin-related investigations, Danner and coworkers16,28 also have elucidated the therapeutic potential of lipid A analogues, which inhibit endotoxin-induced priming of human neutrophils. These may prove useful therapeutically in inhibiting enhancement by endotoxin of superoxide release, thereby decreasing sepsis-associated tissue destruction.25

Myocardial depression also can occur in the absence of endotoxin, however. Natanson and coworkers28 have demonstrated in the canine model that S aureus, a microorganism without endotoxin, causes the same sequence of cardiovascular changes (including myocardial depression) as E coli, which produces measurable endotoxemia. This implies that cardiovascular injury during septic shock involves final common pathways (Fig 1) that are independent of specific bacterial types or toxins. Additionally, Natanson and coworkers have demonstrated in dogs that IV TNF can elicit the same deleterious effects as endotoxin: progressive decreases in arterial pressure, ejection fraction, and systemic vascular resistance, which are reversed only partially with fluid loading.29 By contrast, interleukin-1 administration produced only minimal effects on cardiovascular function in the dog.30

Ognibene and coworkers39 measured cardiovascular parameters serially in patients given interleukin-2, and documented the development of reversible cardiovascular abnormalities analogous to the hemodynamic manifestations of human septic shock. Hence, interleukin-2 joins endotoxin and TNF on the list of possible endogenous mediators of cardiovascular dysfunction in sepsis. Ognibene and coworkers39 have also demonstrated a correlation between levels of the activated complement component C5a (measured by neutrophil aggregation assay) and decreases in systemic vascular resistance; C5a was not correlated, however, with decreased ejection fraction. Hence, C5a probably is an important intermediate mediator of the peripheral vascular abnormalities of septic shock.

In conclusion, studies of human and canine septic shock have demonstrated evidence of myocardial depression and dilatation. These abnormalities appear to be due to a circulating myocardial depressant substance that correlates temporally and quantitatively with the ventricular dysfunction. When administered to animals or humans, a number of known mediators (endotoxin, TNF, and interleukin-2) have been shown to reproduce the cardiovascular patterns of spontaneous septic shock. In preliminary studies, TNF has demonstrated direct myocardial cell depressant capabilities. The ability to inhibit toxins and/or mediators of the septic shock syndrome may improve the high morbidity and mortality currently associated with septic shock in humans.

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The Sun Should Never Set on a Parapneumonic Effusion

It has been documented that pleural effusions are frequently associated with pneumonia, whether it be pneumococcal, staphylococcal, Gram-negative aerobic, or anaerobic.1-4 The most common cause of an empyema or complicated parapneumonic effusion today is anaerobic pulmonary infection.5 This is largely related to the pathogenesis of anaerobic pulmonary infection, since the disease frequently occurs in the alcoholic patient or in those with impaired consciousness and has an insidious course that does not prompt immediate medical attention. Medical consultation usually is sought seven to ten days after initial inoculation of anaerobes in the lung, when necrotization occurs in the form of necrotizing pneumonia, lung abscess, or empyema. Due to the delay in initiation of antibiotic therapy, the patient frequently has a pleural effusion by this time.

The stage of the pneumonia and of the parapneumonic effusion is critical to the outcome. If the patient can be treated early in their course with appropriate antibiotics, resolution of the pleural effusion occurs with minimal pleural sequelae. If too much time elapses, allowing the inflammatory process to proceed unimpeded in the pleural space, control of pleural sepsis and resolution of the pleural inflammation cannot occur without pleural space drainage. This often necessitates a thoracotomy or prolonged open drainage.

Therefore, time is of the essence in the treatment.