MYOCARDIAL DEPRESSION IN SEPSIS

Constantino Jose Fernandes Jr, Nelson Akamine, and Elias Knobel
Critical Care Department, Hospital Israelita Albert Einstein, São Paolo, Brazil

ABSTRACT—Since the ancient Greeks, we have learned that the pathophysiology of the human diseases relies on blood-borne humoral factors. This was the case with the sepsis myocardial depression, whose associated morbidity and mortality remained untouched during the last decades. Despite the growing knowledge of the possible involved mechanisms, our understanding of this serious condition is still in its infancy. Controversies have surrounded the real origin of septic-induced myocardial dysfunction, and it has been ascribed to inflammatory mediators, NO generation, interstitial myocarditis, coronary ischemia, calcium trafficking, endothelin receptor antagonist, and apoptosis. Although not fully understood, myocardial injury/depression remains a challenge for critical care practitioners.

KEYWORDS—Myocardial dysfunction, myocardial injury, myocarditis, troponin, NO

INTRODUCTION

Septic shock is a severe syndrome characterized by hemodynamic changes and dysfunction of one or several organs. It represents one of the primary causes of death in intensive care units, and in the United States, there are approximately 751,000 cases of severe sepsis, of whom 383,000 received intensive care, with approximately 215,000 deaths (1). Approximately 50% of patients admitted to an intensive care unit with hypotension due to sepsis survive, whereas the remaining 50% die of refractory hypotension or multiple organ dysfunction syndrome. In 10% to 20% of these patients with refractory hypotension, there is a clinical picture of low cardiac output due to severe myocardial dysfunction. This dysfunction was and still is the center of great controversy and has been the object of numerous experimental and clinical researches with the objective of progressing in diagnosis and treatment of this syndrome.

BACKGROUND

In the modern era, the concept of reversible myocardial depression or dysfunction was described by Wiggers (2) in 1947. He postulated the existence of a myocardial depressing factor responsible for myocardial dysfunction in hemorrhagic shock. During the 1960s and 1970s, experimental studies showed evidence of transient myocardial dysfunction in several forms of critical disease, including hemorrhagic and septic shock (3, 4).

In 1973, a meta-analysis of seven studies was published correlating the survival of septic patients with the cardiac index. The reduction of the cardiac index correlated with higher mortality rates ($P < 0.02$). These studies were corroborated by animal models of sepsis induced by injections of endotoxins or living organisms (5–7). Almost all models produced shock characterized by reduced cardiac output and increased resistance. Criticism of these studies was based on the comparison of experimentally induced shock with septic shock in humans and on the use of central venous pressure measurements as an estimate of the ventricular end-diastolic volume. Evidence collected during the last four decades suggests that central venous pressure bears a weak correlation with left ventricular (LV) preload in critically ill patients, especially in septic patients (8, 9). Some authors have proposed that the deficit in circulating volume is responsible for the reduced cardiac output in septic shock (10, 11).

Sequential studies have shown that patients in septic shock adequately resuscitated typically displayed a high output and low systemic resistance hemodynamic circulatory condition with myocardial depression despite the high output (12–15). In those patients who died, this hemodynamic pattern persisted until death.

The initial phase of understanding and the study of cardiovascular manifestations in sepsis and septic shock began with the development of portable radionuclide cineangiography techniques (radioisotopic ventriculography) and with the application of volumetric echocardiography in managing the critically ill patient.

ANATOMICAL AND HISTOPATHOLOGIC ASPECTS

The anatomopathologic evaluation of the heart in states of shock dates back to 1948, when Moon (16) described degenerative myocardial changes in 10 patients who were victims of serious infectious processes. From then on, many studies have documented anatomical alterations in several fatal situations such as the adult respiratory distress syndrome Waterhouse-Friederichsen (17) syndrome, evidencing variable degrees of interstitial vasculitis and myocarditis. In 1988, Fernandes Júnior et al. (18) analyzed 10 necropsies of patients who were victims of septic shock and observed the presence of interstitial myocarditis, necrotizing vasculitis, and myocardial abscesses, demonstrating that the heart is affected primarily by endotoxins and mediators, and sometimes by the direct action of bacteria. Of these 10 patients with confirmed structural involvement of the heart, only two showed clinical evidence of myocardial depression, suggesting that...
cardiac involvement in septic shock is much more frequent than was thought, and that there is no good anatomoclinical correlation of this process. In 1994, the same authors (19) published another review with histopathologic findings of the myocardium in 71 autopsies of patients who met morphological criteria of sepsis, comparing them to a control group and observing the presence of interstitial myocarditis in 27% of the sample, bacterial colonization in 11%, necrosis of cardiac fibers in 7%, and interstitial edema in 28%, although this last finding did not demonstrate a significant difference relative to controls.

**PATHOPHYSIOLOGY**

Discussions on the true involvement of the heart in sepsis and septic shock, regardless of hemodynamic conditions, date back to the early 1960s (20), when some studies already used endotoxic shock models in animals. In the 1980s, using nuclear medicine techniques, Parker et al. (14) demonstrated the decreased biventricular ejection fraction (EF) in these septic patients. However, the cause of this dysfunction remained uncertain because there were two theories to explain the phenomenon. The first suggested an ischemic involvement in these patients resulting from coronary hypoperfusion. Several studies, however, such as the one conducted by Cunnion et al. (21) in 1986 with the use of coronary sinus catheterization, proved that this flow was the same or greater in patients in septic shock when compared with normal individuals, and the production of lactic acid at the site was normal. The second theory was based on the proposal made by Wiggers (2) in 1947 on the presence of a myocardial depressor factor obtained in an experimental model of hemorrhagic shock. In the 1960s, many authors described similar substances responsible for myocardial depression. In the mid-1970s, Lefer and Martin (20) documented the existence of a myocardial depressor factor in the blood of dogs in induced endotoxic shock with a hemodynamic pattern, and suggested that it was a peptide with 800 to 1,000 d originated in the pancreas. To demonstrate the existence of a myocardial depressor substance, McConn et al. (22) infused plasma of septic patients in the ostium of coronary arteries of dogs in vivo, demonstrating the presence of two molecules with depressor activity. The first fraction, with a weight of less than 1 kd, showed an immediate depressor effect, whereas the second, with a weight between 1 and 10 kd, showed late depressor activity. Other subsequent studies characterized substances similar to what had been found by Lefer and Martin, but this one was not isolated.

The connection between clinical myocardial depression and the effects of myocardial depressor substances (MDSs) was described by Parillo et al. (23) in the late 1980s by measuring the serum levels of the substances in these patients during the septic phase. The authors initially identified a subpopulation of patients with septic shock and decreased LV EF (mean, 33%) by radioisotopic ventriculography. In parallel, they prepared a culture of myocardial cells of rats using contrast microscopy and an electronic detector of the area of cellular contraction, aiming to document the degree of cell shortening. The serum of these patients was introduced into this cell medium, and a significant drop was noted in the degree and velocity of shortening of these cells when compared with the control group (33% and 25%, respectively). This study established a strong tie between in vivo and in vitro observations of cardiac function and the activity of myocardial depressor substances in septic shock.

Taking into consideration the studies that investigated the activity of MDS, we concluded that this activity is present in two fractions with 0.5 to 5 and greater than 10 kd. This substance is soluble in water but not in ethyl acetate and is heat-labile, characteristics consistent with polypeptides or proteins (24).

Despite the fact that these studies demonstrated some characteristics of MDS, their molecular structure is still not clear. Consequently, investigation began of circulating factors already known to be elevated in sepsis, which could contribute to a better understanding of MDS. These factors are mediators of myocardial depression in sepsis.

The most well-known model of these is that of endotoxin, a component of the walls of gram-negative bacteria. Many studies simulated septic shock with infusions of endotoxins and obtained the same hemodynamic results commonly found in spontaneous septic shock in humans (26). In vitro studies failed to demonstrate a large contractile compartment after the isolated injection of an endotoxin into the atrial muscle of pigs, whereas the infusion of far smaller quantities of endotoxins in pigs in vivo produced significant myocardial depression, suggesting that endogenous factors mediate the response to the endotoxin in vivo. It was demonstrated that the incubation of the endotoxin with activated macrophages produced a supernatant with vascular and myocardial depressor activity. The main inflammatory mediators that contribute to myocardial depression in sepsis include ILs (IL-2, IL-4, IL-6, IL-8, and IL-10), interferon γ, TNF-α, and IL-1β.

The action of IL-2 in septic shock has not yet been well determined; it probably mediates the release of TNF-α and IL-1. Despite having demonstrated characteristics previously described as MDS, IL-4, IL-8, and IL-10 did not cause significant hemodynamic changes when injected in experimental models. None of the three cytokines demonstrated that they cause myocardial depression when tested in vitro. IL-6 represents more of a marker than a mediator in sepsis, and it is a good predictor of mortality in septic shock (26). Its action as a myocardial depressor is controversial because it does not show signs of hemodynamic instability in animal models, whereas in vitro studies showed this effect in cardiac tissue (24).

Gamma interferon shows a mild depressor action when it acts isolatedly, but it acts synergistically with endotoxins, TNF-α, IL-1, and other inflammatory factors both in vivo and in vitro, enhancing their effects (27, 28).

The two cytokines that show the greatest cardiovascular effect in animals and humans are TNF-α and IL-1β. When a small quantity of the endotoxin was injected into humans, increased levels of TNF-α were noted (29, 30), whereas the administration of recombinant TNF-α in animal models led to the appearance of fever, lactic acidosis, hemodynamic changes, and even death (31). Many studies using anti-TNF-α
antibodies both in humans and in animals showed a rapid improvement in cardiovascular parameters, with no drop in mortality (29, 31). The administration of IL-1 in animals also reproduced the hemodynamic effects found in septic shock. One important fact to be highlighted is that, with low doses, many times, TNF-α or IL-1 produced no experimental myocardial depression when administered separately, but when given together with the same doses, they produced synergism between the two cytokines, leading to the depressing effect.

Only TNF-α and IL-1 showed involvement of cardiac cell contraction when injected in vitro and observed by electronic microscopy, a fact that did not occur with the other cytokines.

NO plays a more well-established role in intrinsic vasculature. In normal situations, in the vascular endothelium, by means of calcium and nicotinamide adenine dinucleotide phosphate (reduced form), cNOS converts L-arginine into NO in response to endothelial stimulation by stress or vasodilation mediators such as acetylcholine, bradykinin, or histamine. NO has a short half-life (between 6 and 10 s), but with a great diffusion potential, entering the cytosol of the adjacent smooth muscle cell where it activates soluble guanylate cyclase, producing cyclic guanosine monophosphate, which in turn will promote the sequestration of calcium to inside sarcoplasmic reticulum through L-type calcium channels. Cytoplasmic calcium then diminishes, leading to smooth muscle relaxation and consequent vasodilatation (32). This process also occurs in the cardiac cell, resulting in decreased myocyte contraction.

In sepsis, there is an increased production of platelet-activating factor, thromboxane, and prostacyclins, which are associated with greater mortality. Increased levels of these prostanoids are related to the increased expression of cyclooxygenase 2 in endothelial cells, smooth muscles, and endocardial cells. This enzyme can alter coronary vascular self-regulation, leukocyte activation, and endothelial function, with implications in myocardial dysfunction.

Other substances recently identified as mediators of myocardial depression in sepsis are caspases, intracellular cysteine proteases that participate in the activation of inflammatory cytokines, and cellular apoptosis. Some caspase isoforms are known as m-calpain and μ-calpain. Excessive activation of calpains was implicated in the pathophysiology of inflammation, trauma, and I/R (32). Tissier et al. (25) demonstrated that treatment with calpain inhibitors improved myocardial dysfunction and inflammation produced by endotoxin in rats.

Another molecule discussed lately as possibly related to cardiac depression in sepsis is sphingosine (33). Cellular production of sphingosine could inhibit the sarcoplasmic release of calcium and reduce myocyte calcium, resulting in contractile dysfunction (34).

Charpentier et al. (35) illustrated the probable role of brain natriuretic peptide as a systolic dysfunction marker in sepsis, and this would represent a poor prognosis in these patients. Kneufermann et al. (36) defended the role of Toll-like receptors in inflammatory mediation in sepsis with a possible effect in the cardiovascular collapse in sepsis.

**DIAGNOSIS**

More recently, the release of macromolecules such as troponin I by damaged myocytes was documented. It is not a case of ischemia but of cytotoxic action. Frequently, a reduction in postload disguises possible myocardial dysfunction.

Cardiac output measurement is not considered very sensitive in detecting myocardial depression. The very use of filling pressure measurements to construct Starling curves is inappropriate because of the many changes in ventricular complacency in septic patients. Therefore, filling pressures do not usually reflect ventricular preload. Intense catechol-aminergic stimulation, sustaining a frank hyperdynamic state, tends to cover up depressed ventricular function.

Hemodynamic monitoring has been lately questioned due to its low discriminatory power in diagnosing this condition.

With these limitations, the bedside diagnosis of myocardial depression is based on the determination of the LV EF. In addition, EF evaluation is important especially during the initial phases of septic shock because it is related to the prognosis.

In a healthy patient, a drop in LV EF to less than 50% characterizes heart involvement in sepsis.

In the context of sepsis, an elevation of an initially lowered EF is indicative of a good prognosis. Nonetheless, the finding of a normal EF does not exclude heart involvement.

The need for a more accurate test is evident, but creatine kinase-MB and myoglobin markers proved nonsensitive and nonspecific. Troponin, as previously mentioned, proved to be superior to the others in diagnosing ischemic myocardial damage, and more recently, it also proved to be useful for the diagnosis and prognosis of septic myocarditis (37).

Lately, brain natriuretic peptide proved capable of detecting myocardial depression and prognosing death with 60% sensitivity when levels are greater than 190 pg/mL (35).

**TREATMENT**

To date, the best treatment of this condition is proper management of the septic condition.

Theoretically, more specific measures such as the use of NOS inhibitors and anticytokine antibodies have shown discouraging results.

Immediate management of the patient in septic shock involves an aggressive fluid replacement to restore volemia relative to the vascular continent and allow adequate ventricular filling, slowly optimizing right atrial pressure and pulmonary artery occlusion pressure relative to the cardiac output and tissue extraction of oxygen. Frequently, suprannormal levels of pulmonary artery occlusion pressure are necessary (15–18 mmHg). There is no evidence in this situation that the use of colloids is superior to that of crystalloids.

The logical treatment sequence involves maintenance of tissue perfusion pressure, that is, arterial pressure. In this respect, the use of vasopressors is indicated. In an effort to improve the cardiac output and optimize splanchnic perfusion, inotropic agents are added. Dobutamine represents the natural
inotropic drug to maximize heart function. Despite its great potential of maximizing cardiac output, myocardial oxygen consumption may actually increase. Levosimendan, a calcium sensitizer, may in fact reduce this effect while decreasing systemic vascular resistance indices. The latter may decrease MAP to undesirable levels (38, 39).

REFERENCES