Cardiovascular Dysfunction in Sepsis and Critical Illness

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• Echocardiography • SIRS • Systolic dysfunction
• Myocardial depressant factor

Sepsis, trauma, major surgery, and other noninfectious conditions including autoimmune disease, vasculitis, thromboembolism, and burns can illicit severe, and often uncontrolled, activation of the immune system and mediator cells. Complex and still poorly understood cellular interactions can commence provoking a systemic inflammatory response syndrome (SIRS) with clinical features of tachypnea, hypothermia or hyperthermia, leukocytosis, myocardial dysfunction and hypotension that is hyporesponsive to pressors. Recent evidence also suggests that, as sepsis persists, there is a shift toward an immunosuppressive state.[1] Although there are numerous causes for induction of SIRS, all of which may share common pathways, sepsis is the most thoroughly investigated, principally because it is a leading cause of death in critically ill patients. Sepsis accounts annually for at least 210,000 human deaths in the United States, with a reported mortality as high as 30% to 50%.[1] More striking is that in the 40% of patients who experience myocardial dysfunction as a complication of sepsis, the mortality rises to 70% to 90%.[2] Data for small numbers of cases suggest that myocardial dysfunction accompanies sepsis and SIRS in dogs and cats. However, because the data from small animals are minimal, the following discussion primarily focuses on mechanisms of myocardial dysfunction and potential therapeutic opportunities in humans.

CARDIAC PERFORMANCE IN SEPTIC SHOCK

Humans

Initial studies in humans suggested that the hallmark cardiovascular pattern in septic shock was a low-output, hypodynamic circulation that contributed to cold and clammy skin and a thready pulse with hypotension. However, these studies used central venous pressure as a measure of ventricular preload, as opposed to

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pulmonary capillary wedge pressure, and it is likely that many of the patients had inadequate left ventricular filling.[3] Later studies performed under adequate volume resuscitation found that hypotension was more likely the product of profound reduction in systemic vascular resistance, and the more typical cardiovascular pattern in septic patients was high cardiac output with an increased cardiac index.[4]

As advances in the use of radionuclide-gated blood pool scanning, catheter-derived thermodilution techniques, and echocardiography became commonplace, more accurate measures of ventricular performance and volume could be obtained. These techniques found that, despite normal cardiac output, patients with septic shock did experience myocardial dysfunction. The characteristic cardiac changes seen in survivors of septic shock consist of decreased left ventricular ejection fraction and increased end-diastolic and end-systolic volume indices within 24 hours of the onset of septic shock.[5] Patients experience a reduced post–fluid resuscitation left ventricular ejection fraction, ventricular dilation, and flattening of the Frank-Starling relationship compared with critically ill, nonseptic controls.[6] The myocardial depression is reversible in survivors, with ventricular size and function returning to normal within 7 to 10 days after the episode of septic shock.[5] Nonsurvivors lack the characteristic left ventricular dilation and decreased ejection fraction.[5] It is hypothesized that ventricular dilation may be a compensatory response; hence, in its absence, there is higher mortalitity.[3] Advances in echocardiographic techniques are also providing insight into additional factors, including diastolic dysfunction and myocardial compliance abnormalities that may contribute further to myocardial dysfunction in sepsis.

Dogs

Although canine models have provided valuable information into the mechanisms of cardiovascular dysfunction in sepsis and SIRS for decades, there is little information regarding its prevalence or prognosis with naturally occurring disease. Limitations for assessment and investigation of myocardial performance in dogs with critical illness include infrequent monitoring of cardiac output or pulmonary capillary wedge pressure via Swan-Ganz catheterization and difficulty assessing the load-independent function of the heart.

In 2006, Nelson and Thompson[7] reported a retrospective study of 16 dogs with left ventricular dysfunction associated with severe systemic illness. In this population, critical illness was defined as metabolic derangements that required intensive care to sustain life, and left ventricular systolic dysfunction was defined as a fractional shortening of less than 26% and/or an ejection fraction of less than 46%. Dogs with a left ventricular preejection period/ejection time ratio of more than 0.4 were also considered to have systolic dysfunction. The 2 most common diseases identified producing critical illness with left ventricular systolic dysfunction were sepsis ($n = 5$) and cancer ($n = 5$).[7] Twelve of the 16 dogs (75%) died or were euthanized within 15 days of hospital admission, with an average time until death of 3.6 days. Treatment regimens for the dogs varied considerably so comparison between survivors and nonsurvivors was not performed. The 4 dogs that were discharged had follow-up of 20 days, 3.5 months, 4 months, and 2 years. Longitudinal echocardiographic data were available only for a boxer dog with immune-mediated polyarthropathy, anemia, and hyperglobulinemia that was still alive 2 years after hospitalization. The fractional shortening had risen from 21% at the time of hospitalization to 34% 2 years later, suggesting reversible myocardial depression. Dickinson and colleagues[8] subsequently reported reversible myocardial depression in a 5-month-old Rhodesian ridgeback with sepsis. At the time of hospitalization, the dog displayed an enlarged end-systolic volume index at 41 mL/m^2 that had decreased to 16.5 mL/m^2 3 months later. Recently,