Cardiac Function and Dysfunction in Sepsis

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KEYWORDS

• Cardiac dysfunction • Sepsis • Ventricular function • Hemodynamics • Echocardiography
• Troponin

KEY POINTS

- Cardiac function and dysfunction are important in the clinical outcomes of sepsis and septic shock.
- Cardiac dysfunction results from a variety of pathophysiologic, metabolic microvascular, functional, and anatomic derangements.
- Intrinsic cardiac function is greatly affected by extrinsic factors such as preload, afterload, and neurohumoral responses to sepsis.

INTRODUCTION

Cardiac dysfunction plays a pivotal role in the clinical outcomes of severe sepsis and septic shock. Myocardial depression was first described in 1984, and since then numerous studies have focused on further elucidating the mechanisms causing myocardial depression.[1,2] Although much remains unknown, cardiac dysfunction is not a single clinical entity but is a broad spectrum of syndromes with a multitude of pathophysiologic, metabolic, microvascular, functional, and anatomic derangements. The term septic cardiomyopathy has evolved to describe many of these conditions.[3,4] Further elucidation of the underlying pathophysiology has focused primarily on functional disturbances of the myocardium rather than anatomic abnormalities. However, recent evidence from both human studies and experimental models of sepsis shows that structural changes occur as well.[5–7] In addition, cardiac dysfunction in sepsis is a principal cause of morbidity and mortality in severe sepsis and septic shock; many therapies have focused on treating functional abnormalities, with only limited success. Furthermore, although the heart is the central component of the cardiovascular system, it is also affected by perturbations of the peripheral vascular system during sepsis. These changes in the peripheral vascular system have direct and indirect effects on the loading conditions of the myocardium. The cardiac response to alterations in preload, afterload, and the neurohumoral response during sepsis may be clinically indistinguishable from direct septic cardiotoxicity, which makes accurate diagnosis and treatment of cardiovascular failure during sepsis a highly complex task.

PATHOPHYSIOLOGY

Functional Abnormalities

The underlying pathophysiology of cardiac dysfunction in sepsis is caused by a myriad of genetic, molecular, metabolic, and structural mechanisms that are highly complex and may have both stand-alone unique contributions as well as highly complex intricate influences on each other. Although much is known, many of the pathophysiologic mechanisms are proposed and the full influence of each is yet to be elucidated.

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Genetics

The Human Genome Project and many others have sought to elucidate the genetic expression of specific diseases and syndromes. However, these important links exist only in animal models of sepsis in which there is a suggestion that inducible nitric oxide synthase (iNOS) deficiency may be cardioprotective.[8] Further research must be done to identify the linkage between genomics and sepsis-induced cardiac dysfunction.

Molecular

- Cytokines: activation of the immune system plays a key role in the pathogenesis of sepsis. The innate immune system essentially goes into overdrive with a production of proinflammatory mediators. Tumor necrosis factor alpha, interleukin (IL)-1beta, and IL-6 are considered to be the main mediators that cause cardiac dysfunction in sepsis and are considered to be direct myocardial depressants.[2]
- Nitric oxide (NO) is a widely recognized contributor in sepsis and causes the following:
  - Vasodilation, which in turn causes reduced preload, afterload, and cardiac perfusion. It may also serve as a myocardial depressant.[8,9]
  - Glutathione depletion, which leads to oxidative stress and mitochondrial dysfunction.[10]
- Calcium: intracellular calcium is a potent inotrope. Experimental models suggest calcium channel alterations, which reduce intracellular calcium and ultimately cause myocardial depression[11] (**Fig. 1**).
- Toll-like receptors (TLRs): critical to the initiation of the innate inflammatory response. TLRs recognize specific pathogen-associated patterns of bacterial and viral structures and nucleic acid composition.
- Endothelin-1 (ET-1) is known to play a role in myocardial contractility. In sepsis, ET-1 levels are increased in both the blood and myocardium. There is a suggestion that increased levels are associated with myocardial dysfunction.[12]

Metabolic

- Neurohumoral: early sepsis causes a catecholamine surge from the autonomic nervous system, gut, white blood cells, and macrophages, resulting in massive sympathetic response and stimulation of alpha-adrenergic and beta-adrenergic receptors. This adrenergic stimulation leads to a downregulation of catecholamine receptors, and ultimately catecholamine resistance.[13,14] Autonomic dysfunction is further exacerbated by glial and neuronal apoptosis in cardiovascular autonomic centers.[15]
- Mitochondrial dysfunction[9]: adequate ATP and oxygen delivery is essential for cardiac function. Several mitochondrial disturbances are proposed to play a significant role in cardiac dysfunction during sepsis:
  - Edema of the mitochondrial matrix, which may lead to functional impairment of cardiac myocytes.
  - Oxidative stress: increased superoxide (O_2^-) and NO production can cause direct oxidative damage or inhibition of oxidative phosphorylation, decreased mitochondrial membrane potential, and ultimately decreased oxygen consumption.
  - Altered membrane permeability: affecting the electron transport chain and impaired mitochondrial calcium handling, which may lead to mitochondrial calcium overload and impaired membrane permeability, which in turn, may contribute to cardiac mitochondrial contractile dysfunction.[16]
  - Mitochondrial uncoupling: ATP synthesis may be physiologically uncoupled from oxygen consumption whereby ATP is not synthesized in response to cardiac oxygen consumption.
  - Mitochondrial biogenesis: the process of mitochondrial growth and division may be impaired by a variety of mechanisms (eg, NO, oxidative stress) that occur during sepsis. Mitochondrial biogenesis is thought to be responsible for the reversal of organ damage in sepsis. However, it is possible that mitochondrial biogenesis may not be sufficient or that, alternatively, the newly produced mitochondria are dysfunctional.
  - Mitophagy: the removal of dysfunctional mitochondria via autophagy is important for organ recovery. Ideally, mitophagy and mitochondrial biogenesis should be balanced; however, mitophagy has been shown to be increased in various organs in sepsis (which is proposed to occur in the heart as well). However, decreased mitochondrial mass may occur if mitophagy exceeds mitochondrial biogenesis.

Structural Abnormalities

In addition to functional derangements, recent evidence suggests that structural abnormalities may play a role in the pathophysiology of cardiac dysfunction of sepsis. Increased serum levels of