

# Sepsis and Myocardial Dysfunction: A Mini Review



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## Abstract

Sepsis is one of the leading causes of mortality and morbidity around the world. Myocardial dysfunction is one of the important factors in the hemodynamic compromise seen in sepsis. Numerous mechanisms have been studied in identifying the pathophysiology, however, no definitive hypothesis has been proven. This review attempts to evaluate, and understand some of the known biochemical and pathophysiological mechanisms leading to cardiac dysfunction and sepsis.

## Introduction

Sepsis is the leading cause of mortality and a major healthcare concern worldwide [1]. It is characterized as a life-threatening disease, enhanced by a dysregulated immune host response to a precipitating infection. It's a multifaceted disease, encompassing various organs and may lead to end-organ failure, shock and death. In a healthy human being the pro-inflammatory response triggered by microbes is countered by the body's anti-inflammatory mechanism; however, during sepsis this mechanism gets dysregulated, leading to organ failure.

The association of sepsis and the cardiovascular system has been studied over a period of several decades; however, the exact pathophysiology remains unclear. Myocardial depression is defined as cardiac output that fails to meet the body's metabolic demands [2,3]. Approximately 15% of the deaths related to septic shock are due to myocardial depression [3].

## Myocardial Dysfunction Factors

### Global ischemia

In septic shock, there is a significant change in the microcirculatory system including peripheral vascular dysfunction, endothelial damage and induction of the coagulation cascade which can result in heterogeneous microcirculatory flow. Septic shock is a form of distributive shock, characterized by circulatory abnormalities that are usually related to intravascular volume depletion and

vasodilation, resulting in oxygen supply-demand mismatch and end-organ damage [4]. Studies in animal models showed that cardiac dysfunction occurs if the initial resuscitation is inadequate [5]. Therefore, earlier theories suggested that global myocardial ischemia could be responsible for myocardial dysfunction in sepsis. However, in 1986, Cunnion et al. [6] performed studies on coronary sinus catheterization, which demonstrated that coronary flow was the same or greater in early septic shock patients when compared to normal individuals. Therefore, the observed myocardial dysfunction associated with sepsis is not related to abnormal coronary blood flow and development of coronary ischemia, proving that global ischemia is not the reason for myocardial dysfunction in sepsis. However, it may still be true that abnormal coronary blood flow may play a role in myocardial dysfunction in patients with the pre-existing atherosclerotic disease.

### Endotoxins

Endotoxins are also believed to play a crucial role in causing cardiac dysfunction. They interact with the cell membrane receptor, known as Toll-like receptor4 (TLR-4) found in the cardiac immune cells. Endotoxins such as lipopolysaccharides (LPS), lipoteichoic acid, mannan in fungi, RNA in viruses interact with TLR-4 and initiate inflammation through mediators such as interleukins, cytokines, nitric oxide (NO), and C5 [7]. Although these inflammatory changes have

been clearly demonstrated in gram negative sepsis, there is minimal data in gram-positive sepsis. Thus, while endotoxins and inflammation may play a role, it is not the only cause of myocardial dysfunction in sepsis.

## Myocardial depressant factor

Myocardial depressant factors (MDF) are also believed to play a part in causing cardiac dysfunction in sepsis. In the mid-1970s, Lefer & Martin [8] highlighted the presence of an MDF in the blood of dogs during induced endotoxic shock and suggested that it was a peptide of 800 to 1,000 daltons that originated in the pancreas. Since then numerous MDF such as interleukins 1, and 6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), complement anaphylatoxin (C5a), High mobility group box 1(HMGB1), extracellular histones, matrix metalloproteinase-9 (MMP 9) have been identified and reported in the literature [9]. TNF- $\alpha$  and interleukins are considered to be the most important myocardial depressive factors. In an inflammatory state, TNF- $\alpha$  is usually released from the activated macrophages but, Horton et al showed that TNF- $\alpha$  is also released by the cardiac myocytes in response to sepsis [10]. Monoclonal antibodies directed against TNF- $\alpha$  are believed to improve the left ventricular function; however, they failed to improve survival in patients with sepsis [11,12]. IL-1 alters the cardiac contractility by stimulating the release of nitric oxide synthase (NOS) [13]. The roles of recombinant IL-1 receptor antagonist have been studied, but to date, it has failed to show statistically significant benefit in patients with sepsis [14].

Thus, a multitude of factors, rather than any individual factor are responsible for the onset of sepsis-induced myocardial dysfunction. More prospective studies are needed to elucidate their roles and provide a substrate for future therapeutic interventions.

## Treatment

Cardiac dysfunction in sepsis is believed to be multifactorial; therefore it is vital to identify individual receptors and molecules, so as to develop targeted therapeutic agents. Currently, supportive measures including intravenous crystalloid infusion, broad-spectrum antibiotics, surgical intervention if required to remove the septic foci, and close monitoring in an intensive care unit are the mainstay of treatment. As per the recent surviving sepsis guidelines, aggressive intravenous hydration with crystalloid solution of at least 30mL/kg should be given within the first 3 hours in patients with septic shock to maintain mean arterial pressure  $\geq$ 65mmhg and inotropic support be given to patients not responding to the initial aggressive hydration [15]. One should also be vigilant while administering intravenous fluids as the excessive fluid administration may lead to pulmonary edema due to increased permeability of the microcirculation and cardiac dysfunction, associated with sepsis.

## Conclusion

Prompt recognition of the source of sepsis is of prime importance. Treatment is mainly supportive comprising of aggressive hydration, inotropic support for patients in septic shock, broad spectrum antibiotics, and close monitoring of cardiac hemodynamics in an intensive care setting. A multidisciplinary approach should be maintained. We will need more prospective studies to understand the depth of interaction between sepsis and myocardial dysfunction.

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