

Overview of Pathogenic Mechanisms Involved in Sepsis

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Sepsis is identified as a systemic deleterious inflammatory response to infection or injury [1]. Very recently, the third international consensus definitions have been advocated for sepsis and septic shock. Thus, sepsis is now defined as life-threatening organ dysfunction that is caused by a dysregulated host response to infection [1-3]. Although sepsis has been defined as a systemic inflammatory syndrome, in which there is an identifiable focus of infection [2].

Sepsis is one of the most common reasons for critically ill patients to be admitted to an intensive care unit and, despite advances in overall medical care, it represents a major clinical problem and remains the leading cause of death in the critically ill patient population [2,4].

In sepsis, the immune response that is initiated by an invading pathogen fails to return to homeostasis, thus culminating in a pathological syndrome that is characterized by sustained excessive inflammation and immune suppression [1,3]. A better understanding of the molecular mechanisms involved in the pathogenesis of sepsis and its resultant organ failure has been sought and the development of therapies targeted at preventing or limiting molecular events associated with the progress of fatal organ failure, hence leading to improvement of outcomes [2,3]. Clinical trials aimed at anti-inflammatory therapeutic approaches have largely failed to identify an effective therapeutic target to improve clinical outcomes in sepsis [2,3]. Essential for the clinical development of new sepsis therapies is the selection of patients on the basis of biomarkers and functional defects that provide specific insights into the expression or activity of the therapeutic target [1,3].

Coagulation Factor XI (FXI) contributes to the pathobiology of sepsis-associated thrombosis and is a target for new therapeutics. Through cleavage of disulfide bonds, FXI becomes reduced (rFXI), accelerating intrinsic coagulation cascade activation. The role of rFXI in human sepsis has never been studied. Was determined levels of total FXI and rFXI in critically-ill septic patients with and without overt disseminated intravascular coagulation (DIC) [2,3,5].

In addition, sepsis induces a wide range of effects on the red blood cell (RBC). Some of the effects including altered metabolism and decreased 2,3-bisphosphoglycerate are preventable with appropriate treatment, whereas others, including decreased erythrocyte deformability and redistribution of membrane phospholipids, appear to be permanent and factors in RBC clearance. The effects of sepsis on the erythrocyte, including changes in RBC volume, metabolism and hemoglobin's affinity for oxygen, morphology, antioxidant status, homeostasis, RBC deformability (an early indicator of sepsis), intracellular Ca^{2+} , membrane phospholipid redistribution, membrane proteins, clearance and RBC O_2 -dependent adenosine triphosphate efflux. In future, a better understanding of the mechanisms involved in sepsis induced erythrocyte pathophysiology and clearance may guide improved sepsis treatments. Evidence that small molecule antioxidants protect the erythrocyte from loss of deformability and more importantly improve septic patient outcome suggest further research in this area is warranted. While not generally considered a critical factor in sepsis, erythrocytes appear to be highly susceptible to sepsis induced injury, provide an early warning signal of sepsis and are a factor in the microvascular dysfunction that has been associated with organ dysfunction [6] (Figure 1).

Sepsis induced myocardial dysfunction increases mortality in sepsis, yet the underlying mechanism is unclear [7]. Brain-derived neurotrophic factor (BDNF) has been found to enhance cardiomyocyte function. BDNF was expressed in primary cardiomyocytes, and its expression was significantly reduced after sepsis. Supplementation with recombinant BDNF protein (rhBDNF) enhanced myocardial BDNF and increased survival rate with improved cardiac function, myocardial apoptosis and reduced oxidative stress, which were associated with increased eNOS expression, Trk-B, a BDNF receptor, NO production. It is concluded that BDNF protects the heart against septic cardiac dysfunction by reducing oxidative stress and apoptosis via Trk-B and it does so through activation of eNOS/NO pathway. These findings provide a new treatment strategy for sepsis-induced myocardial dysfunction [7].

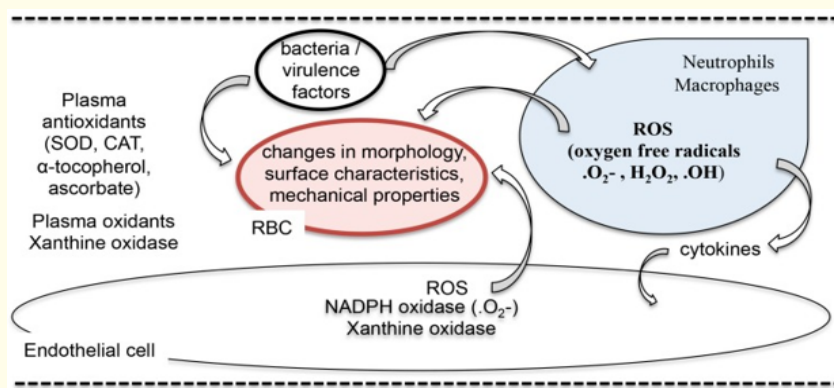


Figure 1: Microvascular dysfunction in sepsis induces a wide range of effects on the red blood cell (RBC) [6].

Recently, scattered foci of disruptions in the actin-myosin contractile apparatus were described in septic human hearts [8]. Also, has been studied calcium flux and cardiomyofilaments. There is now increasing evidence that sepsis induces significant alterations in the myocardial calcium homeostasis in two ways. First, abnormalities in the myocardial calcium current have been described in endotoxemic guinea pigs [9], as well as in cultured rodent cardiomyocytes exposed to the cardiodepressive IL-1β [10]. In line with these findings, myocardial L-type calcium channels have been found to be decreased during endotoxemia [11]. Second, a reduction in myofilament calcium sensitivity has been reported in endotoxemic rabbits [12,13]. The exact mechanisms of these observations are only partially understood, but the decreased response of myofilaments to calcium may be involved in the impaired myocardial contractility and depression of systolic function in septic patients [14]. Moreover, myocardial Ca²⁺ transport across membranes of the sarcoplasmic reticulum (SR) plays a central role in cardiac contraction-relaxation sequence (Figure 2) [14].

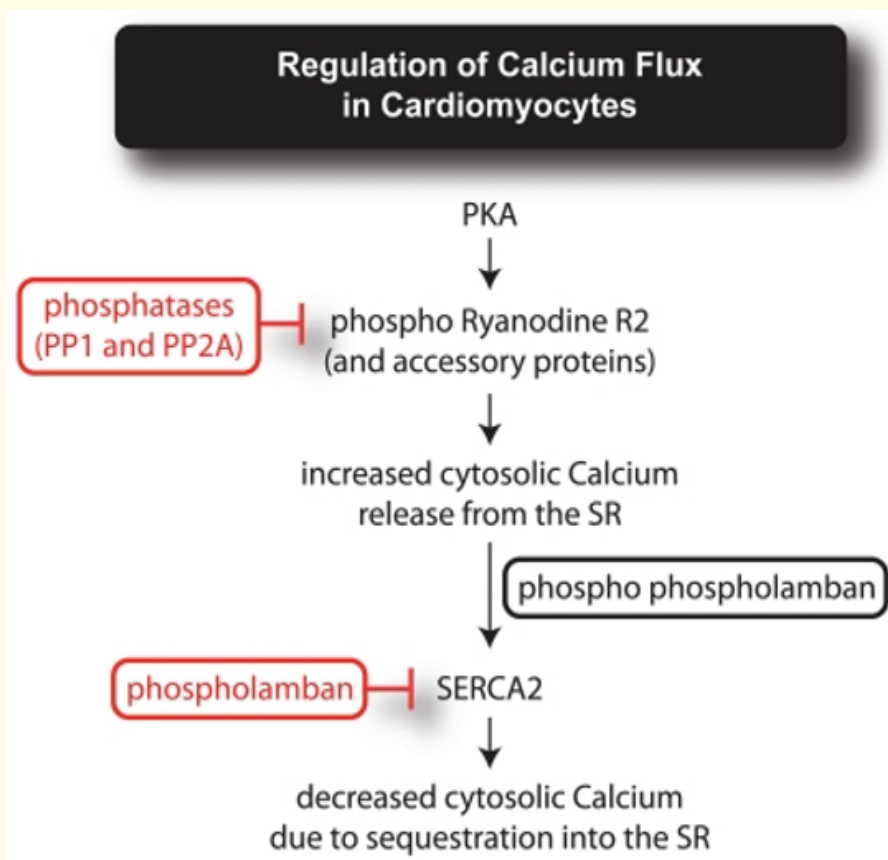


Figure 2: Physiologic regulation of calcium flux in cardiomyocytes [14].

This review article provides an overview of pathogenic mechanisms involved in sepsis, underlying the development of multiple organ dysfunction in sepsis and also, understanding of the molecular mechanisms involved in the pathogenesis of sepsis and its resultant organ failure. It has been sought the development of therapies targeted to prevent or limit molecular events associated with the progress of fatal organ failure [15,16].

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