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How to protect the heart in septic shock: A hypothesis on the pathophysiology and treatment of septic heart failure

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SUMMARY

Heart failure is a well-recognized manifestation of organ failure in sepsis and septic shock. The pathophysiology of septic heart failure is complex and currently believed to involve several mechanisms. So far, the contributory role of high plasma catecholamine levels has not been investigated. In this manuscript, we present a hypothesis suggesting that excessive catecholamine production and exogenous administration of catecholamines may relevantly contribute to the development of heart failure and cardiovascular collapse in patients suffering from septic shock. Substantially elevated plasma catecholamine levels were measured during critical illness and sepsis or septic shock. There is a growing body of clinical and experimental evidence demonstrating that high catecholamine plasma levels exert direct toxic effects on the heart. The pathophysiologic mechanisms involved in catecholamine-induced cardiomyocyte toxicity may involve a combination of inflammation, oxidative stress, and abnormal calcium handling resulting in myocardial stunning, apoptosis and necrosis. Clinical signs of catecholamine-induced heart failure can present with a wide range of symptoms reaching from subtle histological changes with preserved myocardial pump function to severe heart failure exhibiting a distinctive echocardiographic pattern which became known as "Takotsubo"-like cardiomyopathy or the left ventricular apical ballooning syndrome. In a medical intensive care unit patient population, presence of sepsis was the only variable associated with the development of left ventricular apical ballooning. Since several therapeutic interventions influence catecholamine plasma levels in septic shock patients, treatment strategies aiming at the reduction of endogenous or exogenous catecholamine exposure may protect the heart during septic shock and could facilitate patient survival.

Introduction

Severe sepsis and septic shock are the most serious presentations of systemic infection; despite of ongoing scientific and wide-ranging therapeutic efforts both syndromes are still associated with an unacceptably high mortality rate [1]. Heart failure is a well-recognized manifestation of organ failure in sepsis and septic shock [2]. While variable degrees of echocardiographic abnormalities have been reported in over half of all patients presenting with septic shock [3,4], a cardiogenic shock-like circulatory pattern was described in 10–20% of patients suffering from severe sepsis. The degree of septic heart failure relates to the severity of illness and has been associated with increased mortality [2]. In a post-mortem analysis, macroscopic pathologies of the heart were observed in half of the patients succumbing to severe sepsis or septic shock. Non-occlusive myocardial ischemia was the most frequent cardiac pathology suggesting that a mismatch of oxygen delivery and consumption in patients with severe sepsis or septic shock is frequent [5].

The pathophysiology of septic heart failure is complex and currently believed to involve several mechanisms which are summarized in Table 1 [6]. So far, the contributory role of high plasma catecholamine levels to the development of heart failure in patients with severe sepsis or septic shock has not yet been investigated.

The hypothesis

We hypothesize that excessive catecholamine production and exogenous administration of catecholamines relevantly contribute to the development of heart failure and cardiovascular collapse in septic shock patients. In this manuscript, we present a hypothesis

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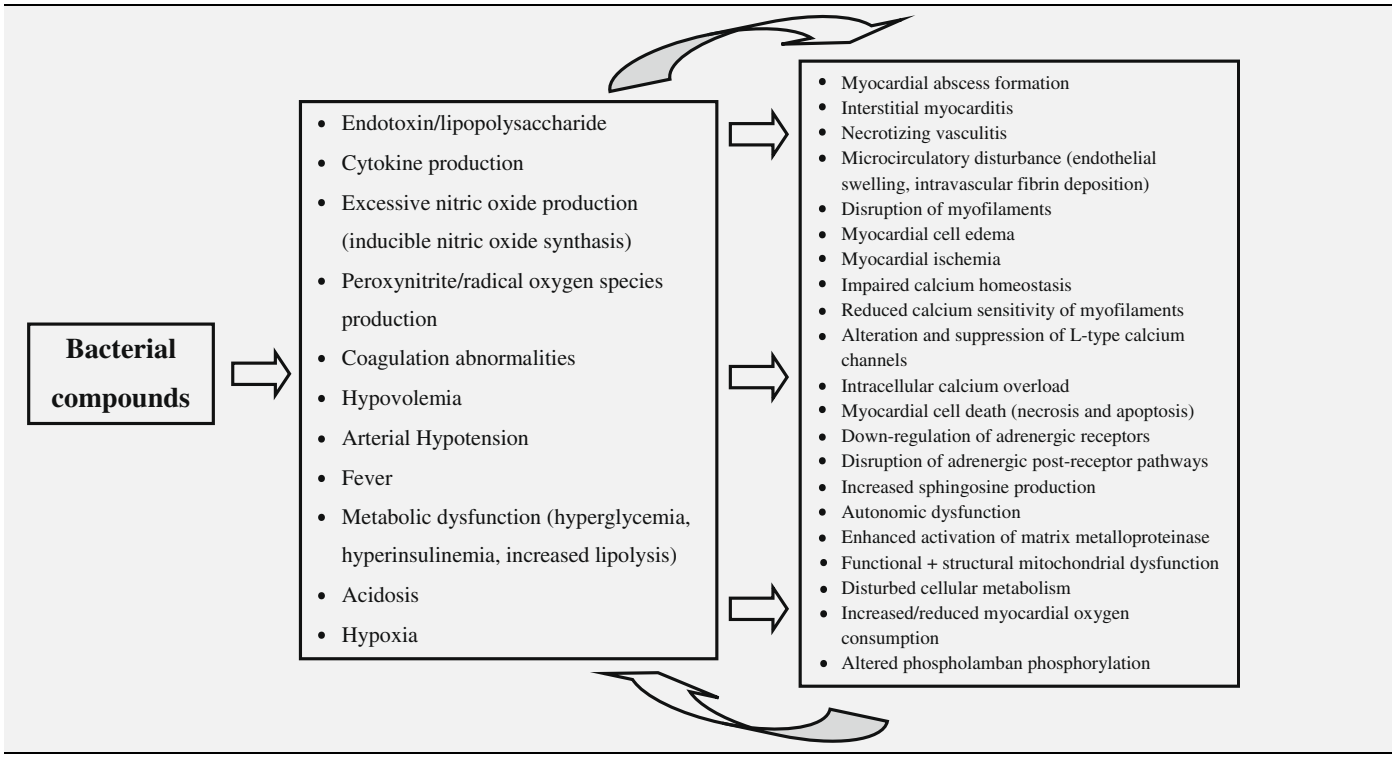
Table 1
Pathogenetic mechanisms currently believed to underlie sepsis-induced heart failure (Lit Rudiger CCM 2007).



regarding the pathophysiologic myocardial events associated with excessive catecholamine exposure and propose a treatment algorithm which may attenuate catecholamine toxicity to the heart.

Evaluation of the hypothesis

Fig. 1 schematically summarizes main pathways which could be involved in the pathophysiology of septic heart failure due to catecholamine toxicity. Arterial hypotension, severe hypovolemia, overwhelming inflammation and systemic activation of the coagulation system during septic shock result in massive stimulation of the sympathoadrenergic system in a physiologic attempt to maintain vital organ perfusion [7]. Even after adequate fluid resuscitation, septic shock patients remain dependent on exogenously administered catecholamines to stabilize hemodynamic function [1]. Therefore, it must be assumed that the heart is exposed to excessive catecholamine concentrations for extended time periods, a condition usually not associated with normal life. Catecholamine toxicity inducing myocardial inflammation, ischemia, cytosolic calcium-overload, hyperglycemia and excessive lipolysis with carbohydrate and free fatty acid accumulation in myocardial cells may end up in mitochondrial dysfunction, myocardial cell necrosis and apoptosis resulting in heart failure.

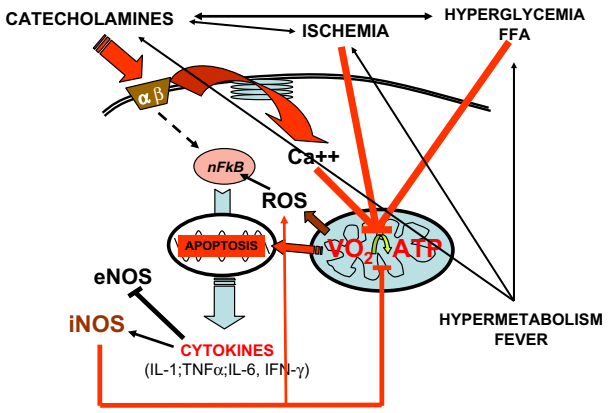


Fig. 1. Main pathways which could be involved in the pathogenesis of septic heart failure due to catecholamine toxicity. FFA, free fatty acids; nFkB, nuclear factor-kappa B; Ca^{++}, calcium; ROS, reactive oxygen species; VO_2, oxygen uptake; ATP, adenosine triphosphate; eNOS, constitutive nitric oxide synthesis; iNOS, inducible nitric oxide synthesis; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

Evidence for excessive activation of the sympathoadrenergic system during critical illness

During septic shock, activation of the sympathoadrenergic system occurs already at an early stage of the disease. In patients with sepsis and evolving shock, a generalized increase in vascular conductivity due to overproduction of vasodilatory mediators, e.g. nitric oxide, is a pathophysiologic hallmark of the disease [1]. At the same time, endothelial dysfunction and leakage result in interstitial fluid loss and subsequently intravascular hypovolemia. Both events rapidly lead to a decline in central blood volume thus reducing ventricular filling and stroke volume [1]. Subtle decreases in arterial and venous blood pressure as well as the magnitude of arterial pulse pressure are sensed by specialized baroreceptors within the arterial and venous system activating the sympathoadrenergic system to maintain systemic perfusion pressure within physiologic ranges [8]. In addition, pressure homeostasis is preserved by the hypothalamo-pituitary-adrenal axis responsible for the release of steroid hormones from the adrenal glands and the hypothalamo-neuropituitary axis controlling vasopressin secretion [9]. Cortisol exerts a "permissive effect" on the responsiveness of the cardiovascular system to catecholamines which has been