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Review

Cardiovascular dysfunction in sepsis at the dawn of emerging mediators

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ABSTRACT

Subcellular dysfunction and impaired metabolism derived from the complex interaction of cytokines and mediators with cellular involvement are on the basis of the cardiovascular response to sepsis. The lethal consequences of an infection are intimately related to its ability to spread to other organ sites and the immune system of the host. About one century ago, William Osler (1849–1919), a Canadian physician, remarkably defined the sequelae of the host response in sepsis: "*except on few occasions, the patient appears to die from the body's response to infection rather than from it.*" Cardiac dysfunction has received considerable attention to explain the heart failure in patients progressing from infection to sepsis, but our understanding of the processes remains limited. In fact, most concepts are linked to a mechanical concept of the sarcomeric structure, and physiological data seems to be often disconnected. Cytokines, prostanoids, and nitric oxide release are high direct impact factors, but coronary circulation and cardiomyocyte physiology also play a prominent role in modulating the effects of monocyte adhesion and infiltration. Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) are involved in the host response. The identification of microRNAs, as well as the cyclic activation of the inflammatory cascade, has further added complexity to the scene. In this review, we delineate the current concepts of cellular dysfunction of the cardiomyocyte in the setting of sepsis and consider potential therapeutic strategies.

1. Introduction

In the last several centuries, going as far back as the Medieval Ages, infectious diseases and sepsis have been the most feared human diseases, killing millions of people over a short period. In 1665, the plague alone accounted for one-tenth of the population of London, while smallpox, cholera, and yellow fever have collectively shortened the lifespan of inhabitants in the Third World for several centuries [1]. The etiologic agent of the bubonic plague, *Yersinia pestis*, is a bacterium transmitted primarily by fleas and the plague itself has become popularized through non-scientific literature across countries and cultures. Moreover, parturition represented a great danger to the mother and baby, and puerperal sepsis was in the past the major cause of perinatal death in women living in the Western world [2,3]. An autopsy is often key in identifying the specific cause of death (Fig. 1), but also to address basic research questions and quality assurance policies. In response, policymakers and fiscal shareholders have recognized the need to address the growing problem of sepsis and its subsequent impact on healthcare expenses [4]. Both the infection itself, and an overwhelming host inflammatory response to infection play dynamic roles in the pathogenesis of sepsis. Table 1 outlines the current clinical criteria for the definition of sepsis. The prognostic outcome of sepsis results from a number of factors that may be preventable. Immune, hormonal, metabolic, bioenergetic and autonomic nervous systems all influence the host response. Myocardial injury in sepsis is mediated complexly by several factors that are being intensely investigated. Revisiting these mediators, both well-known and emerging, may provide insight towards future therapeutic approaches [5]. The purpose of the present review is to delineate current concepts regarding cardiomyocyte dysfunction in the setting of sepsis discussing well-known and emerging

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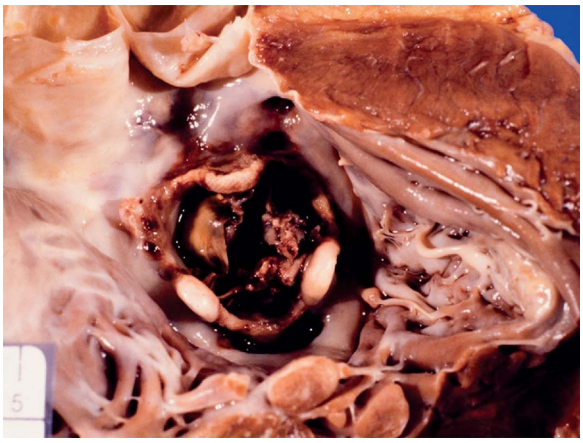

Fig. 1. Postmortem heart in a patient with infective endocarditis post mitral valve replacement. The bioprosthetic valve shows perforated leaflets with friable vegetations. At autopsy, the failing heart showed bilateral chamber dilation and flappy myocardium. Microscopic examination of valvular and perivalvular vegetation showed purulent exudates with numerous neutrophils and Gram-positive cocci (not shown).

Table 1
Current criteria for establishment of the diagnosis of systemic inflammatory response syndrome (SIRS), sepsis, and septic shock based and adapted from previous reports (mainly [22]).

SIRS: ≥2 of the following criteria:
1. Body temperature > 38.5 °C OR < 35.0 °C
2. Heart rate > 90 bpm
3. Respiratory rate > 20 breaths/min
4. P_aCO_2 < 32 mm Hg
5. Mechanical ventilation requirement
6. WBC count > 12 000/mm^3/ < 4000/mm^3 & immature WBC forms > 10%

Sepsis
1. SIRS with documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganisms; or focus of infection identified by visual inspection, e.g., ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)

Severe Sepsis: Sepsis plus ≥1 sign of organ hypo-perfusion or organ dysfunction:
1. Skin with areas of mottled appearance
2. Capillary refilling time ≥3 s
3. Urinary output < 0.5 mL/kg for ≥1 h or renal replacement therapy
4. Serum lactates > 2 mmol/L
5. Mental status showing an abrupt change or abnormal EEG
6. Platelet counts 100 000/mL or DIC
7. Acute lung injury- acute respiratory distress syndrome
8. Echocardiography-based diagnosis of cardiac dysfunction

Septic shock: Severe sepsis + ≥1 of the following
1. Systemic mean blood pressure < 60 mm Hg (or < 80 if previous hypertension was recorded) after 20–30 mL/kg starch or 40–60 mL/kg serum NaCl,
2. Pulmonary capillary wedge pressure with values between 12 and 20 mm Hg
3. Dopamine requirement of 5 g/kg/ min or NE/E 0.25 g/kg/min to maintain mean BP > 60 mmHg (or 80 mmHg if previous hypertension was recorded)

Refractory septic shock:
Dopamine requirement of 15 μg/kg/min or NE/E 0.25 g/kg/min to maintain mean BP > 60 mmHg (or > 80 mmHg if previous hypertension was recorded)

Notes: BP, blood pressure; DIC, disseminated intravascular coagulation; EEG, electroencephalogram; NE/E, norepinephrine/epinephrine; P_aCO_2, arterial carbon dioxide tension; WBC, white blood cells. In particular, serum lactate is considered a very sensitive marker for septic shock. Lactates are usually derived from tissue hypoxia and ischemic colitis and stenotic intestinal arteries may be predisposing factors for sepsis in the elderly. Increased lactate levels determine lactic acidosis, which depresses cardiac function and decreases the response of vasopressors [105]. The measurement of the volume of the left ventricle calculated from 3D echocardiography shows significantly better agreement with smaller bias, lower scatter, and lower intra- and inter-observer variability than 2-D echocardiography [106].

mediators. Cardiomyocytes are complex cells, although their complexity is not truly apparent under the light microscope [6–8]. The sarcomeric structure of cardiomyocytes is particularly unique if we consider the enormous workload that these cells are subjected to from the time of the first heart anlage and throughout adult life. Sarcomeric contraction is specifically regulated by two proteins, troponin-tropomyosin, which block and unblock the myosin-binding sites on actin [9]. Troponin organization, even using single particle reconstruction procedures may not necessarily capture the full understanding of the functional cell biology underlying protein interactions and calcium (Ca^{2+}) sensors modulation. Our understanding of cardiomyocyte cell biology is further complicated by the discovery of the microRNAs (miRNAs) [10]. Oncology has recognized roles of miRNAs in cancer and miRNAs are being investigated in the setting of mitochondrial abnormalities of cardiac illnesses [7,8,11–15]. Cardiomyopathies are a heterogeneous group of diseases characterized by impaired heart muscle function, and the genetics of cardiomyopathy is rapidly evolving [6–8,11,12,14,16–19]. Patients with cardiomyopathy who develop bacteremia and sepsis may be at high risk of further detriment due to an abnormal micro-environment with potential appearance of ischemic necrosis [20]. Over the last several years, the interest in mitochondrial cardiomyopathies has been sparked by some significant discoveries in molecular biology supporting the thesis that genetic factors may play a pivotal role in the pathogenesis of numerous cardiomyopathies [11,14]. The oxidative phosphorylation system (OXPHOS) is crucial for the microenvironment of the cardiomyocyte. Mitochondrial cardiomyopathy is a disease in which the clinical and pathological phenotypes result from mitochondrial diseases due to a pathogenic mutation in mitochondrial and/or nuclear genes causing defects in the OXPHOS system of the cardiac muscle [6,12,14,21].

Mechanisms underlying cardiac dysfunction likely act in a multifactorial fashion, but examining each pathogenic factor in isolation has the advantage to potentially identify future therapeutic approaches that target single or combined components of the syndromic spectrum of sepsis and septic shock [22]. Fig. 2 may summarize these underlying mechanisms, which were previously classified as either 'non-global ischemic' and 'global ischemic' using the old classification method based on the anatomic-pathologic basis. Here, we have reclassified the mechanisms of septic cardiovascular dysfunction as either 'high (direct)' and 'indirect impact factors' which incorporates both anatomic-pathologic concepts and physiological considerations.

2. Cytokines

The inflammatory cascade is central among the ischemic mechanisms of septic cardiovascular dysfunction. In particular, tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) have been thoroughly investigated [23–25]. To study the hemodynamic effects of septic shock, infusing lipopolysaccharide (LPS), an obligatory component of the cell walls of Gram-negative bacteria, into animals, has proven to be an important model. However, it does not seem that LPS alone is completely responsible for the myocardial depression observed in sepsis, due to the observation that only very few patients with septic shock experience detectable LPS levels in plasma [26]. The following studies have also highlighted TNF-α as a septic shock-linked cytokine. Activated macrophages are responsible for most of TNF-α production, but cardiomyocytes may also express TNF-α in response to infection [27]. Despite this interesting observation, exogenous administration of either anti-TNF-α antibodies or soluble TNF-α receptors failed to improve the left ventricular function in patients with septic shock [28]. The other interesting molecule is IL-1, which also plays an important role in the setting of septic shock. Synthesized by monocytes, macrophages, and neutrophilic granulocytes in response to TNF-α, IL-1plays a critical role in the host systemic immune response [29]. The synthesis of IL-1 occurs in association with NO synthase (NOS) stimulation, whose product depresses cardiac contractility [30]. In phase III clinical trials, recombinant IL-1-ra (receptor antagonist of IL-1) administration improves the survival of patients with septic shock, but this difference was not statistically significant [31]. Retrospectively, the clinical trials might have been underpowered, and a call of new randomized clinical