Pathophysiology of Septic Cardiomyopathy

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Septic cardiomyopathy may be broadly defined as an acute cardiac dysfunction unrelated to ischemia that manifests in different ways: arrhythmias, left and/or right ventricular impairment during systole or diastole, with or without reduction in cardiac output. Endothelial, metabolic, and immune response abnormalities are generally involved in the pathogenesis of ventricular dysfunction and arrhythmias during sepsis, whereas the potential role of myocardial ischemia seems limited. Impaired blood flow autoregulation in coronary microcirculation and altered metabolism of lactate, free fatty acid, and glucose likely play a leading role.

Keywords: sepsis ; septic shock ; cardiomyopathy ; inflammation

1. Inflammatory Pathways and Cardiomyocyte Dysfunction

The hyperinflammatory—not counterbalanced—response is historically reported as a paradigm of sepsis. Early clinical trials then focused on blunting inflammatory response by common anti-inflammatory drugs such as glucocorticoids, non-steroidal anti-inflammatory drugs or target therapy, with very limited results [1]. The extreme variability in pro-/anti-inflammatory balance and the wide number of molecular pathways may explain such disheartening results [2][3]. Ancestral signals released by pathogens (pathogen-associated molecular patterns, PAMPs) or by damaged host tissues (damage-associated molecular patterns, DAMPs) and receptors such as Toll-like receptors (TLRs) trigger multiple intracellular pathways, including the activation of nuclear factor-kB (NF-kB) and mitogen-activated protein kinase (MAPK) [4][5][6]. The DAMPs with a recognized role in the pathophysiology of septic cardiomyopathy include: heparan sulphate, which increases intranuclear transcription of pro-inflammatory cytokines and vascular permeability [7]; high mobility group protein B1, which induces loss of calcium from sarcoplasmic reticulum [8]; and histones, which are able to interfere with the production of cellular ATP by reducing mitochondrial membrane potential and causing LV dysfunction and arrhythmias [9]. Among PAMPs, bacterial lipopolysaccharide (LPS) partially mimics hemodynamic effects of septic shock when administered to animal models or humans [10][11]. Detrimental effects of endotoxemia on cardiac contractility are largely due to mitochondrial dysfunction that leads to abnormal calcium handling, disruption of ATP synthesis, endothelium reticulum stress, and autophagy. Furthermore, LPS leads to electrophysiological dysfunctions through a both a direct and cytokine-mediated effect on sodium current kinetics and non-selective cation channel transient receptor potential vanilloid 1 (TRPV1) [12][13][14][15]. Furthermore, LPS and its downstream mediator TNF-α, IL-1β, IL-6, and C5a and ROS [16][17] critically alter calcium (Ca^{++}) homeostasis by blunting the amplitude of intracellular currents and concentrations. Dysfunction of intracellular calcium transporters and decreased calcium sensitivity in cardiac myofilaments (due to phosphorylation of inhibitory troponin I) are cornerstones of the impaired excitation-contraction coupling. Ultimately, endotoxemia impairs sarcolemma diastolic Ca^{++} extrusion with consequent overload [18][19][20][21] that determines systolic and diastolic dysfunction during sepsis [22][23]. The characteristic delayed reversibility of septic cardiomyopathy might be explained by the synthesis of new myofilaments to replace the previously phosphorylated (and therefore inactive) ones.

Signals regulated by the TLRs expressed on myocyte surface (TLR2, TRL3, TLR4 and TLR9) lead to transcription of several pro-inflammatory cardiac depressive factors and cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α and complement anaphylatoxin C5a [24][25]. LV ejection fraction (LVEF) was found higher in septic mouse with TRL3 and TLR9 gene deletion, suggesting their role in the mechanism of sepsis-induced cardiac dysfunction [26]. Likewise, TLR4 regulates oxidative stress in ryanodine receptor 2 involved in the storage of calcium within sarcoplasmic reticulum of cardiomyocytes [27], and its inhibition showed protective effects [28]. C5a is so far the only complement factor with reported direct myocardial depressive effect, despite several cardiac enzymes related to cardiac dysfunction during sepsis, such as serca2, NCX and Na+/K+-atpase, which are complement receptor dependent [29]. Finally, adhesion molecules take part in homing mechanisms and are upregulated during inflammatory response. In murine coronary endothelium and cardiomyocytes, specific adhesion molecules were upregulated after LPS and TNF-α infusion. Moreover, the use of antibody blocking these molecules such as anti-Intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) showed to prevent myocardial neutrophil accumulation and cardiac dysfunction in animal

models of sepsis [30]. On the contrary, neutrophils depletion did not protect against myocardial dysfunction during sepsis, suggesting their lesser cardiotoxic potential.

Nitric oxide (NO) is synthesized by nitric oxide synthase (NOS) in different cells of the CV system including cardiac myocytes, and it exerts important roles in maintaining tissue homeostasis by reducing oxidative stress. Indeed, via the cGMP pathway, NO regulates vascular tone, has an antioxidant effect, inhibits leukocyte and platelet adhesion to the endothelium, and increases myocardial contractility [31]. Inflammation and oxidative stress show deep interplay, fueling each other and facilitating the onset of deleterious vicious circles in different diseases including sepsis. Differently from its endothelial and neuronal isoforms, inducible NOS (iNOS) is not constitutively active and when highly expressed is a major responsible for vasodilatation and hypotension in shock [32]. Indeed, iNOS can produce large amount of NO when an inflammatory response occurs [33]. Sepsis leads to overexpression of iNOS not only in immune cells but also in the myocardium [34]. Such increased expression has detrimental effects on contractile function of cardiomyocytes, in part through the paradoxical induction of reactive oxygen species (ROS), i.e., peroxynitrite [35], in part through the down-regulation of adrenaline receptors and decreased sensitivity to calcium [7]. Confirming the important role played by iNOS in myocardial dysfunction during sepsis, several non-specific anti-NOS drugs such as melatonin and methylene blue showed beneficial effects in terms of cardiovascular function and prognosis in preclinical studies [35][36].

2. Adrenergic System

Increased activation of the sympathetic system is a major compensatory reaction to septic-related vasoplegia. During sepsis, β-adrenergic receptors (βARs) are downregulated, and the responsiveness to catecholamines is reduced in the whole cardiovascular system [37][38]. When persistent, this adaptive response become maladaptive [39]. In myocardial tissue, excessive stimulation of cardiac βARs suppresses their expression and leads to an inhibitory response with reverse of adrenergic G protein coupling [40], intracellular calcium overload [41], increased production of ROS [42], disruption of membrane potential via the inhibition of Na+/K+-ATPase pump [43], and induction of apoptosis [44]. A relevant role is played by Cardiac G Protein-Coupled Receptor Kinase 2 (GRK2). They are the major negative regulators of βAR pro-contractile signal in sepsis-induced myocardial dysfunction [45] and other different cardiac diseases including chronic heart failure and Takotsubo syndrome [46].

3. Microvascular Dysfunction and Vasoactive Peptides

Activation of endothelial cells in consequence of an infective stimulus leads to the synthesis of inflammatory cytokines, increased expression of cell adhesion molecules, loss of the barrier function by glycocalyx shedding, edema, apoptosis, hypercoagulative state and vasoplegia [47]. Several endogenous vasoactive peptides generate and maintain endothelial dysregulation. LPS and cytokines up-regulate cyclooxygenase (COX)-2 (inducible form) and then the production of prostanoids from arachidonic acid. This process mainly occurs in inflammatory cells, myofibroblasts, endothelium and even in cardiomyocytes (i.e., in myocardial infarction) [48][49]. Elevated levels of prostanoids such as thromboxane and prostacyclin are associated with coronary microvascular dysfunction [50]. However, clinical trials have failed so far in proving any beneficial effect of pharmacological COX inhibition on coronary microvascular homeostasis in sepsis. Less is known about the potential role of endothelin-1 (ET-1) in sepsis cardiomyopathy, whereas an increase has been reported in chronic cardiac disease (i.e., heart failure) [51]. ET-1 would have a major role in infectious disease, as a promoter of cytokines release, platelet aggregation and vasoreactivity [52]. In single mouse study, cardiac overexpression of ET-1 was associated with the onset of severe sepsis cardiomyopathy, characterized by interstitial infiltration of macrophages and T lymphocytes and increased levels of the pro-inflammatory cytokines TNF-α, INF-γ, IL-1, and IL-6 [53].

4. Energetic Dysmetabolism

Sepsis is characterized by altered myocardial lipoprotein metabolism and mobilization of triglycerides and free fatty acids to overwhelm the systemic suppression of energy production [54]. Physiologically, about 70% of cardiac ATP is produced via lipid oxidation, while the rest is produced via glucose oxidation. A minor part also derives from the catabolism of lactate and ketone bodies. Under pathological conditions, glucose oxidation becomes the prevalent energetic pathway [55]. During sepsis, a reduction in fatty acid oxidation is not compensated by the increase in glucose catabolism due to altered insulin action, exacerbation of the inhibitory effects of alternative substrates on glycolysis, and blunted glycogen synthesis [56]. Several enzymes involved in intracellular cardiac fatty acid mobilization and oxidation are also inhibited [57][58]. Cardiac transcriptional factors associated with fatty acid oxidation, such as peroxisome proliferator activated receptors (PPARs) are also suppressed in sepsis and their stimulation with PPARs agonists lead to improved survival in septic mice [59]. Mitochondrial dysfunction further contributes to the energetic failure in sepsis cardiomyopathy, thus being a non-negligible

cause of reduced outcome [60][61][62]. Inflammation and oxidative stress alter mitochondrial structure determining swelling, cytoplasmic accumulation of denatured protein and lysosomal lesions [63][64]. Such a damage interferes with the respiratory chain [65] with falling in ATP synthesis, release of calcium and pro-apoptotic proteins [66]. The pro-oxidant environment induced by endotoxemia also trigger cardiac mitophagy, a defensive mechanism for the removal of damaged mitochondria [67]. The antioxidant N-acetylcysteine seems to have a protective roles against contractile dysfunction and mitophagy. Even levosimendam in both mice and human beings has beneficial effects due to calcium sensitization and antioxidant properties [68]. Lastly, when the degree of mitochondrial dysfunction is mild, myocardial hibernation may occur. This is an adaptive, self-protective mechanism during which all functions get reduced. Such a downregulation of mitochondrial gene transcription has been reported in sepsis cardiomyopathy [69] and represents a reversible condition that improves together with the resolution of sepsis [62].

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