

Pathophysiology of Sepsis-Related Cardiac Dysfunction: Driven by Inflammation, Energy Mismanagement, or Both?

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Abstract Sepsis is a systemic inflammatory response that follows bacterial infection. Cardiac dysfunction is an important consequence of sepsis that affects mortality and has been attributed to either elevated inflammation or suppression of both fatty acid and glucose oxidation and eventual ATP

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depletion. Moreover, cardiac adrenergic signaling is compromised in septic patients and this aggravates further heart function. While anti-inflammatory therapies are important for the treatment of the disease, administration of anti-inflammatory drugs did not improve survival in septic patients. This review article summarizes findings on inflammatory and other mechanisms that are triggered in sepsis and affect cardiac function and mortality. Particularly, it focuses on the effects of the disease in metabolic pathways, as well as in adrenergic signaling and the potential interplay of the latter with inflammation. It is suggested that therapeutic approaches should include combination of anti-inflammatory treatments, stimulation of energy production, and restoration of adrenergic signaling in the heart.

Keywords Sepsis · Heart · Metabolism · Fatty acid oxidation · Adrenergic signaling · Inflammation

Introduction

This review article aims to summarize the effects of sepsis on cardiac function, particularly on cardiac metabolism and adrenergic signaling. Specifically, it aims to describe sepsis-driven suppression of cardiac metabolism and energy production, as well as to indicate the relative contribution of cardiac adrenergic signaling inhibition in heart dysfunction that occurs in septic patients and animal models of sepsis.

Sepsis: an “Inflam-Metabolic” Disease

Sepsis is defined as a systemic inflammatory response. It follows bacterial infection and can lead to severe sepsis and septic shock characterized by hypotension, ischemia, multiple organ failure, and death. Sepsis is a major health complication causing patient mortality and increased health care cost [1].

Approximately 1 million cases are reported annually in the USA and about 50 % of patients with sepsis require intensive care unit (ICU) treatment. Sepsis is responsible for 10 % of all ICU admissions [1, 2]. The incidence of sepsis is expected to increase due to a higher incidence of severe sepsis in older patients, an increased number of people living with chronic diseases and therapies aiming to suppress the native immune system [2].

The exuberant septic inflammatory response in the organism is complicated by secondary end organ damage. In particular, cardiovascular derangements such as decreased peripheral resistance and increased vascular permeability leading to tissue hypoperfusion are of clinical importance in the therapeutic approach of sepsis. Feared complications in severe sepsis and septic shock are multiorgan failure (MOF) and hemostatic derangements leading to disseminated intravascular coagulation (DIC).

Cardiac dysfunction is a consequence of severe sepsis [3–5] and is characterized by impaired contractility [6], diastolic dysfunction, as well as reduced cardiac index and ejection fraction (EF) [7]. Cardiac dysfunction is an important component of multiorgan failure that is caused by severe sepsis [8, 9]. Septic patients with either systolic or diastolic dysfunction or a combination of both have higher mortality than those diagnosed with sepsis but without diastolic or systolic dysfunction [10]. The mechanisms that underlie myocardial depression during septic shock are not well known. Circulating inflammatory cytokines interleukin (IL)-1 [11, 12], IL-8 [12], and tumor necrosis factor (TNF) α [11, 13], which are increased during septic shock, may account for cardiac dysfunction as they have been associated with altered production of nitric oxide [14–16] and altered calcium homeostasis [17, 18]. Impaired β -adrenergic signaling leading to reduced cardiac contractility is also present in sepsis [19]. Moreover, growing evidence associates septic cardiac dysfunction with impaired metabolism and reduced energy production in cardiomyocytes. The heart produces ATP primarily via fatty acid and glucose oxidation, which both are strongly decreased in experimental animal models of sepsis [20, 21]. Despite reduced cardiac lipid uptake, sepsis leads to intracellular lipid accumulation. Lipid accumulation must therefore result from impaired fatty acid oxidation [21, 22] and conversion of non-oxidized fatty acids into triglycerides.

There are several experimental models [23] that mimic the effects of sepsis. The most common setup includes injection of *Escherichia coli* lipopolysaccharide (LPS), which is a component of the bacterial cell wall. LPS induces profound inflammation and pathophysiological consequences similar to those found during septic shock. In addition, sepsis can be induced experimentally by cecal ligation and puncture (CLP) or bacterial infusion. Less frequently used sepsis experimental models are based on injection of TNF α or IL-1.

Clinical Facts About Sepsis

Clinical treatment of sepsis is complex with a high mortality of 20–50 % requiring intensive medical treatment. For stage-adapted treatment and estimation of mortality risk, several scoring systems are in use, with the APACHE-II Score (as an outcome score) and the SOFA score (severity of multiorgan failure) among them.

Optimization of management of sepsis is intensively investigated. Cornerstones of the guideline-directed therapy of sepsis are immediate initial volume resuscitation and the identification of the source and causative pathogen allowing a test-appropriate antibiotic therapy, with an initial empiric antibiotic regimen within the first hour after diagnosis. Furthermore, optimization of organ perfusion and tissue oxygen supply are important measures for the management of the septic patient in the intensive care setting.

The high incidence and unsatisfactory therapeutic outcome of sepsis call for new therapeutic approaches and a large number of potential therapies are currently investigated. Among those, strategies to inactivate or remove cytokines and endotoxins by hemabsorption [24] or measures aiming at immunomodulation showed promising results. Immunotherapeutic approaches include administration of interferon (IFN)- γ [25], GM-CSF [26], or IL-7 [27].

Inflammation: a Potential Driving Force of Septic Cardiac Dysfunction

The inflammatory component of the pathophysiology of sepsis is complex, involving the activation of plasmatic (complement activation, coagulation) and cellular (macrophagic, endothelial, thrombocytic, cellular immunity) systems. The innate immune response leads to a strong activation of the cytokine system [28], which has plethoric effects on a variety of organs and the vasculature, leading to changes in vascular permeability, endothelial function, and activation of further mediators such as bradykinin, histamine, the complement, and coagulation system. Cytokines play an important role in the pathology of sepsis: pro-inflammatory mediators such as TNF α , IL-1, IL-6, IL-8, IL-12, and IFN- γ are counteracted by anti-inflammatory cytokines (IL-10, TGF-beta, IL-4) [28]. However, controversies have developed over the role of cytokines as primary target for new therapeutic approaches since a large number of clinical trials investigating anti-inflammatory agents failed [29]. On the other hand, in the process of the disease, a secondary or simultaneously occurring [29] phase of prolonged sepsis-induced immunosuppression can be observed, which further illustrates the complexity of the disease [30, 31].

The production of inflammatory response-related cytokines, such as TNF α and interleukins IL-1 and IL-8, follows association of LPS with plasma LPS-binding protein (LBP).

This complex targets CD-14 and TLR4 receptors and turns on signaling mechanisms that finally result in the production of cytokines. LPS-mediated signaling starts from the cytoplasmic portion of TLR4 that is called Toll/IL-1 receptor (TIR) domain and is mediated by several intracellular proteins such as MyD88, IRAK-1, IRAK-4, TNF receptor-associated factor (TRAF)-6, TGF- β -activated kinase 1 (TAK1), TAK1-binding proteins, TAB1, and TAB2. TAK1 phosphorylates either the IKK complex, which leads to activation of the NF- κ B pathway, or the MKK7 that activates the c-Jun N-terminal kinase (JNK) signaling pathway [32]. Nevertheless, NF- κ B [33] and JNK [34, 35] are well-established targets of LPS stimulus and they induce production of inflammatory response-related cytokines, such as TNF α and IL-1.

TNF α production by macrophages is increased during sepsis and has been considered as a potential target for experimental and clinical therapeutics. Indeed, genetic ablation of TNF receptor 1 (TNFr1 $^{-/-}$) prolonged survival in mice that underwent polymicrobial sepsis with CLP [36]. Accordingly, treatment of BALB/C mice with anti-TNF α antibodies prior to administration of LPS improved survival rate [37]. Interventions aiming to inhibit the TNF α pathway seem to be effective in preventing morbidity and mortality in non-human primates, as well. Treatment of baboons with anti-TNF α antibody that was given either simultaneously or 2 h prior to administration of live *E. coli* reduced release of cytokines such as IL-1, IL-8, and monocyte chemoattractant peptide-1 (MCP-1) [38, 39] and offered complete protection against vital organ dysfunction, stress hormone release, and death [40]. Although anti-TNF α treatment was successful in preventing inflammatory response and improving survival in septic animal models, the use of either anti-TNF α antibodies [41, 42] or soluble TNFr [43, 44] that neutralize circulating TNF α failed to attenuate mortality in septic patients. The discrepancy in efficiency between animal and human studies may pertain to the pretreatment or early treatment of animals with anti-TNF α as opposed to septic patients that received anti-TNF α treatment much later during the progression of the disease. Nevertheless, pretreatment with anti-TNF α reduces the levels of TNF α and IL-8 [39] and attenuates the TNF α -driven effects of sepsis. This suggests that other non-TNF-mediated processes cause much of the mortality in humans.

IL-1 is produced by macrophages, monocytes, and neutrophils in response to TNF α and ignites iNOS production [45], which suppresses cardiac contractility [46]. Human genetic polymorphisms that are associated with reduced levels of IL-1 receptor antagonist (IL-1ra), i.e., enhanced IL-1 signaling, have been associated with increased septic mortality [47]. Thus, IL-1 signaling has been indicated as a potential therapeutic target for treatment of septic patients. This hypothesis was supported by studies in animal models that associated inhibition of IL-1 with improved response in sepsis. Pretreatment of rabbits with IL-1ra resulted in smaller mean arterial

pressure decrease and less TNF α and IL-1 increase, following *Staphylococcus epidermidis* injection [48]. Treatment of mice with combination of IL-1ra and TNFr, which neutralizes circulating TNF α , improved survival following sepsis induction by either LPS administration or CLP [49]. Despite these remarkable protective effects of IL-1 signaling inhibition in the cardiovascular system and survival in sepsis animal models, treatment of septic patients with IL-1ra did not incur any significant improvement [50].

The lack of success of anti-inflammatory therapies in septic patients, such as administration of corticosteroids [51–53], IL-1 receptor antagonist [50, 54], or anti-TNF α [55], despite the significant improvement in cardiac function or survival of septic animal models may be attributed to a number of reasons. Due to advances in intensive medical care, patients survive the initial hyperinflammatory phase, progressing to the fatal state of sepsis-induced immunosuppression. Consequently, recent efforts focus on host innate and adaptive immunity such as T cell exhaustion in sepsis [56] and other mechanisms of cell-mediated immunity [29, 57–59]. Moreover, species differences or the way that anti-inflammatory interventions were applied in animals may explain the failure of anti-inflammatory therapies in septic patients. Most of the animal studies were based on the use of either knockout and transgenic mice or administration of anti-inflammatory treatments prior to or simultaneously with experimental induction of sepsis. This design indicated the importance of the prevention of inflammation as a therapeutic approach in the development of sepsis and subsequent organ dysfunction. As opposed to the animal models, anti-inflammatory treatments were applied in septic patients after diagnosis of the disease, when inflammation and organ failure were already in progress. Other components of the pathophysiology of sepsis, such as energetic starvation of the heart and other organs, might occur later during sepsis and that likely were not corrected with the anti-inflammatory treatments.

Complications of Cardiac β -Adrenergic Signaling in Sepsis

Impaired β -adrenergic signaling is another component of septic cardiac dysfunction and may be due to the pro-inflammatory NF- κ B signaling. Cardiac β_1 - and β_2 -adrenergic receptors (β ARs) are the main stimulatory receptors of cardiac function with distinct and in some cases opposite roles in cardiac physiology and pathology [60–63]. For instance, cardiomyocyte contraction is stimulated by β_1 ARs but not β_2 ARs. Cardiac β_1 AR signaling is generally considered pro-apoptotic via its cAMP signaling pathway that activates both protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac). Conversely, β_2 AR signaling is anti-apoptotic (Fig. 1) [60–63]. The inhibitory effect of cardiac β_2 AR in apoptosis is mediated by this subtype's signal switching from G_s to $G_{i/o}$ protein-mediated, which is a feature

that cardiac β_1 ARs lack [64–68]. Furthermore, upon agonist-mediated activation and GRK2-mediated phosphorylation β_1 AR does not readily bind the receptor adapter proteins beta-arrestins (β arrs) following its phosphorylation by G protein-coupled receptor kinases (GRKs) [69–71]. Finally, the interaction of β_2 AR with β arrs can have pleiotropic effects in cardiac myocytes, such as inhibition of apoptosis and promotion of survival via PI3K activation [64] and NF- κ B inhibition (Fig. 1) [72–74].

Early stages of sepsis are characterized by elevated catecholamine levels [75–77], which most likely constitute a compensatory adrenergic response aiming to augment cardiac contractility and heart rate [78, 79]. However, this adaptive response ultimately becomes maladaptive as excessive stimulation of cardiac β ARs and particularly of the pro-apoptotic β_1 AR cause myocardial damage due to intracellular calcium overload and induction of cell death. The sympathetic overstimulation in critically ill patients—the so-called catecholaminergic storm—is detrimental for the heart in the long run as it can lead to impaired diastolic function, tachycardia and tachyarrhythmias, myocardial ischemia, stunning, apoptosis, and necrosis [80]. In addition, the progression of septic cardiac dysfunction is associated with reduced β AR density [81], and there is evidence for significant cardiac desensitization and

downregulation of β ARs potentially caused by cytokines [82]. These changes have been observed in the myocardium of patients who survived septic shock [83]. Thus, sympathetic overstimulation appears incapable of stimulating cardiac function any further and the myocardium becomes unresponsive to catecholamines.

The lack of β AR responsiveness during sepsis has been attributed to either auto-oxidation by reactive oxygen species (ROS), as superoxide dismutase (SOD) administration simulated the β -adrenergic responses in an animal model of septic shock [84], or to elevated NO levels [85, 86]. Cardiac GRK2 is the major negative regulator of β AR pro-contractile signaling [87]. Desensitization of β ARs and eventual termination of cAMP signaling reduce dramatically cardiac inotropic and adrenergic reserves (Fig. 1). Since GRK2 is markedly elevated in other types of heart failure, such as ischemic cardiomyopathy, its blockade (Fig. 1) has been proposed as an attractive therapeutic strategy for heart disease treatment [87]. The essential role of GRK2 inhibition in maintaining β_2 AR pro-contractile signaling in the heart was recently uncovered in a murine post-MI heart failure model [88]. In this study, cardiac-specific overexpression of a GRK2 inhibitor, β ARKct, in mice with β_1 AR gene ablation enhanced the pro-contractile signaling of β_2 AR [88]. The mechanism that underlies this

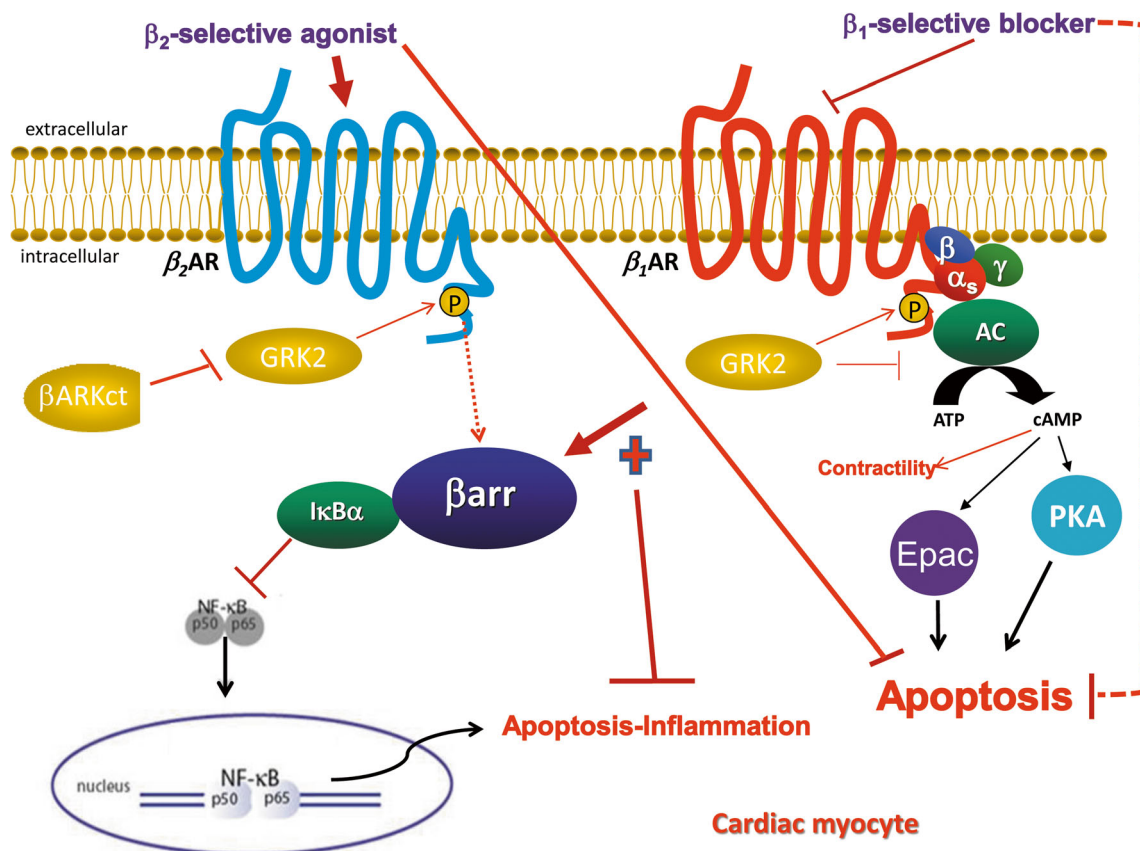


Fig. 1 Schematic illustration of the β AR-elicited signaling pathways modulating apoptosis/inflammation in the heart, discussed in the present article. Potential therapeutic strategies for cardiac sepsis are also depicted. See text for details and for molecular acronym descriptions

effect includes inhibition of β arr binding. An interesting observation from this study that can be extrapolated in septic cardiac dysfunction was that β arr inhibition was associated with degradation of I κ B α , activation of NF- κ B, and increased expression of inflammatory markers [88]. The authors suggest that GRK2 inhibition reduces phosphorylation of β_2 AR and therefore weakens binding of β arr to β_2 AR. This results in less β arr-dependent scaffolding of I κ B α , which normally stabilizes I κ B α and prevents NF- κ B activation (Fig. 1) [88]. Thus, reduced β arr binding is likely associated with NF- κ B activation and inflammation. Accordingly, although there is still no evidence for the role of β arr in septic cardiac inflammation, it has been shown that both β arr1 and β arr2 inhibit NF- κ B signaling in vitro [73]. Global β arr2 $^{-/-}$ mice with CLP-induced sepsis have elevated plasma IL-6 levels and die faster than septic wild-type mice [89]. These findings indicate β arr activation as an attractive candidate for the alleviation of cardiac inflammation that is elevated in sepsis, when β -AR desensitization and increased binding of β arr to β -ARs occur.

NF- κ B has a central role in cardiac inflammation during septic cardiac dysfunction [90]. Also, β_1 AR- and β_2 AR-driven signaling pathways induce phenotypically opposing effects on cardiac apoptosis and β arr activation may be a critical switch for that. Therefore, blockade of β_1 AR signaling [91, 92] or enhancement of cardiac β_2 AR signaling [93] or β arr-mediated NF- κ B inhibition via activation of β_2 AR [94] may all be valid therapeutic strategies to inhibit NF- κ B and inflammation in the septic heart (Fig. 1). Indeed, β AR agonists, such as isoproterenol and dobutamine, β_2 AR-selective agonists like clenbuterol [95–97], and β_1 -selective blockers like esmolol [98] are being tested in animal models and in clinical trials of cardiac sepsis. Enhancement of β arr-mediated NF- κ B scaffolding/inhibition via β_2 AR activation could be achieved either with a gene therapy approach aiming to increase cardiac levels of β arrs or with a β_2 AR ligand capable of acting as β arr-“biased” agonist, e.g., the β -blocker carvedilol [71]. Indirect enhancement of this signaling modality by elevating GRK2 activity is not recommended, as this would severely impair cardiac function [87, 88]. Thus, interventions that augment β arrs during sepsis may lead to combined improvement of β -AR signaling and alleviation of inflammatory pathways in the heart.

Septic Cardiac Dysfunction as a Consequence of Energetic Starvation

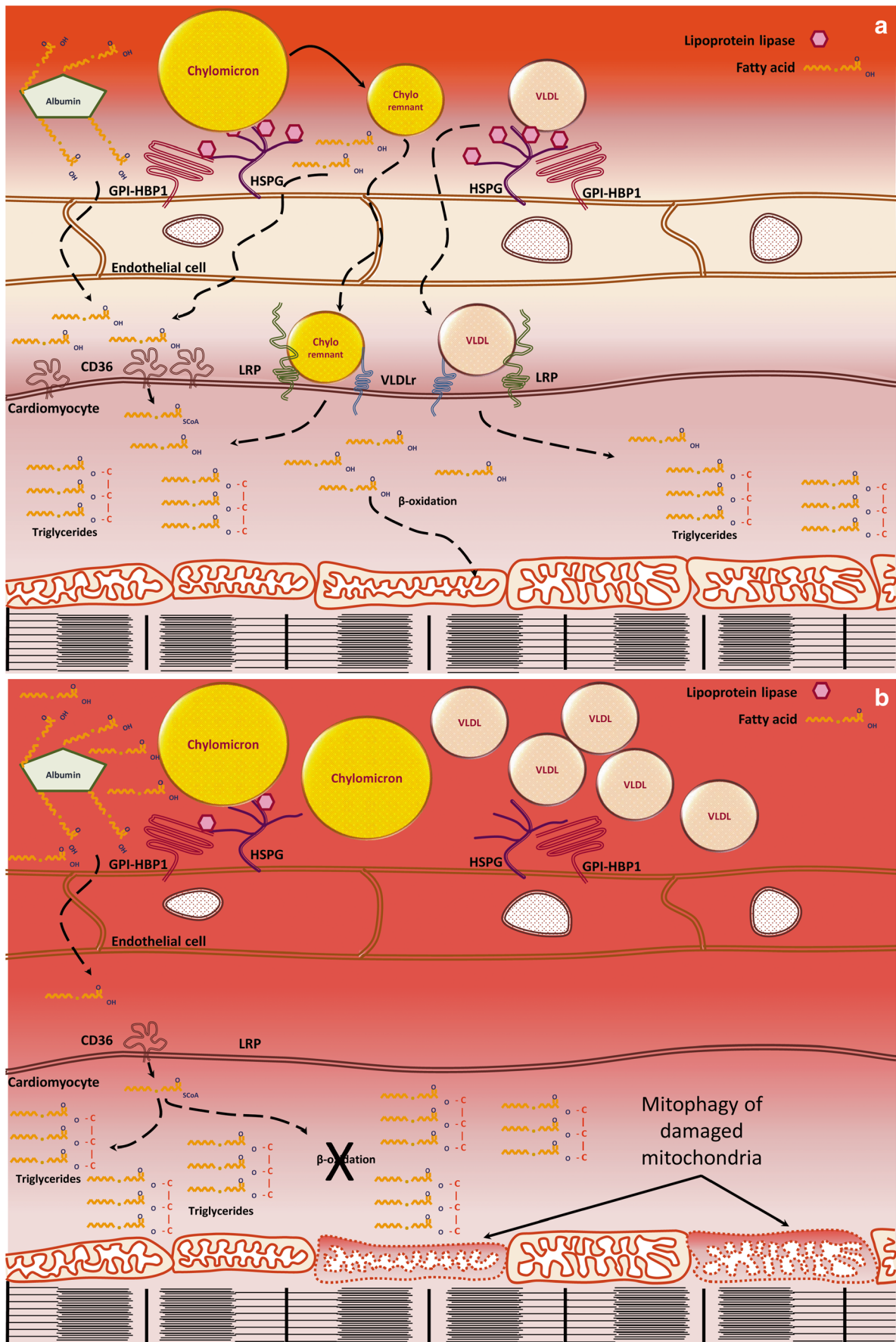
Sepsis is associated with altered lipoprotein metabolism characterized by elevated plasma triglyceride and free fatty acid levels [21, 99–101] and suppression of energy production in several organs, including the heart [20, 21, 22•] (Fig. 2). Increased plasma triglyceride levels are due to compromised intravascular lipolysis and reduced lipid uptake by tissues [102, 103], as hepatic lipoprotein production remains normal

[104]. Sepsis-induced energetic deficiency of organs constitutes another critical component of the pathophysiology of the disease. This defect becomes even more important for the heart due to its vast energetic demands. Approximately 70 % of cardiac ATP is produced via lipid oxidation, while the rest is produced primarily via glucose oxidation. Some ATP is also derived from catabolism of lactate and ketone bodies. In pathologic conditions that are characterized by reduced cardiac work such as heart failure, fatty acid oxidation is reduced and glucose oxidation is increased to compensate for ATP production [105, 106]. In contrast, in sepsis, the reduction of cardiac fatty acid oxidation is not compensated by increased glucose catabolism, as insulin resistance and suppressed glucose utilization occur [107–109]. As oxygenation of the heart does not seem to change in sepsis [110], the observed cardiac energetic deficiency is attributed primarily to defective supplementation of the heart with substrates that are used for ATP production.

Septic hearts have reduced expression of a broad range of fatty acid metabolism genes. Moreover, they demonstrate mitochondrial dysfunction. Cardiac supplementation of fatty acids is compromised due to reduced activity of cardiac lipoprotein lipase (LpL) due to lower LpL expression and increased expression of Angptl4, an inhibitor of LpL [21, 111]. Besides reduced LpL activity, sepsis reduces the expression of fatty acid transporter CD36 [112] and the very-low-density lipoprotein receptor (VLDLr) [113], aggravating even further uptake of lipids by the heart (Fig. 2). Efficient lipoprotein clearance from circulation during sepsis can contribute to the removal of bacterial endotoxins, as these stick on lipoproteins [114], particularly chylomicrons [115]. Thus, the observed reduced expression of lipoprotein receptors during sepsis may constitute a defensive mechanism to prevent the delivery of these toxins to the heart.

Intracellular cardiac fatty acid mobilization and oxidation are inhibited due to reduced expression of fatty-acid-binding protein [116], acyl-CoA synthetase [117], and carnitine palmitoyl transferase-1 [112]. Furthermore, cardiac expression of transcriptional factors, which are strongly associated with fatty acid oxidation, such as peroxisome proliferator-activated receptors (PPARs), retinoid-X receptors (RxRs), and thyroid receptors (TRs), as well as their coactivator PPAR γ -coactivator-1 (PGC-1) are lower during sepsis [20, 21, 22•, 112]. Accordingly, cardiomyocyte-specific constitutive expression of PGC-1 β [22•] or PPAR γ [21] as well as pharmacological activation of PPAR γ [21] or prevention of cardiac PPAR α downregulation [20] induce fatty acid oxidation and correct cardiac function during sepsis. Interestingly, this improvement occurs despite increased expression of cardiac inflammatory markers.

Rosiglitazone-mediated systemic PPAR γ activation improves survival in LPS-treated mice [21] or mice with CLP [118]. These results suggest that improved energy production



◀ **Fig. 2** Cardiac fatty acid metabolism in health and in sepsis—**a** cardiac fatty acid oxidation in normal hearts: fatty acids are taken up by cardiomyocytes via CD36 or with the contribution of lipoprotein remnant receptors, such as VLDLr and LRP. Cardiomyocyte fatty acids can be stored in triglycerides or used for ATP production via β -oxidation in mitochondria. **b** During sepsis, CD36, lipoprotein lipase, and lipoprotein remnant receptors are downregulated, leading to increased fatty acid and triglyceride-carrying lipoprotein content in the circulation. In addition, cardiac β -oxidation is inhibited and mitochondrial number is reduced via mitophagy, resulting in intracellular accumulation of the unused fatty acids in triglycerides

is crucial for several organs during sepsis. As PPAR γ activation is also associated with reduced inflammation [119–123], it might also be postulated that the improvement in survival during sepsis is due to alleviation of inflammation. However, when PPAR γ activation was applied to mice that do not express adiponectin (APN), an adipocyte-derived protein [124–126] that promotes fatty acid oxidation in peripheral organs, such as the heart [127] and skeletal muscles [128], the survival benefit of this nuclear receptor agonism was blunted [118]. On the other hand, the administration of rosiglitazone in wild-type mice with either polymicrobial sepsis [118] or endotoxemia [21, 129] improved survival. In some studies, the beneficial effect of PPAR γ activation in cardiac function [21] or in survival rates [129] was not associated with significant alleviation of inflammation. Another study showed that pharmacological activation of a different inducer of fatty acid oxidation, PPAR δ , also protects cardiac function but PPAR δ agonist also alleviated inflammation [130]. In accordance with animal studies showing the beneficial effect of fatty acid oxidation, a clinico-metabolomic study that analyzed plasma from septic patients showed that markers of reduced fatty acid utilization in tissues, such as higher concentration of carnitine esters and fatty acids, were associated with increased lethality [131•]. Thus, although inflammation is an important component of sepsis-driven dysfunction of the heart and other organs, improvement in energy production appears to confer survival benefit at least for the early stages of the disease.

The energetic deficiency of septic hearts has also been associated with mitochondrial dysfunction [132, 133]. Mitochondrial dysfunction is triggered by increased production of ROS that occurs in septic hearts, as has been shown in LPS-treated mice [134] and rats [135]. This is associated with reduced levels of complex II and IV of the oxidative phosphorylation machinery and reduced enzymatic activity of several mitochondrial enzymes, such as NADH cytochrome c reductase, succinate cytochrome c reductase, and cytochrome c oxidase [136]. In several cases, mitochondrial dysfunction is paired with autophagy, which is a defensive mechanism for the removal of damaged mitochondria and therefore is called mitophagy. Cardiac mitophagy is induced during sepsis [21, 137]. Accordingly, Park2 deficiency, which

compromises autophagic mechanisms in mice, results in impaired recovery of cardiac contractility following administration of a sublethal dose of LPS [137]. The central role of ROS in the impairment of mitochondrial function and eventual induction of mitophagy in sepsis was demonstrated in FVB mice that were treated with LPS and the antioxidant *N*-acetylcysteine, as well as in LPS-treated mice that overexpress catalase [134]. Both pharmacologic and genetic antioxidant interventions prevented LPS-related contractile dysfunction and were associated with reduced levels of autophagy, presumably due to limited ROS accumulation and prevention of mitochondrial damage. In agreement with the studies in animal models, treatment of septic patients with levosimendan, a calcium sensitizer with antioxidant properties, improves cardiac function [138]. Although the beneficial effects of levosimendan on cardiac function could be attributed to its established positive inotropic effects [139], the improvement in mitochondrial number and function that was observed in muscle biopsies from septic patients that were treated with this drug [140] indicates that its beneficial effects in cardiac function may be at least partially accounted for by improved cardiac mitochondrial health.

Conclusion

Sepsis-related cardiac dysfunction is associated with increased inflammation, impaired energetics, and attenuated adrenergic signaling in the heart. While each of these components is important to be resolved in order to correct cardiac function, it seems that therapeutic approaches in septic patients should probably include a combination of anti-inflammatory treatment along with stimulation of energy production in the heart. Moreover, interventions that aim to restore cardiac adrenergic signaling and particularly the function of β arr may have dual effects by improving contractility and reducing cardiac inflammation.

Compliance with Ethics Guidelines

Conflict of Interest Konstantinos Drosatos, Anastasios Lymperopoulos, Peter Johannes Kennel, Nina Pollak, P. Christian Schulze, and Ira J. Goldberg declare that they have no conflict of interest.

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- Of major importance

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