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Review

The role of mitochondria in sepsis-induced cardiomyopathy☆

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ABSTRACT

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Myocardial dysfunction, often termed sepsis-induced cardiomyopathy, is a frequent complication and is associated with worse outcomes. Numerous mechanisms contribute to sepsis-induced cardiomyopathy and a growing body of evidence suggests that bioenergetic and metabolic derangements play a central role in its development; however, there are significant discrepancies in the literature, perhaps reflecting variability in the experimental models employed or in the host response to sepsis. The condition is characterised by lack of significant cell death, normal tissue oxygen levels and, in survivors, reversibility of organ dysfunction. The functional changes observed in cardiac tissue may represent an adaptive response to prolonged stress that limits cell death, improving the potential for recovery. In this review, we describe our current understanding of the pathophysiology underlying myocardial dysfunction in sepsis, with a focus on disrupted mitochondrial processes.

1. Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. This new definition highlights the central role of organ dysfunction in the pathogenesis of sepsis and as a determinant of poor outcome. Sepsis, however, remains a complex and incompletely understood syndrome that covers a broad and often non-specific range of clinical signs and symptoms, and variably affected organs. A hallmark of sepsis-induced multi-organ failure is the common paucity of cell death and frequent recovery of organ function in survivors. These findings, along with other evidence, imply a metabolic shutdown rather than structural damage as a key pathophysiological mechanism.

Despite advances in knowledge, sepsis remains a major global health problem estimated to affect over 30 million people every year worldwide [2]. It still carries a high mortality, significant long-term physical, psychological and cognitive disability in many survivors, and has staggering economic and societal costs. The incidence of sepsis is rising, perhaps due to an ageing population with more chronic comorbidities, and increasing medical interventions [3]. Unfortunately, multiple large-scale clinical trials performed over the last three decades have failed to yield any novel, effective therapeutic intervention. Management thus remains largely supportive with avoidance of iatrogenic harm.

The cardiovascular system is essential for the maintenance of adequate organ perfusion. Not surprisingly, therefore, cardiovascular dysfunction affects the progression of sepsis. Indeed, the presence of profound circulatory abnormalities, along with metabolic and cellular derangements, defines a subset of patients associated with a much higher mortality (i.e. septic shock).

The purpose of this review is to describe the pathophysiology of myocardial dysfunction in sepsis, with a focus on the role played by mitochondria in its pathogenesis.

Abbreviations: LPS, lipopolysaccharide; CASP, colon ascendens stent peritonitis; CLP, cecal ligation and puncture (CLP); cNOS, constitutive nitric oxide synthase; CO, carbon monoxide; DAMPs, danger-associated molecular patterns; Drp1, dynamin-related protein 1; iNOS, inducible nitric oxide synthase; Mfns, mitofusins; mPTP, mitochondrial permeability transition pore; mtNOS, mitochondrial NOS; NO, nitric oxide; NRF-1 and -2, nuclear respiratory factors 1 and 2; PAMPs, pathogen-associated molecular patterns; OPA1, optic atrophy 1; PARP, poly(ADP-ribose) polymerase; PGC-1α and β, PPAR (peroxisome proliferator-activated receptor)-γ coactivator-1 α and β; PPAR, peroxisomal proliferator-activated receptors; RNS, reactive nitrogen species; ROS, reactive oxygen species; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum calcium-ATPase; SIC, sepsis-induced cardiomyopathy; Tfam, mitochondrial transcription factor A; UCPs, uncoupling proteins

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2. Sepsis-induced cardiomyopathy (SIC): the clinical picture

The occurrence of cardiovascular abnormalities during sepsis has been recognised for over 50 years [4,5]. However, an intrinsic myocardial dysfunction in patients with septic shock was first described in 1984 by Parker and colleagues, who reported an increase in ventricular volumes and a decreased ejection fraction [6]. SIC has generally been defined as an intrinsic and reversible systolic and diastolic dysfunction of both the left and right sides of the heart induced by sepsis [7]. However, there is no consensus on specific diagnostic criteria [8], and different studies have used markedly different criteria to identify SIC. This variability has resulted in an apparently shifting prevalence of SIC, ranging from 24 to 72% [9–13]. It is however clear that the prevalence of SIC rises with increasing disease severity [14].

These early studies suggested a protective effect of ventricular dilation [6]. However, more recent studies using similar loading-dependent variables have failed to identify a positive effect on outcome [10,15,16]. On the contrary, utilising more sensitive markers of cardiac dysfunction such as tissue Doppler, mitral flow Doppler and speckle tracking that are less dependent on loading conditions, cardiac dysfunction appears to be strongly associated with a worse outcome [9,17–21]. These differences underline the complexity of the disease, the heterogeneity of patient cohorts, and the sometimes conflicting methodologies used for SIC diagnosis. Part of this complexity stems from the difficulty in differentiating an intrinsic cardiac dysfunction from abnormalities in vascular and autonomic status.

An important characteristic of SIC is its potential reversibility observed in numerous studies [6,11,22,23]. However, this concept of reversibility has not been tested in large outcome studies with robust methodologies, so the evidence is currently inconclusive [24].

While cardiac function has been extensively studied in human sepsis, much less data are available on concurrent structural cardiac damage [25]. Both macroscopic and microscopic findings of myocarditis have been noted at post-mortem [26–29] while evidence of non-ischemic cardiac injury compatible with inflammation or tissue acidosis was observed in vivo using cardiac magnetic resonance [30]. The cardiomyocytes of septic patients showed scattered foci of disruption of the contractile apparatus and translocation of connexin-43, an indication of cell injury [28,31]. Of note, only minimal signs of cardiomyocyte apoptosis or necrosis were seen, suggesting that cell death does not account for the severity of SIC in clinical patients [31,32]. Low levels of cardiomyocyte apoptosis and necrosis were also confirmed in large animal experimental studies [33,34]. Cardiomyocyte death has been noted in some rodent models of sepsis [35–37] but this may reflect the severity and acuity of the model, variations in resuscitation, and species differences. Despite the frequent finding of minimal cardiomyocyte death, a correlation has been found in septic patients between a rise in cardiac troponins, a circulating biomarker of cell injury, and both mortality [38–40] and the degree of myocardial dysfunction [40]. This apparent paradox can be explained by the non-necrotic release of troponins [41,42], further supporting the concept of reversible intrinsic myocardial damage.

3. Preclinical studies

Given these limited clinical studies, most evidence for the pathophysiology underlying SIC has originated from preclinical models. Ex vivo models include the study of the isolated whole heart (i.e., Langendorff model), papillary muscles, permeabilised muscle fibres and isolated cardiomyocytes or mitochondria [43]. In vivo models have utilised a variety of species, insult types and severity, study duration, and degree of supportive care provided. Insult types used to model sepsis in animals include injection of pathogen components (e.g. endotoxins or zymosan), administration of live bacteria (e.g., intravenous, intraperitoneal or intratracheal injection of bacteria, intraperitoneal inoculation with fecal slurry, implantation of bacterial and fibrin clots), or disruption of the host barriers resulting in polymicrobial sepsis (e.g., caecal ligation and puncture, CLP, or colon ascendens stent peritonitis, CASP). Each model presents unique features that attempt to recapitulate specific aspects of clinical sepsis in humans. The details, and limitations, of the different approaches have been described in numerous reviews [44–46] and minimum quality thresholds to move preclinical research forward have been recently proposed [47]. Of note, a large proportion of the pre-clinical sepsis literature is based on endotoxin models. The administration of endotoxin produces a reproducible, rapid and robust activation of the innate immune system. However, endotoxin fails to recapitulate the complexity of sepsis pathophysiology and numerous differences are present between the sepsis and the endotoxin phenotypes. For these reasons, current guidelines discourage extensive use of models based on endotoxin administration [48].

Other specific concerns raised in preclinical models of sepsis include the use of animals that are young, without comorbidities, of the same gender, and the absence of supportive therapies such as antibiotics or fluid [44]. This heterogeneity has resulted in variable physiological responses and outcomes that could, at least partially, explain the conflicting results and the failure of novel therapies to translate to the clinical setting.

4. Pathophysiology of SIC

4.1. Extramitochondrial mechanisms

Numerous circulating factors likely contribute to the cascade of events leading to SIC. These extracellular mediators include both pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) and host-produced danger-associated molecular patterns (DAMPs). These endogenous danger signals include cytokines, heat-shock proteins, high-mobility group box 1, histones, activated complement components, and mitochondrial DNA. In preclinical studies, all these molecules act, directly or indirectly, as myocardial depressant factors. However, in septic patients, no correlation was found between any measured circulating cytokine and myocardial dysfunction [49]. This suggests that the final effect on the heart of circulating factors is likely to result from the interaction of a wide range of signalling pathways rather than any single individual factor.

Circulatory dysfunction caused by variable degrees of volume depletion, vasodilation, loss of vascular tone and myocardial depression is a hallmark finding of sepsis. As the consequent hypotension could result in a decrease in myocardial perfusion and oxygen delivery, global myocardial ischemia was originally proposed as a potential aetiology underlying SIC. In experimental sepsis coronary reserve was reduced, affecting the ability to increase both coronary blood flow and myocardial oxygen extraction [50,51]. However, coronary blood flow was shown to be either normal or increased in both septic patients and experimental animals, along with a net lactate consumption and increased availability of oxygen to the myocardium [52–54]. These findings argue against a role for myocardial ischemia and oxygen limitation. Some authors have suggested that SIC could be caused by abnormalities within the myocardial microcirculation rather than a macrocirculatory deficit [55,56]. This hypothesis is supported by experimental evidence of increased microvascular heterogeneity [57,58] and endothelial activation [34,59] in both ex vivo and in vivo septic hearts. However, the myocardium of septic animals had normal levels of high-energy phosphates and no evidence of cellular hypoxia [34,60,61]. These results, coupled with the lack of significant cardiac cell death described earlier in both clinical patients and experimental animals [31,33,34], do not lend support to microcirculatory dysfunction playing a major role in SIC.

Other abnormalities proposed to contribute to the pathogenesis of SIC include disruption of the contractile apparatus [25], altered calcium trafficking [62], metabolism changes [63], disrupted cardiac electrical

conduction [64,65], autonomic dysregulation, and abnormalities in adrenergic signalling [66,67]. However, none of these mechanisms can satisfactorily explain the paradox in sepsis of organ failure without significant cell death, in the presence of normal tissue oxygen tensions, and with a rapid recovery of function in survivors [68]. As mitochondria are the primary oxygen consumers and source of ATP within the body, the role of this organelle merits consideration.

4.2. Mitochondrial mechanisms

The heart requires significant amounts of energy to sustain its continuous contractile activity. As it cannot store energy for more than a few heartbeats, a constant supply of energy substrate is necessary, and this must be able to adapt rapidly to any changes in demand [69]. Oxidative phosphorylation provides the vast majority of this energy supply. Given this dynamic, high-energy flux state, it is not surprising that mitochondria occupy between 22 and 37% of cardiomyocyte volume across different mammalian species [70,71]. Highly efficient supply-demand matching mechanisms have also evolved to allow an immediate response to changes in metabolic requirements.

Besides their role in ATP production, mitochondria also play an essential role in numerous other cell functions such as calcium homeostasis, hormone metabolism, thermoregulation, reactive oxygen and nitrogen species production, cell signalling, and are key regulators of apoptosis and cell death. Mitochondrial dysfunction and bioenergetic failure are thus increasingly recognised as central to the pathophysiology of numerous cardiovascular diseases, such as heart failure or ischemia-reperfusion injury. Mitochondrial pathways are also being explored as potential therapeutic targets [69,72].

As discussed above, sepsis is characterised by a paradoxical physiological and biochemical organ dysfunction with minimal cell death, adequate tissue oxygenation and reversibility in survivors [73]. These findings suggest a key role for both a cellular bioenergetic deficit, and more specifically mitochondrial dysfunction, and a metabolic shutdown, in the pathogenesis of sepsis-induced organ failure. This topic has been subject to scientific investigation for over four decades [74]. Interest was stimulated by a 2002 publication from our group showing mitochondrial dysfunction in skeletal muscle taken from patients in septic shock [75]. A correlation was seen between the degree of mitochondrial dysfunction (reduced activity of Complex I and ATP depletion), increased nitric oxide production and decreased glutathione concentration, and both disease severity and outcome. Since then numerous other studies have investigated the role of mitochondria in sepsis in both patients and experimental in vivo and in vitro models. Despite this body of evidence, it is still unclear whether mitochondrial dysfunction is the cause, an effect, or even an adaptive mechanism allowing survivors to recover organ functionality in the face of a prolonged and severe systemic insult [76,77].

In the following sections, we will review the evidence for the presence of mitochondrial dysfunction in sepsis-induced cardiomyopathy, its role in the pathogenesis of the disease, and possible causative mechanisms. A summary of the proposed pathways leading to mitochondrial dysfunction is presented in Fig. 1. Lack of consensus on the meaning of “mitochondrial dysfunction”, along with the variability in techniques used to assess it, makes direct comparison of different studies difficult and may, at least partially, explain the heterogeneity of results published to date [78].

5. Mitochondrial dysfunction in sepsis

5.1. Electron transport chain and oxidative phosphorylation abnormalities

Oxidative phosphorylation involves the transfer of electrons from the Krebs cycle, via reduced NADH and $FADH_2$, to the enzymes (Complexes I-IV) and transporters (ubiquinone and cytochrome C) constituting the mitochondrial electron transport chain. As the electrons move down the chain, protons are pumped from the mitochondrial matrix into the inter-membrane space, with a chemiosmotic gradient generated across the inner mitochondrial membrane. This process generates a mitochondrial membrane potential and a pH gradient, which together result in a proton-motive force which supplies the energy to drive phosphorylation of ADP to ATP by the F_OF_1-ATPase (ATP synthase or Complex V). Oxygen is the final electron acceptor at the level of Complex IV, with O_2 being converted into water [73]. Of note, oxidative phosphorylation is the primary consumer of oxygen in the body.

Oxidative phosphorylation abnormalities can compromise ATP generation resulting in a bioenergetic deficit. This has long been postulated to be a critical phenomenon in the development of sepsis-induced organ failure [73,79]. These abnormalities have been variously recognised by decreases in oxygen consumption, ATP synthesis and cellular content, decreased state 3 respiration and respiratory control ratio (i.e., state 3/state 4 ratio), decreased mitochondrial membrane potential, reductions in activity and/or expression of respiratory complexes, and an increase in state 4 respiration or uncoupling. Depletion in mitochondrial antioxidant capacity and mitochondrial DNA content, compromised biogenesis, and morphological abnormalities are also recognised. An extensive explanation of the methods used for evaluating mitochondrial function and the associated nomenclature goes beyond the scope of this review, but can be found in the excellent article by Brand and Nicholls [80].

No studies have yet directly evaluated cardiac mitochondrial function in human septic patients. Evidence, albeit relatively sparse, for mitochondrial dysfunction has been shown in other organs and tissues taken from patients including skeletal muscle [75,81,82], platelets [83–85] and peripheral blood mononuclear cells (PBMCs) [86–89]. These studies showed a clear association between the degree of mitochondrial dysfunction, disease severity and patient outcomes. Mitochondrial dysfunction was also identified in human hepatic mitochondria isolated from healthy surgical patients and exposed to endotoxin [90].

Several inconsistencies are however present between these various studies, for example, in the location of respiratory enzyme inhibition and the degree of uncoupling [75,85]. Other reported conflicting findings include an increase in skeletal muscle mitochondrial activity following infusion of endotoxin into healthy volunteers [91] or a rise in mitochondrial membrane potential in neutrophils taken from septic patients [92]. These differences may relate to the methodology used [93], to the tissue being investigated, to timing with respect to the disease process, or to disease severity. It could also be speculated that a subset of patients with sepsis might develop organ failure only due to some of the poorly characterised non-mitochondrial mechanisms mentioned above without presenting mitochondrial dysfunction. However, the lack of appreciable cell death does suggest that these non-mitochondrial mechanisms must relate predominantly to modifications in metabolism (e.g. hormonal influences).

Extrapolating changes in mitochondrial function in circulating blood cells to less accessible vital organs may not be reliable (e.g., heart, brain, kidney, liver) [78]. For instance, neutrophils possess few mitochondria and their energy provision is mainly through glycolysis, whereas cardiomyocytes are replete with mitochondria with fatty acid oxidation being the primary energy substrate.

Differences in mitochondrial function between different organs have been demonstrated in various lab models with, for example, a time-dependent decrease in mitochondrial respiration in the heart but not the kidney in neonatal rat endotoxemia [94], and decreased respiratory activity in the heart yet increased respiratory activity in the liver in response to endotoxic shock in adult rats [95]. Rabbits exposed to endotoxin also showed a decrease in cardiac respiratory function and complex activity while skeletal muscle was affected to a lesser extent [96]. These findings raise the possibility that the cardiac mitochondria are more sensitive to damage during sepsis and the absence of

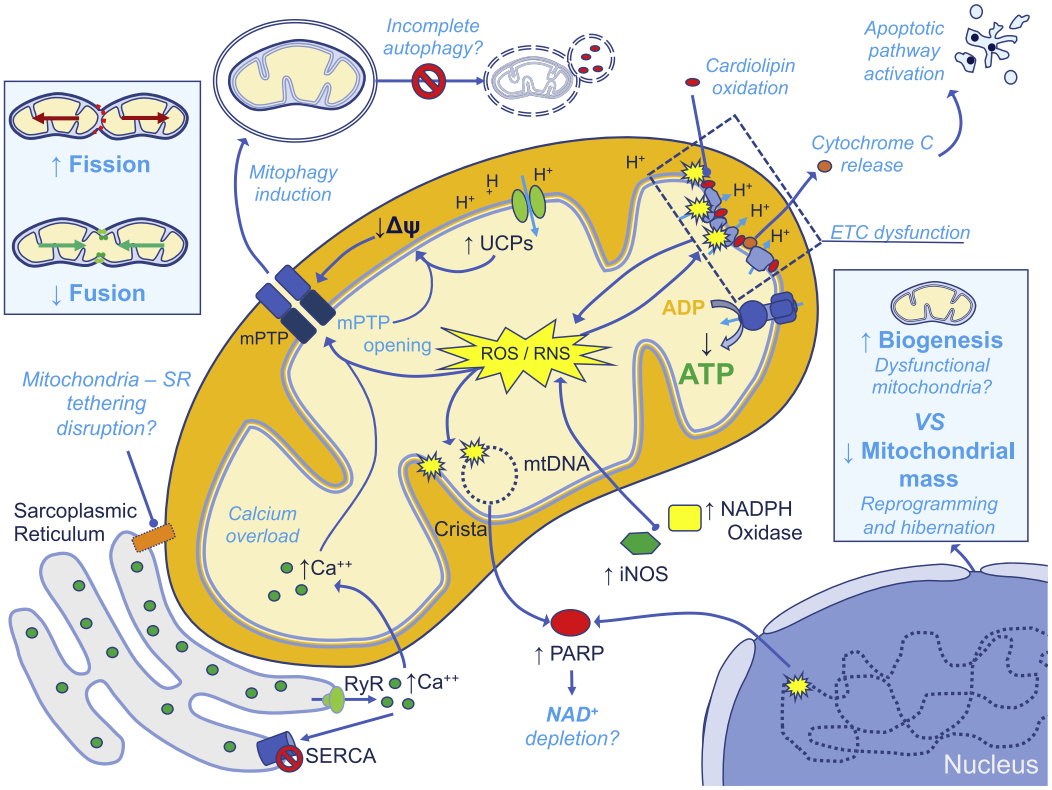

Fig. 1. Summary of the proposed mechanisms leading to mitochondrial dysfunction in Sepsis-Induced Cardiomyopathy. Δψ, mitochondrial membrane potential; ETC, electron transport chain; iNOS, inducible nitric oxide synthase; mPTP, mitochondrial permeability transition pore; PARP, poly(ADP-ribose) polymerase; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum calcium-ATPase; UCPs, uncoupling proteins.

mitochondrial abnormalities in other organs or cells does not exclude their presence within the myocardium.

In contrast to the limited human clinical literature, cardiac mitochondrial dysfunction has been extensively evaluated in both in-vivo and in-vitro experimental studies. Most identify dysfunction across different species and models of sepsis and have found an association between impaired cardiac contractility and worse outcomes [25]. The majority of experimental studies have utilised rodent models of septic peritonitis [78], induced by CLP, CASP or intraperitoneal injection of fecal slurry. Mitochondrial changes reported include uncoupling, altered redox status and decrease in oxygen consumption, ATP generation, mitochondrial membrane potential, and respiratory complex activities [35,97–106]. Similar changes have also been observed in rodent models of endotoxemia [107–110] or non-peritoneal sepsis [111]. The mitochondrial changes observed in these rodent models have been associated with cardiac dysfunction, notably contractility, as assessed by ex-vivo isolated preparations (Langendorff heart) [97,100,106] or in-vivo (e.g., echocardiography) [108,109,111].

Cardiac mitochondrial dysfunction has also been noted in non-rodent septic models, including feline [112,113], porcine [114], canine [34] and primate [115] species. The latter study evaluated the response to bacteraemia in baboons, a species that is physiologically and phylogenetically closely related to humans. This study demonstrated how sepsis induces a decrease in respiratory complex activities proportional to the number of bacteria infused, thereby showing a correlation between the degree of dysfunction and insult severity. Exposing isolated adult or neonatal cardiomyocytes to septic serum, PAMPs or DAMPs could also recapitulate the features of mitochondrial dysfunction seen in clinical or experimental studies [108,116–119]. These findings underpin a likely important role of circulating factors in the pathogenesis of sepsis-induced myocardial dysfunction.

Not all experimental studies show uniform signs of cardiac mitochondrial dysfunction in sepsis. In a 48 h study evaluating rat endotoxemia, a transient decrease in mitochondrial respiration was only seen in the early phases of sepsis (6 h) despite the occurrence of both cardiac dysfunction and mitochondrial structural abnormalities [120]. Other studies revealed opposite results. In endotoxemic rats, Supinski and Callahan showed only a late decrease in mitochondrial function (48 h) [121]. Similar results were reported in a CLP model where cardiac ATP depletion and a decrease in respiratory complex activities were only noted in late (18 h), but not early (9 h) sepsis [122]. Dawson et al., however, reported an enhancement in cardiac mitochondrial function in endotoxin-treated animals [123], while Smeding and colleagues found a decrease in cardiac contractility at 2–4 h that was not associated with functional changes in mitochondria [124]. In a porcine model, cardiovascular dysfunction was not associated with significant abnormalities in myocardial mitochondrial respiration in septic pigs [125].

Reasons for such heterogeneity in the results have been discussed earlier. Nonetheless, a pattern emerges that does suggest a significant role for mitochondrial dysfunction in the pathogenesis of sepsis-induced cardiomyopathy. In the following sections, we will focus on possible causes of this dysfunction.

5.2. Mitochondrial structural damage

Adequate mitochondrial function is highly dependent on the complex ultrastructure of this organelle. For example, the cristae are home to many key mitochondrial proteins and their shape determines the inner membrane surface area, the efficiency of oxidative phosphorylation reactions and the diffusion of solutes [126,127]. A strong causal link is emerging between mitochondrial structure and function in health and disease [128,129]. Thus, mitochondrial ultrastructural damage may play an important role in the pathogenesis of cardiac mitochondrial dysfunction in sepsis. Clearly, accessing human cardiac tissue from septic patients is problematic so studies to date have relied

on post-mortem specimens. Cowley et al. first reported morphological abnormalities of cardiac mitochondria in 1979 [130]. Since then, we could only find two similar studies [29,31]. These identified hydropic mitochondria and damage to the cristae yet, significantly, these changes occurred in the absence of significant irreversible acute cellular injury or cell death. Whether these alterations represent pre-terminal organ hypoperfusion or post-mortem deterioration does, however, remain a possibility [130]. Assuming skeletal muscle is a surrogate for cardiac tissue, our lab showed only limited mitochondrial structural abnormalities despite evidence of biochemical mitochondrial dysfunction [81], while Fredriksson and colleagues failed to detect any skeletal muscle morphological differences between their septic patients and controls [82].

In experimental settings, mitochondrial structural abnormalities have been confirmed across a wide range of species and septic models [34,100,112,113,120,122,131–135]. Findings included mitochondrial swelling, condensed or cleared mitochondrial matrix, myelin figures, cristae abnormalities, internal vesicles and disruption of mitochondrial membranes. As with humans, most of these studies report minimal, if any, concurrent evidence of myocardial apoptosis or necrosis. While the majority of these lab studies demonstrated an association between mitochondrial structural damage and dysfunction, this is not consistent [134]. Similarly, some studies could not identify mitochondrial morphological abnormalities despite the presence of significant cardiomyopathy and mitochondrial dysfunction [35,124,136]. Taken collectively, these data suggest that, despite being common in sepsis, overt morphological damage to cardiac mitochondria is not a prerequisite for cardiac mitochondrial and contractile dysfunction. The conflicting experimental data in animal models combined with limited evidence in human patients leave open the question as to whether mitochondrial structural damage plays a significant role in the pathogenesis of SIC or represents merely a late consequence of other pathways of mitochondrial dysfunction and organ failure.

5.3. Oxidative and nitrosative stress

Under physiological conditions, mitochondria are the primary source of reactive oxygen species (ROS) within cells. Even in healthy cells, the electron transport chain is not entirely efficient; electrons can leak out and react with oxygen at multiple sites before they reach complex IV. This electron leak results in the generation of ROS in the form of superoxide anions and hydrogen peroxide. The percentage of electron flow diverted to ROS production in physiological conditions is commonly cited as 1–2% [137]. However, this has been suggested to be an overestimation, especially in vivo and in conditions of increased demand [138,139]. In health, mitochondrial ROS plays an important signalling role [140].

To date, up to 11 mitochondrial sites of ROS production have been identified, with maximal ROS production capacity associated with, in order of importance, sites on respiratory complexes III, I and II [139]. The degree of electron leak depends on the amount of reduced electron donors present at that particular site. A disruption of the electron transport chain will increase ROS production upstream. Conversely, an upstream inhibition, an increase in ATP synthesis, or uncoupling of oxidative phosphorylation will all result in a more oxidative redox state at the site of electron leak and, consequently, a decrease in ROS production. In summary, mitochondrial dysfunction can increase ROS production, but this depends on the nature of the abnormality and its location within the electron transport chain [139]. Increases in ROS production at the level of the electron transport chain may reflect a decrease in 'efficiency' of oxidative phosphorylation and may, therefore, be associated with reduced ATP synthesis [141].

Most of these mitochondrial ROS are released within the mitochondrial matrix. While hydrogen peroxide is freely permeable and rapidly diffuses into the cellular cytosol, superoxide diffuses more slowly and tends to be processed by the mitochondrial antioxidant system. Manganese superoxide dismutase converts superoxide into hydrogen peroxide, which is then processed to water by the glutathione/thioredoxin system.

An imbalance between ROS production and mitochondrial antioxidant defence capacity results in progressive accumulation of ROS and oxidative stress. High concentrations of ROS can interfere with the signalling cascade and lead to both reversible and irreversible macromolecular damage to proteins, lipids, and DNA oxidation [140].

Cardiolipin is an example of a specific mitochondrial target of oxidative damage. This phospholipid is uniquely expressed on the inner mitochondrial membrane and plays an essential role in the maintenance of cristae architecture and the organisation of the electron transport chain enzymes into supercomplexes, facilitating efficient mitochondrial respiration [142]. Moreover, cardiolipin contributes to anchoring cytochrome C to the inner mitochondrial membrane [143]. Cardiolipin is particularly sensitive to oxidative damage due to its proximity to sites of ROS production and the presence of unsaturated fatty acids within its structure. Cardiolipin oxidation disrupts electron transport chain supercomplexes and releases cytochrome C, resulting in an inhibition of mitochondrial respiration, an increase in ROS production and activation of apoptotic pathways [143]. Moreover, mitochondrial damage is associated with cardiolipin externalisation from the inner to the outer mitochondrial membrane, a process that has been shown to activate mitophagy [144,145]. The role of cardiolipin in sepsis has been investigated with the administration of a novel mitochondrially-targeted antioxidant (SS-31) that selectively binds to cardiolipin [146]. Treatment of septic mice improved outcome and organ dysfunction of brain, lung, liver and kidney by decreasing mitochondrial dysfunction, oxidative stress, inflammation and apoptosis [147,148].

Another example of a mechanism of mitochondrial dysfunction mediated by oxidative stress is the activation of poly(ADP-ribose) polymerase (PARP). Oxidative stress induces DNA strand breaks which, in turn, activate PARP, a DNA repair enzyme. Over-activation can lead to cellular energy depletion and mitochondrial damage through incompletely understood pathways but perhaps involving NAD^+ depletion [149]. Despite being mainly localised within the nucleus, PARP appears to be also present within mitochondria; it has been hypothesised that it could directly inhibit electron transport chain complexes during conditions of oxidative stress [150]. Myocardial PARP activation was observed in septic patients in association with impaired cardiac function and mitochondrial structural damage [29]. PARP genetic deletion or pharmacological inhibition reduced cardiac injury, improved cardiac function and increased survival in a variety of animal models of sepsis [151–153].

Oxidative stress has been extensively described in studies of both experimental [120,154–157] and human [29,75,81,158,159] sepsis; it is now widely recognised as a central component of sepsis pathophysiology [43,73,160–162].

Evidence from animal studies suggests that oxidative stress, from a simultaneous increase in mitochondrial ROS production and a down-regulation or depletion of mitochondrial antioxidant systems, may play a key role in the pathogenesis of SIC. A clear association has been reported between the degree of oxidative damage and the severity of cardiac dysfunction [120,121,156,163–165]. A temporal association has been described between oxidative stress, myocardial inflammation, down-regulation of mitochondrial ROS scavengers, myocardial dysfunction and outcome in rodent CLP and pneumonia models; mitochondrial damage and oxidative stress preceded cardiac inflammation, and the abnormalities were reversed by up-regulation of the mitochondrial antioxidant system [166,167]. Studies using mitochondria-targeted antioxidants such as Mito-Vit-E [111,157] and Mito-Q [99,168] have shown outcome benefits and improvements in myocardial and mitochondrial function. However, an important caveat is that these treatments were administered at or soon after the septic insult and this is not reflective of clinical reality where the septic patient

usually presents after many hours or days of progressive deterioration. At least these experimental studies indicate a causative role of oxidative stress in the development of SIC.

Apart from mitochondria, another major intracellular producer of ROS is NADPH oxidase, a cytosolic enzyme present in many cells, in particular phagocytes [140]. This enzyme is however also present within the heart. On exposure to septic plasma, cardiomyocyte NADPH oxidase was activated, contributing to ROS production and conversion of cardiomyocytes to a proinflammatory phenotype [169]. NADPH oxidase expression and activity increased in murine cardiac tissue in response to endotoxin; this was associated with an increase in cytoplasmic and mitochondrial ROS, mitochondrial dysfunction, cardiac dysfunction, and activation of apoptosis [108,170,171]. These cardiac changes could be prevented by inhibition of NADPH oxidase, but this was not necessarily associated with any outcome improvement [108,170].

Another mechanism that contributes to reactive species formation in sepsis is the excess generation of nitric oxide (NO) and even more reactive products such as peroxynitrite following reaction between NO and superoxide [172]. Constitutive and inducible nitric oxide synthases (cNOS and iNOS) are both expressed within the heart [173]. Among its numerous biological effects, NO induces, in a dose-dependent manner, vasodilation, decreased cardiac contractility and vascular hyporeactivity to catecholamines, inhibition of platelet and neutrophil adhesion, modulation of cytokine release, inhibition of mitochondrial respiration yet can also stimulate mitochondrial biogenesis. While NO has an overall protective effect in health [174], the marked overproduction in sepsis generated by over-expression of iNOS [175] can result in pathophysiological consequences. The existence of a mitochondrial NOS (mtNOS) has been suggested [103] but this remains controversial. iNOS induction has been demonstrated in various cell types and organs, including cardiac tissue taken from human patients who died from sepsis [28,160,176]. Skeletal muscle nitrite/nitrate levels, a marker of NO production, correlate with the degree of mitochondrial dysfunction, illness severity and outcome in patients with septic shock [75]. These reactive nitrogen species (RNS) are critical mediators of NO-induced cytotoxicity via oxidative damage, protein nitrosylation and a longer-lasting protein nitration. This nitrosative stress has been demonstrated in cardiac tissues from both human patients [28,176,177] and experimental animals [112,178,179].

Oxidative and nitrosative stress act synergistically in causing mitochondrial damage and dysfunction with further, irreversible, inhibition of the electron transport chain at multiple sites [172,180]. This mitochondrial damage results in a bioenergetic deficit and a consequent decrease in cardiac contractility [181].

Beneficial effects on cardiac function and survival have been seen following the administration of both non-selective and selective NOS inhibitors in CLP and LPS rat models [182,183]. However, these findings did not translate into outcome benefit in patients with septic shock, where both a non-specific NOS inhibitor and a NO scavenger resulted in increased mortality [184,185]. Timing of administration, dosing and off-target effects may have contributed to these conflicting results. Indeed, some experimental data suggest a beneficial role for NOS in sepsis with positive effects on cardiac mitochondrial biogenesis [186]. Endothelial NOS deficiency was also associated with worse systemic inflammation and myocardial dysfunction in mice with polymicrobial sepsis [187]. Both endogenous and exogenous NO could downregulate inflammasome activation, whereas iNOS deletion or pharmacological inhibition resulted in the accumulation of damaged mitochondria, an increase in cytokine production and higher mortality [188]. Similarly, a clear benefit from non-specific antioxidant therapies has not been demonstrated in large clinical trials [189]. For example, *n*-acetylcysteine treatment aggravated sepsis-induced organ failure, in particular cardiovascular dysfunction, in clinical patients with sepsis [190]. In summary, oxidative and nitrosative stress are likely to play a central role in mitochondrial damage and dysfunction in the context of sepsis-induced cardiomyopathy through complex and incompletely understood pathways. However, their protective functions should not be ignored so the challenge is to titrate NO-modulating therapies to achieve optimal benefit.

5.4. Proton leak and uncoupling

Even under physiological conditions, the coupling of mitochondrial substrate oxidation to ATP synthesis is not particularly efficient, with a proportion of protons returning from the intermembrane space to the mitochondrial matrix bypassing the F_0F_1-ATPase [191]. This incomplete coupling is predominantly determined by a process called proton leak, also known as mitochondrial uncoupling. Proton leak can occur in the absence of any structural damage to the inner mitochondrial membrane and is closely linked to mitochondrial membrane potential [192]. A higher membrane potential is associated with an increase in proton leak, while a raised proton leak rate causes an increase in oxygen consumption and a decrease in membrane potential [191].

Mitochondrial ROS production is dependent on mitochondrial membrane potential. Thus, mild uncoupling, by lowering membrane potential, may represent a protective mechanism that acts as a safety valve to decrease ROS production and protect the mitochondria from oxidative damage [193]. ROS, in turn, have been shown to activate uncoupling, further supporting the role of uncoupling as a protective mechanism [194]. Mitochondria have a basal constitutive proton leak, the mechanism of which is not entirely understood but is likely determined by mitochondrial carrier proteins such as adenine nucleotide translocase [195]. It should be noted that the proton gradient is also utilised by mitochondrial transport mechanisms to drive the movement of ions or metabolites across the mitochondrial membrane; however, due to their relatively low density, the contribution of these transporters to basal proton conductance is likely to be minimal [195].

Mitochondria can also display an inducible proton leak, mediated by various mitochondrial transporter proteins, including the uncoupling proteins (UCPs). UCPs are a family of mitochondrial proteins structurally related to UCP1, or thermogenin, a protein expressed in brown adipose tissue that plays an important role in heat generation. UCP2 and UCP3 are the main mitochondrial proteins responsible for inducible proton leak outside brown adipose tissue and are both expressed in the heart. UCP2 and UCP3 do not play a role in basal proton leak, but various stimuli can induce their activity, including sepsis. An increase in proton leak and mitochondrial uncoupling proteins have been reported during sepsis in several tissues, in both animal models [85,196–200] and patients [85,199], however literature specific to the heart is sparse.

An increase in UCP2 mRNA expression, but not UCP2 protein levels, was described in a rat model of peritoneal sepsis [201], whereas LPS treatment to dogs up-regulated both UCP2 expression and protein levels, in association with an adverse effect on ATP synthesis [202]. Endotoxemia in rats and mice also induced an increase in cardiac UCP2 and UCP3 mRNA in association with mitochondrial ultrastructural and functional damage, decreased ATP production, oxidative stress, and cardiac dysfunction [108,120,163,203]. In contrast with these findings, cardiac UCP2 and UCP3 transcription was decreased in a CLP mouse model [165].

Conflicting evidence is also present on whether UCPs exerts a protective or detrimental effect in the context of sepsis. UCP2 upregulation increased sensitivity to LPS-induced acute lung injury [197] and liver injury [204] while its downregulation improved inflammation, survival and intestinal barrier function in mouse and rat CLP models of sepsis [199,205]. By contrast, UCP2 was protective in a model of sepsis-induced acute kidney injury [205], while UCP2 down-regulation increased cardiac and mitochondrial dysfunction in endotoxemic mice [163]. UCP2 overexpression in cardiomyocytes was associated with a decrease in ROS production, higher mitochondrial membrane potential and reduced cell damage on exposure to endotoxin [206] while gene

silencing or pharmacological inhibition of UCP2 had an opposite, detrimental effect [163,207]. Based on the above evidence it appears plausible that a mild uncoupling, induced via UCP2 and UCP3 up-regulation, plays a protective role in reducing oxidative damage in sepsis, particularly in cardiomyocytes.

5.5. Mitochondrial permeability transition

Another mechanism that modulates the complex interaction between mitochondrial ROS and mitochondrial dysfunction is mitochondrial permeability transition pore (mPTP) opening. mPTP opening is due to a sudden change in permeability of the inner mitochondrial membrane, which is normally extremely low, to allow passage of molecules < 1.5 kDa in size [208]. The molecular structure of the mPTP is still debated [209] but ATP synthase appears essential for its formation [210]. mPTP opening is often referred to as a pathological event causing mitochondrial depolarisation, disruption of oxidative phosphorylation, calcium release and matrix swelling. These processes can result in ATP depletion, outer mitochondrial membrane damage and release of pro-apoptotic factors such as cytochrome C [208]. Stimuli inducing mPTP opening include calcium overload, oxidative and nitrosative stress, adenine nucleotide depletion and dissipation of the mitochondrial membrane potential [211].

Some authors have postulated that irreversible mPTP opening may have an evolutionary purpose of identifying dysfunctional mitochondria that need to undergo selective autophagy (mitophagy), and therefore the mPTP may play a beneficial role in maintaining mitochondrial turnover and function [212]. However, if the permeability transition extends to a significant portion of the mitochondrial network, cell viability could become compromised [213]. Others have suggested that the mPTP may act as a checkpoint integrating energy metabolism information with cell death pathways [214].

Inhibition of the mPTP has shown cell protective effects in a wide variety of tissues and disease models; its therapeutic potential has been explored primarily in the context of ischemia-reperfusion injury and the heart [208,215]. The role of the mPTP has also been evaluated in experimental SIC. Cardiomyocytes exposed to LPS showed evidence of mPTP opening, indicated by increased sensitivity to calcium, in association with mitochondrial membrane depolarisation and ROS release [108,118,163,216]. These changes could be reversed by inhibitors of mPTP opening such as cyclosporin A [108] and melatonin [163], or up-regulation of 14–3-3 proteins that act as modulators of apoptotic pathways [216]. A similar increase in mPTP opening, accompanied by cardiac and mitochondrial dysfunction, was also observed in cardiac mitochondria isolated from septic animals [37,106,109,112]. Inhibition of mPTP with cyclosporin A prevented myocardial dysfunction, inflammation and apoptosis in LPS-treated rats [37] and improved survival, cardiac contractility and mitochondrial function in CLP mice [106]. Similarly, cyclosporin A pre-treatment normalised cardiac performance, mitochondrial function and structure in LPS-treated cats [112]. However, inhibiting mPTP opening resulted in greater myocardial protein carbonylation, a marker of oxidative stress, suggesting that the functional benefit of mPTP inhibition may come at the cost of greater ROS production.

Studies evaluating cyclosporin A, a calcineurin inhibitor, as an mPTP inhibitor in sepsis should be interpreted with caution. Calcineurin has many functions in cardiac metabolism and contractility other than mPTP modulation. A beneficial effect on cardiac function could be seen with calcineurin inhibitors that do not affect mPTP opening [112,217]. mPTP opening could also be attenuated in septic animals by activation of mitochondrial aldehyde dehydrogenase [109], an oxidative stress protective enzyme; up-regulation of BCL-2 [106], an anti-apoptotic protein; or NOS inhibition [182]. These treatments resulted in an improvement in both cardiac function and survival, highlighting the close interaction between oxidative/nitrosative stress, mPTP and apoptotic pathways.

In opposition to the high-conductance permanent mPTP opening described above, a low-conductance transient mPTP opening that shares similar mechanisms has also been reported. This opening is also favoured by calcium and ROS and results in a decrease in membrane potential, a reduction in mitochondrial calcium and the release of an oxidative burst. Transient mPTP opening is proposed to be a physiological protective mechanism acting as a “release valve” against calcium and ROS overload [218–221]. Transient mPTP opening has been primarily reported in cardiac mitochondria, and increases in frequency following ischemia, oxidative stress, cardiac stimulation and heart failure [222–224]. Moreover, transient mPTP opening has been proposed to be a critical mediator of cardiac preconditioning [225]. The occurrence of transient mPTP opening has not been evaluated in sepsis and it is unclear whether the increase in cardiac mPTP opening seen in septic models represents a permanent or transient phenomenon. However, given its significance in cardiovascular physiology, transient mPTP opening is likely to occur in SIC, and may potentially play a role as an intermediate, protective, state before transitioning to a permanent, and detrimental, opening. These data thus support the role of the mPTP and its interaction with oxidative stress in the genesis of the structural and functional mitochondrial abnormalities seen in the septic heart, with activation of apoptosis, decreased membrane potential, ATP depletion and overall cardiac dysfunction.

5.6. Mitochondrial calcium homeostasis

Calcium is an essential determinant of mitochondrial function and is, with ADP, the primary modulator of oxidative phosphorylation. Calcium stimulates oxidative phosphorylation at multiple sites within the mitochondria, determining an overall increase in ATP synthesis. This is particularly important in cardiomyocytes to allow tight matching of ATP supply and demand, and to respond rapidly to changes in cardiac workload and energy requirements [226]. In the heart, mitochondrial calcium uptake is facilitated by the presence of microdomains between intracellular calcium stores (i.e. the sarcoplasmic reticulum, SR) and mitochondria. These microdomains maintain in close proximity the site of calcium release within the SR (ryanodine receptors) and the site of calcium uptake in the mitochondria (i.e. the voltage-dependent anion channel and mitochondrial calcium uniporter in the outer and inner mitochondrial membranes, respectively). The SR-mitochondria link is maintained by tethering proteins such as mitofusins that are also involved in mitochondrial fission/fusion processes. This system allows a synchronisation of mitochondrial calcium, the main determinant of ATP supply, with ATP requirements generated by the excitation-contraction coupling process [227]. Mitochondrial calcium is also essential to maintain an adequate mitochondrial antioxidant capacity and to mitigate against the increase in ROS formation driven by an increase in ATP synthesis [228]. Mitochondrial calcium also carries detrimental effects, with mitochondrial calcium overload being a primary determinant of mPTP opening, especially in the presence of oxidative stress [226]. Therefore, it is not surprising that disturbances in mitochondrial calcium have been implicated in the pathophysiology of numerous diseases, including heart failure [229].

Abnormalities in intracellular calcium homeostasis have been investigated in the septic heart. Most models of sepsis reveal a decrease in cytosolic calcium transients (i.e. the difference between systolic and diastolic calcium), and this is associated with an increase in diastolic cytoplasmic calcium and a decrease in SR calcium content [62]. These findings appear to be due to dysfunctional SR calcium transporters, in particular ‘leaky’ ryanodine receptors (RyR) and the sarco/endoplasmic reticulum calcium-ATPase (SERCA) that generate, respectively, an increased release and a decreased reuptake of calcium [62]. Changes in cellular calcium concentrations are exacerbated by a desensitisation of the myofilament to calcium [62] or by changes in expression of calcium handling proteins [135].

Despite a significant literature suggesting a central role of

intracellular calcium imbalance in the pathogenesis of SIC, few studies have specifically evaluated the role of mitochondrial calcium. Myocardial mitochondrial calcium content increased in endotoxemic rats in association with abnormalities in mitochondrial respiration, membrane potential and myocardial dysfunction [230,231]. These defects could be reversed by pre-treatment with a caspase inhibitor [230] or dantrolene, an inhibitor of SR calcium release [231]. Similar findings were observed in vitro whereby mitochondrial calcium increased in cardiomyocytes following a 1-h exposure to endotoxin in a dose-dependent manner; dantrolene was again able to reverse the calcium overload [108]. Our lab evaluated mitochondrial calcium changes following electrical pacing in cardiomyocytes isolated from septic rats [35]; the rate of calcium increase was lower than in sham cardiomyocytes, and this was associated with other signs of mitochondrial dysfunction. Interestingly, a decreased area for potential contact between mitochondria and SR, and an increased distance between these organelles was noted on electron microscopy. These structural abnormalities could induce dysfunction of the mitochondria-SR microdomain, and be the cause of the slower calcium uptake observed. These findings could also represent an adaptive and protective response to prevent mitochondrial calcium overload at the expense of reduced energetic efficiency.

Myocardial calcium homeostasis has not been evaluated in human septic patients. However, large observational studies have recently reported that chronic use of calcium channel blockers leading up to hospital admission is associated with reduced mortality from sepsis [232,233]. Other experimental studies also support the protective effects of calcium channel blockers [234–236], with a specific beneficial effect on cardiac function [237].

5.7. Mitochondrial dynamics

Given the central role mitochondria play in cellular metabolism it is essential that their function is maintained through quality control mechanisms aimed at removing and replacing dysfunctional mitochondria, adapting to changing conditions, preserving bioenergetic efficiency, and preventing cell death. Disorders of these pathways are implicated in the pathogenesis of a variety of diseases [238]. These quality control systems include processes of fission, fusion, mitophagy and biogenesis.

The opposing processes of fission and fusion are the primary determinant of mitochondrial size, shape and number within the cell mitochondrial network. In non-proliferating cells, mitochondrial division (fission) is essential for segregation and removal of damaged mitochondria, while mitochondrial fusion facilitates distribution of ATP production within the cell, exchange of material between healthy mitochondria, and replenishment of damaged mitochondrial macromolecules. Mitofusins (Mfn1 and Mfn2) and optic atrophy 1 (OPA1) are the main proteins that regulate fusion for the outer and inner mitochondrial membranes, respectively, while fission is primarily mediated by dynamin-related protein 1 (Drp1). Mitochondrial fusion proteins also have pleiotropic non-fusion effects including tethering of mitochondria to the sarcoplasmic reticulum, modulation of apoptosis and mitophagy, and involvement in mitochondrial cristae modelling. As the mitochondrial network is relatively stable in adult cardiomyocytes and has only limited remodelling capabilities, these pleiotropic effects may play a role in cardiac disease [239].

The role of fission and fusion has been evaluated in experimental sepsis, although few studies have focused on cardiac mitochondria. Morphological changes compatible with fission and fusion processes could be noted on electron microscopy in rat hearts at 24 hour post-endotoxin administration [134]. A severe CLP model of murine sepsis showed an imbalance in cardiac fission and fusion, with activation of Drp1 and a downregulation of OPA1, in association with mitochondrial structural abnormalities, mitochondrial dysfunction and a decrease in cardiac contractility [165]. Activation of Drp1 was also noted in the hearts of LPS-treated mice, together with decreased mitochondrial size, increased fragmentation and abnormalities in morphology and function [240]. In contrast, OPA1 expression was mildly increased following sub-lethal LPS dose administration to mice [213]. These conflicting results are likely to reflect differences in the type and severity of insults. An imbalance between mitochondrial fission and fusion, along with persistent mitochondrial fragmentation, was also noted in the liver of septic rats; administration of an inhibitor of fission pathways (Mdivi-1) produced beneficial effects on mitochondrial function and apoptosis [241]. Interestingly, the same drug failed to improve contractile and mitochondrial function in the hearts of endotoxemic mice, suggesting an organ-specific response [240].

Autophagy is a process by which damaged proteins and organelles are delivered, in double-membrane vesicles (autophagosomes), to lysosomes for degradation. Autophagy can maintain cellular homeostasis or be involved in cell death. Mitophagy is a selective form of autophagy aimed at removing dysfunctional mitochondria before permeabilisation of the outer mitochondrial membrane, and the resultant induction of cell death pathways, occur.

Autophagy is activated in the heart during sepsis, although it is unclear whether this is protective or detrimental. Activation of autophagy and a decrease in mitochondrial content, evaluated via multiple techniques, were noted in the hearts of CLP- [100] and LPS-treated rodents [134,240,242]. An activation in cardiac autophagy was identified within 4 h of CLP in mice. Despite an increase in autophagic vacuolation, co-localization of autophagosomes and lysosomes decreased in septic animals, suggesting an impaired interaction and reduced autophagosome degradation. This incomplete autophagy was associated with cardiac dysfunction, ATP depletion, apoptosis and necrosis that could be all reversed with rapamycin, a stimulator of complete autophagy [243]. Similar findings were observed in vitro where induction of autophagy protected cardiomyocytes from LPS-induced cell death, whereas inhibition of autophagy achieved the opposite result [244].

LPS can induce not only early autophagy but also the more selective process of mitophagy [213]. Clearance of damaged mitochondria via activation of mitophagy is likely to promote the resolution of cardiac and mitochondrial dysfunction seen in the late phases of endotoxemia (48 h), given that this recovery was partially impaired in mice deficient of PARK2, a key regulator of cardiac mitophagy. Interestingly, despite the increase in mitophagy and the reduced expression in biogenesis-associated genes, an overall decrease in mitochondrial mass could not be detected. A beneficial role of mitophagy was also demonstrated in LPS-treated and CLP mice, where a deficiency in sestrin2, a protein responsible for mitochondrial priming in autophagy, was associated with an increase in mortality [245]. However, a deficiency in Rubicon, a Beclin 1-binding protein that negatively modulates autophagosome maturation, resulted in an enhanced autophagic flux and improved cardiac function [246]. A similar upregulation of cardiac autophagy was seen in LPS-treated mice, where induction of autophagy was associated with a potentially detrimental increase in oxidative stress. Overexpression of catalase reversed both oxidative stress and the increase in autophagy, in association with an improvement in survival [247]. Interestingly, cardiac-specific overexpression of the endogenous mitochondrial antioxidant thioredoxin-1 also improved outcomes in CLP mice, but this was in association with a stimulation, rather than a suppression, in autophagy [165]. The role of autophagy in LPS-induced cardiac dysfunction has also been evaluated in vitro with conflicting results: pharmacological inhibition could reverse contractile dysfunction in neonatal cardiomyocytes [247], but resulted in an increase in apoptosis and mitochondrial dysfunction in both neonatal cardiomyocytes and HL-1 cells [203,248].

Cells replace the damaged mitochondria removed by mitophagy via the process of mitochondrial biogenesis. PGC-1α and β [PPAR (peroxisome proliferator-activated receptor)-γ coactivator-1 α and β] are master regulators of mitochondrial biogenesis. PGC-1 interacts with specific nuclear receptors (i.e. peroxisomal proliferator-activated receptors, PPARs) and activates multiple transcription factors, including

NRF-1 and -2 (Nuclear respiratory factors 1 and 2), which subsequently promote Tfam (mitochondrial transcription factor A) expression. This coordinated signalling cascade results in an increase in mitochondrial DNA copy number and mass. Cardiac mitochondrial biogenesis has been evaluated in several experimental models of sepsis with somehow conflicting results.

Neonatal cardiomyocytes show a higher resistance to LPS-induced apoptosis compared to adult cardiomyocytes, and this resistance is postulated to be secondary to biogenetic processes [203]. Endotoxemia in rats resulted in an early (6 h) activation of mitochondrial biogenesis via upregulation of factors including PGC-1α, NRF-1, NRF-2 and Tfam [120,134]. Oxidative stress, with subsequent damage and depletion of mitochondrial DNA, is thought to be a primary driver of this response. Interestingly, despite a partial recovery in mitochondrial mass and architecture at 24–48 h post-LPS administration, mitochondrial function was not restored; this raises questions as to whether new mitochondria generated during sepsis could be dysfunctional and that overactivation of biogenesis might be maladaptive [120,134]. However, by contrast, LPS-induced oxidative stress down-regulated cardiomyocyte biogenesis in vitro, and this could be reversed by mitochondrially-targeted antioxidants [157]. Nitrosative stress could also play a role in the activation of biogenesis, with NOS2-deficient mice being unable to recover their cardiac mitochondrial mass following an endotoxin challenge [186]. These studies highlight the complex interaction between oxidative stress and biogenesis, with ROS having the potential to have both detrimental and protective effects on mitochondrial mass and function.

As mentioned, some studies reported a reduction, rather than an increase, in markers of cardiac biogenesis (e.g. PPAR or PGC-1 protein expression) in both in vitro and in vivo models of sepsis [98,157,165,213,242,249,250]. The reduction in biogenesis was associated with metabolic reprogramming, mitochondrial damage and contractile dysfunction, and could be prevented by mitochondrially-targeted antioxidants [157], overexpression of PGC-1 [249], or by PPAR agonism using rosiglitazone [242]. The latter treatment also improved survival rates in vivo. A link between regulators of biogenesis and cardiac dysfunction was also observed in PPAR-deficient septic mice: the lack of this nuclear receptor prevented the heart from developing an appropriate hyperdynamic response and decreased fatty acid oxidation in the early phases of sepsis [136].

Suppression of biogenesis in sepsis could also be reversed by administration of a carbon monoxide (CO) donor that concurrently resulted in an improvement in survival. Both these effects were postulated to be induced by a mild stimulation of oxidative stress [98]. A role for endogenous CO was also demonstrated in a variety of cell types in vitro, where LPS stimulated biogenesis by upregulation of heme-oxygenase 1, a CO-producing enzyme [251].

No specific data are available for mitochondrial dynamics in the human heart during sepsis, but some limited evidence is available for other organs. In biopsies taken from patients who died of sepsis there were signs of raised autophagy in the kidney, but not in the heart [31]. An increase in autophagosomes was also noted in the liver of septic patients [252]. We took muscle biopsies from septic patients and showed a decrease in expression and levels of mitochondrial respiratory enzymes, indicating a decrease in mitochondrial mass that was greater in non-survivors. This was counteracted, but only in patients who went on to survive, by early activation of biogenesis via upregulation of PGC-1, in association with an improved ATP content, suggesting that biogenesis might play a protective role [81]. Similarly, Fredriksson and colleagues showed an increase in expression of NRF2 and Tfam, but not PGC-1, in skeletal muscle biopsies taken from septic patients. These results suggest a partial activation of biogenesis, also supported by maintained mitochondrial protein synthesis and a trend toward an upregulation of mitochondrial-related genes in a global transcriptional analysis [253].

The study of mitochondrial dynamics is particularly important to establish whether mitochondrial quality, quantity, or a combination of both, determines cell and organ dysfunction in sepsis. Some authors have suggested that a decrease in mitochondrial density rather than a direct inhibition of specific enzymes causes the decrease in mitochondrial respiratory activity seen in sepsis [82]. This uncertainty stems in part from the variety of methodologies used in the assessment of mitochondrial mass and the normalisation of mitochondrial activity by mitochondrial content [254]. Studies looking at the transcriptomic and proteomic response to sepsis could help address this question. Endotoxin treatment to healthy human volunteers induced a transcriptional reprogramming in peripheral blood monocytes with an extensive suppression of mitochondrial genes [255]. A similar reprogramming was also observed in cardiac tissue from patients who died of sepsis. In comparison with other cardiac diseases, the septic heart shows a marked decrease in the expression of numerous genes, including most of those encoding mitochondria-located ATP production proteins [256]. Experimental sepsis induces significant changes in gene and protein expression. Global changes in the cardiac transcriptome were noted in rodent models of polymicrobial sepsis, with modulation of bioenergetic metabolism and mitochondrial function genes [135,257]. Moreover, the cardiac and liver proteomes were also altered in CLP rats, with the majority of downregulated proteins being associated with mitochondrial function [258].

The evidence for mitochondrial reprogramming in response to sepsis that emerges from these studies provides an alternative explanation to the prevailing tenet of mitochondrial damage as the primary mediator of dysfunction. It is was therefore postulated that both genetic and cytopathic mechanisms may contribute to the bioenergetic deficits seen in sepsis [93].

5.8. Myocardial hibernation

If sepsis-induced mitochondrial dysfunction is, at least partially, due to a mitochondrial reprogramming, it is legitimate to query the evolutionary advantage of a coordinated activation of pathways leading to a decrease in cell metabolism and energy production. An answer could come from looking at similarities in the heart's response to sepsis and ischemia.

Myocardial hibernation is a well-described phenomenon in the human heart that occurs following ischemia and results in an adaptive downregulation of myocardial oxidative metabolism and function. This protective process sacrifices cardiac contractility to decrease energetic demands and match a reduced oxygen supply, therefore preventing ATP depletion, excessive ROS production and cardiomyocyte death [259]. The metabolic phenotype of the hibernating ischemic heart in human patients and experimental animals matches what is seen in nature in species that undergo seasonal hibernation or similar ‘metabolic shutdown’ processes such as torpor or estivation [260]. Myocardial hibernation has not been extensively described outside cardiac ischemia and hypoxia, but sepsis is one of the diseases in which hibernation has been proposed to play a role [261]. Changes compatible with cardiac hibernation were seen in the hearts of experimental septic animals, with an increase in myocardial glucose uptake, glucose transporter levels and glycogen storage [262]. Proposed mediators of this metabolic suppression include hormones, inflammatory mediators or endogenous gases such as NO, CO and hydrogen sulfide. These gaseous signalling molecules act in various ways, including inhibition of complex IV and activation of various transcription factors that regulate mitochondrial gene expression (e.g. Nrf2 or hypoxia-inducible factor 1) [68,262]. Indeed, the administration of exogenous donors of CO or hydrogen sulphide has shown positive effects in experimental sepsis [98,263]. The coordinated genomic response observed in the septic human heart further supports a cardiac-specific hibernation, with a decrease in the expression of genes involved not only in ATP production but also ATP consumption (i.e. sarcomeric contraction and excitation-contraction coupling) [256].

Taken together, these data raise the possibility that many of the

mitochondrial changes seen in the septic heart represent a protective process rather than a purely pathological phenomenon. This fits with the more general idea that organ failure in critical illness is primarily a functional rather than a structural abnormality and may constitute an adaptive response to prolonged stress [77,264]. This 'metabolic shutdown' trades a temporary cell and organ dysfunction for the maintenance of cell viability. Avoiding cell death confers the possibility of a recovery in organ function in those patients that go on to survive [68].

6. Conclusion

Sepsis-induced cardiomyopathy is a commonly recognised manifestation of sepsis and is associated with worse patient outcomes. There is significant experimental evidence that mitochondrial dysfunction is involved in the development of SIC, although causality has not been definitively established. Data regarding cardiac mitochondrial dysfunction in human sepsis are limited and indirect. Evidence in laboratory studies can be conflicting, likely due to inconsistencies introduced by the models and techniques used.

The proposed mechanisms leading to mitochondrial dysfunction are multiple, ranging from structural damage to abnormalities in the mitochondrial life cycle, and with no clearly established temporal sequence. The degree to which each of the implicated mechanisms contributes to mitochondrial dysfunction is currently unknown. However, a pattern does seem to be emerging: mitochondrial pathways activated in sepsis appear, in moderation, to be potentially protective, however, if left unchecked, progress to detrimental effects. Therefore, SIC could represent an adaptive, protective mechanism, with a trade-off between short-term organ function and longer-term tissue viability. Persistent mitochondrial abnormalities with lack of recovery could be responsible for the transition from adaptive to maladaptive organ dysfunction. If so, any targeted therapeutic strategy must avoid any abrogation of the protective effects.

The current lack of tools to evaluate cardiac mitochondrial function directly in human patients emphasises the need for continuing preclinical research to better understand SIC pathophysiology. Harmonisation of experimental methodologies will be necessary to move the research agenda forward. Developing a consensus definition and diagnostic criteria for SIC, with novel and sensitive biomarkers of mitochondrial damage and function, will facilitate this research; this includes identification of putative targets and subsequent testing of directed therapies.

Transparency document

The Transparency document associated with this article can be found, in online version.

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