The International Journal of Biochemistry & Cell Biology 81 (2016) 307–314

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Cardiac dysfunction, mitochondrial architecture, energy production, and inflammatory pathways: Interrelated aspects in endotoxemia and sepsis

Silvia Alvarez*, Tamara Vico, Virginia Vanasco

Institute of Biochemistry and Molecular Medicine (IBIMOL, UBA-CONICET), School of Pharmacy and Biochemistry, University of Buenos Aires, Junín 956, C1113AAD Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 9 June 2016
Received in revised form 22 July 2016
Accepted 27 July 2016
Available online 28 July 2016

Keywords:
Sepsis
Endotoxemia
Heart
Bioenergetics

ABSTRACT

Septic patients with myocardial dysfunction have a 3-fold increase in mortality compared with patients without cardiovascular impairment, and usually show myocarditis, disruption of the contractile apparatus, increased amounts of interstitial collagen, and damaged mitochondria. The presence of nitric oxide and cytokines in cardiac tissue constitute the molecular markers and the intracellular messengers of inflammatory conditions in the heart due to the onset of sepsis and endotoxemia, derived from the nuclear factor-κB pathway activation and proinflammatory gene transcription. Sepsis occurs with an exacerbated inflammatory response that damages tissue mitochondria and impaired bioenergetic processes. The heart consumes 20–30 times its own weight in adenosine triphosphate every day, and 90% of this molecule is derived from mitochondrial oxidative phosphorylation. Cardiac energy management is comprised in sepsis and endotoxemia; both a deficit in energy production and alterations in the source of energy substrates are believed to be involved in impaired cardiac function. Although several hypotheses try to explain the molecular mechanisms underlying the complex condition of sepsis and endotoxemia, the current view is that these syndromes are the result of an intricate balance between prevailing levels of mitochondrial stress, biogenesis/autophagy signaling and mitochondria quality control processes, rather on a single factor. The aim of this review is to discuss current hypothesis of cardiac dysfunction related to energy metabolism and mitochondrial function in experimental models of sepsis and endotoxemia, and to introduce the importance of lipids (mainly cardiolipin) in the mechanism of cardiac energy mismanagement in these inflammatory conditions.

1. Introduction

Sepsis constitutes a major cause of death following trauma and a persistent problem in surgical patients. Three related syndromes, with the common background of sepsis, are recognized in increasing order of severity: systemic inflammatory response syndrome (SIRS), septic shock, and multiple organ failure (MOF). The onset of sepsis is characterized by fever, usually accompanied by tachycardia and tachypnea. These symptoms characterize SIRS, and evolve to septic shock when hypotension and loss of conscience appear and to MOF when organ dysfunction develops (Dianzani, 1996). The prevalent hypothesis regarding the mechanism of the three related syndromes is that they are caused by an excessive defensive and inflammatory response. Sepsis is a paradigm of acute whole body inflammation, with massive increases of NO and inflammatory cytokines in the biological fluids, with systemic damage to vascular endothelium, and with impaired tissue and whole body respiration despite adequate O_2 supply (De Angelo, 1999; Goris et al., 1985; Pinsky, 2001).

End-organ damage and organ failure in sepsis affect significant organs of the body, including the heart. Myocardial dysfunction is a well described complication of severe sepsis and endotoxemia, which includes both systolic and diastolic dysfunction (Cimolai et al., 2015). A number of mechanisms have been proposed to be involved in myocardial dysfunction in this syndrome, including toxins, cytokines, NO, complement activation, apoptosis and energy metabolic derangements (Romero-Bermejo et al., 2011; Rudiger and Singer, 2007).

The aim of this review is to discuss the different experimental approaches to study sepsis and endotoxemia, the current hypothe-

* Corresponding author at: Institute of Biochemistry and Molecular Medicine (UBA-CONICET), School of Pharmacy and Biochemistry, University of Buenos Aires, Junín 956, C1113AAD, Buenos Aires, Argentina.
E-mail address: salvarez@ffyb.uba.ar (S. Alvarez).

http://dx.doi.org/10.1016/j.biocel.2016.07.032
1357-2725/

sis that try to explain the occurrence of cardiac dysfunction related to energy metabolism and mitochondrial function, and to introduce the importance of lipids (mainly cardiolipin) in the mechanism of cardiac energy mismanagement in these inflammatory conditions.

2. Animal models of endotoxemia and sepsis

When utilizing sepsis and endotoxemia models, a number of important questions arise. What is the relevance of skeletal muscle data to "more vital" organs such as liver or heart? Are these changes causal or epiphenomenal? Ethical and technical difficulties constrain the availability of vital human biopsy tissue, especially when repeated sampling is desirable to monitor disease progression and concurrent mitochondrial function. Consequently, it is advisable to develop representative animal models that reflect many, if not all, of the biochemical and physiological abnormalities evidenced in patients. However, experimental models of sepsis and endotoxemia show considerable variation in organ function and ultraestructural damage, due in no small part to the model itself.

One of the animal models most extensively used is the ip injection of the *E. coli* lipopolysaccharide (LPS) in an approximate dose of 10 mg/kg (Alvarez and Boveris, 2004; Escames et al., 2003). The studies are performed after 6 h of treatment, where the peak of acute inflammation effects is observed. LPS induces a receptor mediated signaling cascade that leads to nuclear factor-κB (NF-κB) activation and the transcription and subsequent release of cytokines and other proinflammatory mediators by monocytes and macrophages. The intracellular events that lead to the activation of NF-κB are complex and seem to be controlled by the redox status of the cell (Flohe et al., 1997).

The generation of peritonitis on rats better simulates the human disease process; two procedures are utilized. The cecal-ligation and puncture procedure is performed in anesthetized animals (Lopez et al., 2006; Watts et al., 2004).This model of sepsis results in septic shock, lactic acidosis, and hypothermia 12 h after the surgery; mortality is about 13%. Another procedure to generate peritonitis is the ip injection of fecal slurry (dose: 6.25 ml/kg). This is prepared from the bowel contents of rats, suspended in saline solution and filtered to remove fibrous material (Brealey et al., 2004). The animals can be studied at 24, 48 and 72 h after the induction of sepsis. By 24 h, 17% of rats can be classified as moderate septic; at 48 hs, 41% of rats are in the same level of sepsis; at 72 h, 73% of the rats still alive can be classified as mild and 27% as moderate. This model of sepsis results in animals with a fall in mean blood pressure and a rise in serum urea, creatinine, and alkaline phosphatase.

It is relevant to mention that the use of genetically modified strains of mice is a useful way to explore the importance of particular gene products in the pathogenesis of sepsis and endotoxemia. For example, the use of $TLR4^{-/-}$ mice allowed describing Toll like receptors (TLRs) as regulators of the LPS cellular response (Hoshino et al., 1999). Other examples include the use of mice that overexpress LC3 (Lo et al., 2013) or TSG-14 (Dias et al., 2001) to analyze the importance of autophagy or involvement of the mentioned factor in the response, respectively.

Ideally, it is advisable to generate a long-term septic model closely resembling the human disease process, combining physiological and biochemical markers of mitochondrial function. Such model would enable monitoring the temporal changes, comparison of vital and less vital organs, and serve as a potentially useful test bed for therapies.

3. Inflammatory pathways in endotoxemia and sepsis

The inflammatory component of the pathophysiology of sepsis is complex, involving activation of plasmatic (complement activation and coagulation) and cellular (macrophagic, endothelial, trombocytic, cellular immunity) systems. The innate immune response leads to a strong activation of the cytokine system (Schulte et al., 2013), which effects on cardiac tissue and vasculature lead to changes in vascular permeability and endothelial function (Ince et al., 2016). In this situation, the endothelium shifts from an anticoagulant surface to a procoagulant surface (Dauphinee and Karsan, 2006). Moreover, also endothelial cells can upregulate iNOS expression increasing the production of NO (Morikawa et al., 2000).

The classical pattern recognition molecule in these syndromes, sepsis and endotoxemia, is LPS. It is an important structural component of the outer membrane of gram-negative bacteria. It consists of three parts: the bioactive lipid A, an oligosaccharide core, and an O side chain; being lipid A a relative conservative region and essential for host recognition. Association of LPS with plasma LPS-binding protein (LBP) facilitates the interaction of LPS with CD14 (a glycosilphosphatidylinositol-anchored protein preferentially expressed in monocytes/macrophages and neutrophils) (Takeda et al., 2003), which in turn modulates LPS recognition and transfers LPS to the TLR4/MD-2 receptor complex. TLR4 is part of TLR family that consists of 10 members (TLR1-TLR10), and the TLR involved in the recognition of LPS. MD-2 has been identified as a molecule associated with the extracellular portion of TLR4 that enhances LPS responsiveness (Akashi et al., 2000). This complex turns on signaling mechanisms that finally result in the production of cytokines (Drosatos et al., 2015).

LPS-mediated signaling starts from the cytoplasmic portion of TLR4 that is called TIR (Toll/IL-1 receptor) domain and is mediated by several intracellular proteins such as MyD88 (myeloid differentiation primary response gene 88), TIRAP (TIR domain containing adaptor protein), TRIF (TIR domain containing adaptor inducing IFN-β), TRAM (TRIF-related adaptor molecule) (Lu et al., 2008). This signaling mechanism continues through MyD88-dependent and MyD88-independent (or TRIF-dependent) pathways (Lu et al., 2008). MyD88 is essential for the production of inflammatory cytokines in response to a variety of microbial components. However, LPS is still able to induce activation of NF-κB in MyD88-deficient macrophages, but with delayed kinetics (Kawai et al., 1999).

The MyD88-dependent pathway provides the recruitment of the adaptor molecules (TIRAP and MyD88) to the TIR domain. This leads to the phosphorylation of IRAKs, and ubiquitination of TRAF-6. Ubiquitination is thought to be a step that directs modified target proteins to the proteasome, where they are degraded. However, ubiquitination of TRAF6 mediates activation of NF-κB and JNK/p38 through a process that does not require protein degradation (Takeda et al., 2003). The consequence of this activation is the release of pro-inflammatory cytokines. The MyD88-independent pathway results in the activation of IRF-3 which allows the transcription of genes with an interferon response element and chemokine genes (Fitzgerald et al., 2001). The whole mechanism is overviewed in Fig. 1.

The transcription factor NF-κB seems to be a central target for activators or inhibitors of the inducible isoform of NO synthase (iNOS) expression. Although the mechanism of iNOS induction is not fully understood, it clearly involves the transcription of mRNA and novel protein biosynthesis (Ruetten and Thiemermann, 2000). LPS, IL-1β, TNF-α, and oxidative stress, for instance, have been shown to induce iNOS expression in different cell types by activating NF-κB (Kleinert et al., 2000). Cytokines constitute a heterogeneous group of proteins produced by different cell types that modulate the functions of proximate cells, including the secretion of other cytokines with synergistic or inhibitory effects. In acute inflammation, proinflammatory cytokines and lipid mediators play a key role in triggering the expression of iNOS in various cell types. Interestingly, inhibitors of the activation of NF-κB can also inhibit

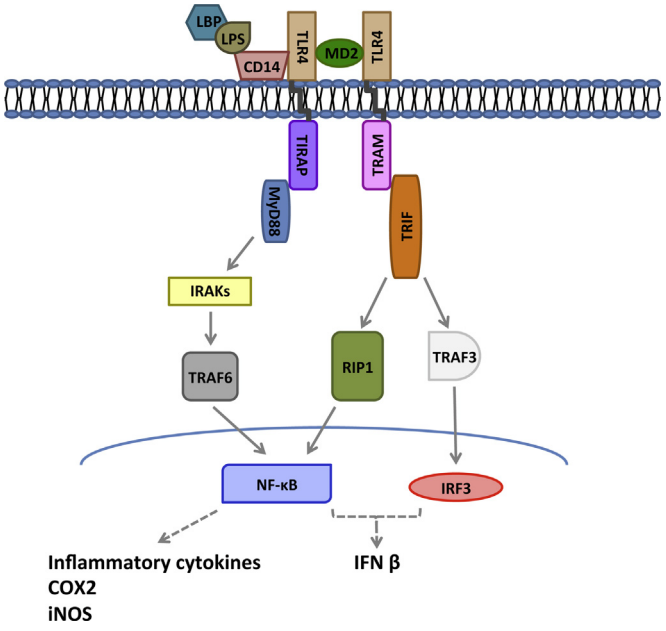

Fig. 1. Simplified model of LPS-signalling. Circulating LBP recognizes LPS in plasma and brings it to CD14. This aids the loading of LPS onto the LPS receptor complex TLR4/MD2. Subsequent signals activated by TLR4 can be subdivided into those dependent on MyD88 (and TIRAP) (represented by the events illustrated on the left side of the scheme), and those independent of MyD88 that use TRIM and TRAF as adapters (depicted on the right side of the scheme). In the MyD88 dependent pathway, IRAKs and Traf 6 are activated, as well as the transcription factor NF-κB. This transcription factor induces the expression of proinflammatory cytokine and other inflammatory actors (as COX2 and iNOS) genes. In the MyD88 independent pathway, RIP1 and TRAF3 are activated, which in turn activate the transcription factor IRF3 and NF-κB. These events lead to the expression type 1 interferon and interferon-inducible genes.

the induction of iNOS (Ruetten and Thiemermann, 2000). In inflammatory conditions, the production of NO can rise from 20 up to 600 uM in plasma.

Nitric oxide influences many aspects of the inflammatory cascade ranging from its own production by immunocompetent cells to the recruitment of leukocytes. When considering the multifaceted roles of NO, it is not surprising that the pharmacological inhibition of the production of NO in inflammation may have either detrimental or protective effects (Boveris et al., 2002b). In general, NO produced by the constitutive endothelial NOS (eNOS) is considered protective. This early NO production is essential in maintaining vascular function. Induction of the inducible NOS isoform (iNOS) has been demonstrated in almost all forms of acute inflammation; in these conditions the overproduction of NO is found to be cytotoxic (Szabó, 2000).

More than two decades have passed since the discovery that an enhanced formation of NO contributes to the circulatory failure in patients with septic shock (Thiemermann and Vane, 1990). Although the effects of selective inhibitors of iNOS activity have not been evaluated in controlled clinical trials, there is good evidence that an enhanced formation of NO by iNOS contributes to the circulatory and heart failure associated with sepsis and endotoxemia in humans (Ruetten and Thiemermann, 2000).

4. Cardiac dysfunction

It has been observed that septic patients with myocardial dysfunction have a 3-fold increase in mortality compared with patients without cardiovascular impairment (Blanco et al., 2008). Experimental approaches using *in vivo* animal models (Merx et al., 2005), isolated hearts (McDonough and Virag, 2006), and cultured cells (Ren et al., 2002), and human studies (Poelaert et al., 1997) have demonstrated that decreased contractility and impaired myocardial compliance are major factors in myocardial dysfunction in sepsis.

The pathophysiological mechanisms underlying sepsis-associated myocardial dysfunction are not fully understood. Parker and colleagues (Parker et al., 1984) reported that decreased left ventricle ejection fraction (LVEF) and ventricular dilatation as evidenced by increased LV end-diastolic volume index returned to normal in survivors over 7–10 days, suggesting that myocardial depression is a reversible condition (Smeding et al., 2012). This is one of reasons why it is thought that the problem is rather functional than structural. However, some studies show that structural changes in the heart may also occur (Fenton et al., 2004; Turner et al., 1999).

Myocardial infiltration of immune cells is a recognized feature of severe sepsis; the predominant cell types found include polymorphonuclear cells and monocytes/macrophages (Smeding et al., 2012). The cardiac functional correlate with myocardial infiltration has been evaluated in several studies. The use of LPS in Sprague-Dawley rats showed interstitial edema, infiltration by white blood cells and decreased myocardial function (analyzed as LV developed pressure and dP/dT_{max} and dP/dT_{min}) (Fauvel et al., 2001; Neviere et al., 2001). Another study revealed subepicardial acute inflammation and increased interstitial space followed by decreased LVEF (Chagnon et al., 2006). Using the same experimental model, but in rabbits, Goddard and colleagues (Goddard et al., 1996) reported increased concentration of leukocytes in myocardial capillaries, cytoplasmic vacuolation, zonal contraction banding, and decreased LV contractility defined by Emax (maximum elastance).

Mitochondrial dysfunction and ineffective O_2 utilization (cytopathic hypoxia) has also been observed (Fink, 2001), and functionally correlates with cardiac performance. Using an endotoxemia model in rats, it was shown decreased LV developed pressure and diastolic dysfunction *ex vivo*, related to cytochrome c loss and decreased mitochondrial respiration (Fauvel et al., 2002; Suliman et al., 2004). In cats, it was described significant reductions in dP/dT and dP_{max}/dT and increased LV relaxation time associated to decreased respiratory control ratio (Joshi et al., 2006). Studies using cecal-ligation puncture model in mice and rats described reduced contractility, decreased cardiac work, and reduced ratio of hydraulic work to O_2 consumed associated with decreased tissue energy levels (Larche et al., 2006; Watts et al., 2004).

Taking these observations into account, various mechanisms can explain the development of myocardial depression in sepsis and endotoxemia. Of note, the degree of myocardial structural derangement and functional impairment relates to illness severity (Rudiger and Singer, 2007). Future integrative studies are needed to distinguish the importance and hierarchy of these mechanisms (acute inflammation and mitochondrial dysfunction). Finally, it is worth considering that myocardial depression could, in some situations, protect the heart by reducing cellular energy expenditure in a situation when energy generation is impaired due to mitochondrial dysfunction and microcirculatory abnormalities. Analogies can be drawn to ischemia-induced hibernation (Rudiger and Singer, 2007), a well-recognized phenomenon in patients with ischemic heart disease, serving as regulatory event that maintains myocardial integrity and viability (Heusch et al., 2005). Similar cellular changes to those seen during hibernation have been reported in septic animals in conjunction with diminished cardiac performance (Levy et al., 2005). This concept worth further investigations as it may carry major implications for patient management.

5. Mitochondrial structure and function in endotoxemia and sepsis

5.1. Mitochondrial architecture and cell fate

Heart requires large amounts of energy to sustain contractile function, and is the major consumer of energy in the body on a weight basis. It has been shown that during heart failure, the myocardium has low ATP content due to decreased ability to generate ATP by oxidative metabolism, and thus it is unable to effectively transfer chemical energy to contractile work (Maack and O'Rourke, 2007).

Patients who died from sepsis showed myocarditis, disruption of the contractile apparatus, increased amounts of interstitial collagen, and damaged mitochondria (Rossi et al., 2007; Torgersen et al., 2009). Speculatively, persistence of structural alterations may, among others, contribute to the morbidity, decreased health-related quality of life, and increased mortality observed in hospitalized septic patients (Smeding et al., 2012).

In adult cardiomyocytes, mitochondria largely exist as discrete rounded organelles packed together between myofibrils. They are also clustered within the perinuclear and subsarcolemmal regions, but in no instance do they normally form interconnected networks (Dorn, 2015). Thus, when compared with nonmyocytes, cardiomyocytes mitochondria appear fragmented (Dorn, 2015). This observation can be explained in a biomechanical way: a collection of individual cardiomyocyte mitochondria is intrinsically more deformable than a highly interconnected framework. Normal mitochondrial morphology includes well-defined double membrane with normal cristae arrangements and preserved morphology and size. Our laboratory showed that 6 and 18 h after LPS injection (10 mg/ kg dose) in Sprague-Dawley rats, cardiac mitochondria displayed several abnormalities, such as formation of internal vesicles, loss and/or disruption of cristae, cleared matrix and swelling (Vanasco et al., 2014). Using similar endotoxemia models, other authors informed condensed mitochondrial matrix, and shortened cristae (Gotloib et al., 1992; Zang et al., 2007). Decreased mtDNA copy number was also observed decreased (Suliman et al., 2004; Vanasco et al., 2014). Using CLP model, decreased membrane integrity, less electron density, enlargement of mitochondria and destruction of cristae was informed (Gonzalez et al., 2014; Watts et al., 2004).

It has been informed that mitochondrial abnormalities observed and previously described in this review, may decrease at longer periods after LPS challenge (Gotloib et al., 1992; Vanasco et al., 2014). For example, 24 h after LPS administration to Sprague-Dawley rats, mitochondria of different size and mitochondrial structures compatible with fission/fusion processes were observed (strangulated or interconnected mitochondria) (Vanasco et al., 2014). Volume density returned to normal values although some cristae disruption was still observed.

During sepsis-induced inflammation, cell survival requires the full support of energy metabolism, and damage to mitochondria may initiate apoptosis, trigger necrosis, or both, by several mechanisms (Piantadosi et al., 2007). These mechanisms manifest biochemically through oxidation, nitration, or nitrosation of mitochondrial structural components, causing failure of the energy supply or activation of the core apoptotic pathway (Su, 2002). The latter pathway is regulated by the calcium-dependent mitochondrial permeability transition pore (PTP) and by Bcl-2 family proteins that link mitochondrial function to apoptosome formation (Green and Kroemer, 2004).

In order to restore functional cardiac mitochondria population in these inflammatory syndromes, it has been suggested that the activation of the mitochondrial biogenesis process may rapidly adjust mitochondrial mass, functionality and distribution (Hickson-Bick et al., 2008; Lancel et al., 2009). Maintenance of a healthy mitochondrial population is essential for cellular function and survival, and is controlled by balancing biogenesis and turnover of mitochondria by mitophagy. This multifaceted protective system involves a highly-integrated nuclear transcription network controlled by energy-sensing and inflammation- and redox-sensitive transcription factors and co-activators involved in mitochondrial biogenesis, anti-oxidant enzyme induction, cell survival, and immune tolerance (Piantadosi and Suliman, 2012a,b). Mitochondrial biogenesis is a bigenomic program of nuclear- and mitochondrial-encoded gene regulation that needs, in consequence, a proper interplay between nucleus and mitochondria and coordinated transcription of activating factors. In this program, the master activator PGC-1α (PPARγ coactivator 1-α protein) integrates physiopathological signals with mitochondrial biogenesis and oxidative metabolism (Wu et al., 1999). Authophagy comprises a lysosomal-mediated degradation process that involves more than 30 proteins. Autophagic activities thus need to be highly regulated to sense intracellular stress, through mechanisms involving cellular redox signaling (Levonen, 2014; Levonen et al., 2014).

The relevance of work the of Vanasco et al. (2008) is that it highlights the importance of analyzing the time course (0–24 h) of different events related to cardiac mitochondrial fate and function in an *in vivo* acute inflammatory model as endotoxemia. Briefly, and taking the discussed data into account, blood NO levels are observed increased at 6 h of LPS challenge and remained increased at all time-points analyzed; the expression of PGC-1α and mtTFA was also observed increased since 6 h. Autophagy occurred at a later period, as observed by the increase of LC3-II expression al 18 h; this observation was accompanied by a decrease in mitochondrial DNA content. Mitochondrial mass was observed increased only 24 h after the initiation of the endotoxemic process. Unfortunately, the analysis of mitochondrial function at these time points showed that, in this experimental model, partial restoration of mitochondrial architecture may not be accompanied by improvement of mitochondrial function (Vanasco et al., 2014).

Yuan et al. (Yuan et al., 2009) showed in a similar model that autophagy is activated prior to mitochondrial biogenesis. It is unclear if autophagy is induced as part of a cellular program leading to apoptosis or as an attempt to remove damaged mitochondria. Consequently, the final scenario in heart during endotoxemia and sepsis derives from a complex relationship between different processes aimed to cope with decreased energy producing capacity of the organ. These processes mainly include mitochondrial biogenesis, autophagy and cell death (apoptosis and/or necrosis). The analysis of the relationship between these processes opens a new and vacant area of investigation that emerges as potential target for pharmacological intervention.

5.2. Energy mismanagement I: lipids in energy production in heart and mitochondria

The heart consumes 20–30 times its own weight in ATP every day, and 90% of this ATP is derived from mitochondrial oxidative phosphorylation. Cardiac mitochondrial bioenergetics is compromised in sepsis and endotoxemia; both a deficit in energy production and alterations in the source of energy substrates are believed to be involved in impaired cardiac function.

Energy substrates primarily used by the heart include fatty acids and carbohydrates (Lopaschuk et al., 2010). Fatty acids are the main energy substrate of the heart and provide the majority of cofactors necessary for mitochondrial oxidative phosphorylation. Also, lipids interaction is dynamical and affecting membrane characteristics. Since electron transport carriers reside in the mitochondrial inner membrane, lipid composition and characteristics can profoundly affect mitochondrial bioenergetics.

Fatty acid and glucose metabolism interregulate each other; increasing fatty acid oxidation in the heart decreases glucose oxidation, while increasing glucose oxidation inhibits fatty acid oxidation (Randle et al., 1963). In the heart, metabolism of fatty acids (as palmitate) accounts for 60–90% of the total energy production (20.1 kJ/L O_2) in the form of ATP. In other words, oxidation of 1 palmitate molecule consumes $23O_2$ molecules and produces 105 ATP molecules. Carbohydrates (as glucose) contribute with the remaining 10–40% (21.7 kJ/LO_2). Six O_2 molecules are consumed per 31 ATP molecules produced from full oxidation of 1 glucose molecule (Fillmore et al., 2014). Although palmitate does contain more energy per gram of substrate (40.5 kJ/g) as compared to glucose (20.1 kJ/g), both substrates present similar ATP molecule produced/O_2 molecule consumed yield (Ventura-Clapier et al., 2011) This analysis helps to understand why the shift to elevated fatty oxidation rate/glucose oxidation rate ratio may reduce cardiac efficiency. In sepsis and endotoxemia, decreased rates of fatty acid oxidation have been observed that cannot be compensated by increased glucose catabolism (Drosatos et al., 2013). It has been suggested that efficiency of fatty acid oxidation in this inflammatory syndrome might be decreased relative to circulating triglyceride levels due to a depletion of carnitine (necessary for the transport of long-chain fatty acids into mitochondria and subsequent β-oxidation) (Proulx et al., 1997). Thus, depletion of carnitine may have an important role in the onset of cardiac energy deficiency.

Cardiolipin (CL) is a unique lipid dimer with two phosphates head groups and four acyl side chains, thus giving it a conical structure. It is almost exclusively present in mitochondrial membranes, and is important for mitochondrial architecture and function. In eukaryotic cells the fatty acid composition of CL is modified from that of its precursors to a cell-dependent composition (Schlame, 2013). The most dramatic modification occurs in heart mitochondria where 80% of the fatty acid chains are 18 carbons long with double bonds between carbons 9/10 and carbons 12/13 (linoleic acid, $18:2^{\Delta 9,12}$). Cardiolipin promotes membrane curvature and formation of inner membrane cristae, and plays an important role in maintaining membrane fluidity and osmotic stability (Paradies et al., 2014). Many of the respiratory complexes and carrier proteins require CL for optimal assembly and function, as it helps to organize the respiratory complexes into supercomplexes to facilitate optimal electron transfer (Mileykovskaya and Dowhan, 2014a,b). It has been informed a direct correlation between reduced CL levels and disruption of the architecture of supercomplexes in heart mitochondria (Mileykovskaya and Dowhan, 2014a,b). Due to its structure (high content of unsaturated fatty acids) and location (near the site of ROS production), CL is particularly vulnerable to oxidative damage (Paradies et al., 2010). Oxidation of CL disturbs microdomains in the inner mitochondrial membrane and causes loss of curvature. Also, in these conditions 4-hydroxynonenal and other reactive lipid electrophiles can be formed (Yin and Zhu, 2012). It was indicated that oxidized cardiolipin can act as a pro-inflammatory factor, potentially causing or promoting heart failure and playing an important role in inflammatory conditions as observed in sepsis and endotoxemia (Wan et al., 2014). Moreover, it causes cyt c release from mitochondria causing the activation of cell death mechanisms. All of these observed consequences of damaged CL may result, through alteration of the normal mitochondrial lipid milieu, in respiratory chain dysfunction and may set the stage for apoptosis (Szeto, 2014).

5.3. Energy mismanagement II: mitochondrial dysfunction

Although the precise mechanism by which sepsis and endotoxemia lead to cardiac failure is not clear, there has been awareness about the central role of mitochondrial dysfunction in the genesis of cardiac failure (Boveris et al., 2002a; Escames et al., 2007). Although microvascular flow redistribution occurs, we and others have shown that mitochondrial dysfunction is important in these conditions indicating that an inadequate use of cellular O_2 coexists with impaired O_2 delivery (Fink, 2001; Vanasco et al., 2008).

During oxidative phosphorylation, electrons from reduced substrates are transferred to O_2 through a chain of electron transporters, and the energy provided by these electron transfer reactions is used to transfer protons across the mitochondrial inner membrane. The energy stored in the resulting chemiosmotic gradient is used to generate ATP by F_oF_1 ATP synthase. During electron transfer, some electrons *leak* and react with O_2 producing superoxide anion, which in turn is converted to H_2O_2 by Mn-SOD. Complex I of the electron transport chain releases reactive oxygen species (ROS) in the matrix, whereas complex III generates ROS on both sides of the mitochondrial inner membrane (Han et al., 2001). The production of ROS by mitochondria is an important issue in cell fate. Low levels can activate adaptive signaling pathways, but higher levels result in oxidative damage, release of cytochrome c, and ultimately cell death.

Mitochondria provide energy to the cardiomyocyte through the synthesis of ATP by F_oF_1 ATP synthase that is located in the inner mitochondrial membrane. Therefore, in sepsis and endotoxemia, any alteration in the respiratory chain, in the electrochemical proton gradient, or in the F_oF_1 ATP synthase activity would lead to bioenergetics dysfunction and organ failure. Moreover, mitochondrial ATP content has been suggested to be related to patient outcome (Brealey et al., 2002; Carre et al., 2010).

The main classic mitochondrial properties that reflect their energy-producing physiological function are: O_2 consumption rate in state 3 (rapid respiration), respiratory control ratio (O_2 consumption in state 3 and state 4 ratio), mitochondrial inner membrane potential and ADP/O ratio (Boveris et al., 2000). Mitochondria are defined as dysfunctional when these parameters, related to those in normal mitochondria, are found to be decreased. Consequently, these organelles decrease their ability to adapt themselves to the destabilizing effects of cellular stress. Mitochondrial dysfunction is a mitochondrial syndrome that has been described for heart in ischemia/reperfusion (Makazan et al., 2007) and endotoxic and septic shock (Alvarez and Evelson, 2007; Crouser, 2004). It is characterized by decreases in the rates of state 3 respiration and ATP synthesis and increases in the rate of state 4 respiration (although sometimes normal values are observed), mitochondrial size and turnover. Additionally, this scenario may be accompanied by increased production rates of superoxide anion and hydrogen peroxide (Alvarez and Boveris, 2004).

Previous results from our laboratory have shown heart mitochondrial bioenergetics dysfunction with decreased O_2 uptake and ATP production in endotoxemia when analysis where performed after 6 h of the LPS-challenge (Vanasco et al., 2012). In this study, mitochondrial O_2 consumption in state 3 was observed decreased both with malate-glutamate (complex I) and succinate (complex II) as respiratory substrates, although this observation was more pronounced when complex I substrates were used. This data agree with previous results showing that cardiac mitochondrial complex I activity was found inhibited in endotoxemia (Vanasco et al., 2008).The lower rates of electron transfer through complex I observed in endotoxemia, critically restrict ATP synthesis and significantly increase superoxide and hydrogen peroxide production; a situation that leads to further organ damage through a self-sustaining process. It has been claimed that mitochondrial ATP content is critical in endotoxemia and sepsis to determine patient outcome (Boveris et al., 2002a; Galkin et al., 2009).

As previously described in this review, mitochondrial biogenesis emerges as a compensatory mechanism to increase mass of new mitochondria although this observation does not necessar-

ily imply that resultant mitochondria are functional. In line with this idea, we have analyzed cardiac mitochondrial function during mitochondrial biogenesis in endotoxemia at different time points (Vanasco et al., 2014), observing that restoration of normal mitochondrial architecture is not accompanied by improvement of mitochondrial function. This situation may imply that the compensatory mechanism network activated might not be adequate to cope with the cardiac damage caused by systemic inflammation. In line with this observation (Russell et al., 2004) demonstrated that cardiomyocyte-specific overexpression of PGC-1α resulted in a markedly increased mitochondrial biogenesis but also in heart failure. It is worth to indicate that other groups (Nisoli et al., 2004) have found that mitochondrial biogenesis was accompanied by increased O_2 consumption through coupled cellular respiration functionally linked to enhanced ATP production in different cell lines.

If the development of organ dysfunction is related to cellular energetic failure, then strategies aimed at preventing impairment of mitochondrial energy production may be potentially beneficial. The use of α-lipoic acid in an experimental endotoxemia model improves cardiac mitochondrial function, as assessed determining oxygen consumption by mitochondria and complexes I, II and IV activities (Vanasco et al., 2008). Other studies have shown that this compound can attenuate LPS-induced cardiac bioenergetics dysfunction through restoration of PI3 K/Akt-signalling pathway, which is usually inhibited in endotoxemia (Jiang et al., 2013). It is relevant to mention the beneficial effects of specific mitochondrial antioxidants as mitoQ (reduces mitochondrial ROS formation, and maintains mitochondrial membrane potential, thus improving cardiac function) (Supinski et al., 2009) and Szeto-Schiller peptides (reduce mitochondrial ROS formation, and mitochondrial swelling, and protect mitochondrial respiratory chain complexes) (Dare et al., 2009).

6. Conclusions and perspectives

Little is known about the relationship between cell decision to survive and maintain energy metabolism or to go through different mechanisms of cell death. The classical idea that mitochondrial damage disrupts ATP production leading to cell death is an accurate description of a subset of organ pathologies in which the injury is rapid and profound, as cardiac ischaemia-reperfusion. In penumbral territories, such as sepsis and endotoxemia, this view is too simple. In conclusion, it seems that in these syndromes, and its associated-heart failure, outcome is a consequence of a highly intricated whole body response to acute inflammation involving multiple pathways. Recovery of cardiac mitochondrial function following sepsis and endotoxemia is more likely to depend on a complex balance between prevailing levels of mitochondrial stress, biogenesis/autophagy signaling, and mitochondria quality control processes, rather on a single factor. The scenario is complex and overall mechanisms by which this acute inflammatory condition leads to bioenergetics derangement and cardiac dysfunction remain to be established. It is necessary to study and associate cardiac mitochondrial structure with mitochondrial functionality, to overcome open questions regarding mechanisms leading to cardiac failure and eventually death. It is necessary to understand that this acute inflammatory syndrome is made more complex by other aspects of endotoxemia and sepsis that are out of the scope of this review: the relevance of the endothelium system, blood rheology, oxygen and nutrients supply, and previous overall state of the patient, among others.

As mitochondrial dysfunction contributes to impaired cardiac function and cellular energetic expenditure, new therapeutic opportunities should be considered. An interesting idea is that once permanent mitochondrial dysfunction has developed, optimization of the residual cellular ability to produce energy, and/or a reduction in metabolic requirements, may prevent the ATP level from dropping below the threshold that stimulates cell death pathways. Additional investigations detailing the mechanisms and timing of mitochondrial injury during sepsis and endotoxemia are needed before it is possible to develop highly effective mitochondrial protection strategies for application in the clinical setting.

References

Akashi, S., Shimazu, R., Ogata, H., Nagai, Y., Takeda, K., Kimoto, M., Miyake, K., 2000. Cutting edge: cell surface expression and lipopolysaccharide signaling via the toll-like receptor 4-MD-2 complex on mouse peritoneal macrophages. J. Immunol. 164, 3471–3475.

Alvarez, S., Boveris, A., 2004. Mitochondrial nitric oxide metabolism in rat muscle during endotoxemia. Free Radic. Biol. Med. 37, 1472–1478.

Alvarez, S., Evelson, P.A., 2007. Nitric oxide and oxygen metabolism in inflammatory conditions: sepsis and exposition to polluted ambients. Front. Biosci. 12, 964–974.

Blanco, J., Muriel-Bombin, A., Sagredo, V., Taboada, F., Gandia, F., Tamayo, L., Collado, J., Garcia-Labattut, A., Carriedo, D., Valledor, M., De Frutos, M., Lopez, M.J., Caballero, A., Guerra, J., Alvarez, B., Mayo, A., Villar, J., 2008. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. Crit. Care 12, R158.

Boveris, A., Costa, L.E., Poderoso, J.J., Carreras, M.C., Cadenas, E., 2000. Regulation of mitochondrial respiration by oxygen and nitric oxide. Ann. N.Y. Acad. Sci. 899, 121–135.

Boveris, A., Alvarez, S., Navarro, A., 2002a. The role of mitochondrial nitric oxide synthase in inflammation and septic shock. Free Radic. Biol. Med. 33, 1186–1193.

Boveris, A., Arnaiz, S.L., Bustamante, J., Alvarez, S., Valdez, L., Boveris, A.D., Navarro, A., 2002b. Pharmacological regulation of mitochondrial nitric oxide synthase. Methods Enzymol. 359, 328–339.

Brealey, D., Brand, M., Hargreaves, I., Heales, S., Land, J., Smolenski, R., Davies, N.A., Cooper, C.E., Singer, M., 2002. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet 360, 219–223.

Brealey, D., Karyampudi, S., Jacques, T.S., Novelli, M., Stidwill, R., Taylor, V., Smolenski, R.T., Singer, M., 2004. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. Am. J. Physiol. Regul. Integr. Comp. Physiol. 286, R491–497.

Carre, J.E., Orban, J.C., Re, L., Felsmann, K., Iffert, W., Bauer, M., Suliman, H.B., Piantadosi, C.A., Mayhew, T.M., Breen, P., Stotz, M., Singer, M., 2010. Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am. J. Respir. Crit. Care Med. 182, 745–751.

Chagnon, F., Bentourkia, M., Lecomte, R., Lessard, M., Lesur, O., 2006. Endotoxin-induced heart dysfunction in rats: assessment of myocardial perfusion and permeability and the role of fluid resuscitation. Crit. Care Med. 34, 127–133.

Cimolai, M.C., Alvarez, S., Bode, C., Bugger, H., 2015. Mitochondrial mechanisms in septic cardiomyopathy. Int. J. Mol. Sci. 16, 17763–17778.

Crouser, E.D., 2004. Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. Mitochondrion 4, 729–741.

Dare, A.J., Phillips, A.R., Hickey, A.J., Mittal, A., Loveday, B., Thompson, N., Windsor, J.A., 2009. A systematic review of experimental treatments for mitochondrial dysfunction in sepsis and multiple organ dysfunction syndrome. Free Radic. Biol. Med. 47, 1517–1525.

Dauphinee, S.M., Karsan, A., 2006. Lipopolysaccharide signaling in endothelial cells. Lab. Invest. 86, 9–22.

De Angelo, J., 1999. Nitric oxide scavengers in the treatment of shock associated with systemic inflammatory response syndrome. Expert Opin. Pharmacother. 1, 19–29.

Dianzani, M., 1996. Líinfiammazione, Unione Tipografico-Editice ed. Torinese.

Dias, A.A., Goodman, A.R., Dos Santos, J.L., Gomes, R.N., Altmeyer, A., Bozza, P.T., Horta, M.F., Vilcek, J., Reis, L.F., 2001. TSG-14 transgenic mice have improved survival to endotoxemia and to CLP-induced sepsis. J. Leukoc. Biol. 69, 928–936.

Dorn II., G.W., 2015. Mitochondrial dynamism and heart disease: changing shape and shaping change. EMBO Mol. Med. 7, 865–877.

Drosatos, K., Khan, R.S., Trent, C.M., Jiang, H., Son, N.H., Blaner, W.S., Homma, S., Schulze, P.C., Goldberg, I.J., 2013. Peroxisome proliferator-activated receptor-gamma activation prevents sepsis-related cardiac dysfunction and mortality in mice. Circ Heart Fail 6, 550–562.

Drosatos, K., Lymperopoulos, A., Kennel, P.J., Pollak, N., Schulze, P.C., Goldberg, I.J., 2015. Pathophysiology of sepsis-related cardiac dysfunction: driven by inflammation, energy mismanagement, or both? Curr. Heart Fail. Rep. 12, 130–140.

Escames, G., Leon, J., Macias, M., Khaldy, H., Acuna-Castroviejo, D., 2003. Melatonin counteracts lipopolysaccharide-induced expression and activity of mitochondrial nitric oxide synthase in rats. FASEB J. 17, 932–934.

Escames, G., Lopez, L.C., Ortiz, F., Lopez, A., Garcia, J.A., Ros, E., Acuna-Castroviejo, D., 2007. Attenuation of cardiac mitochondrial dysfunction by melatonin in septic mice. FEBS J. 274, 2135–2147.

Fauvel, H., Marchetti, P., Chopin, C., Formstecher, P., Neviere, R., 2001. Differential effects of caspase inhibitors on endotoxin-induced myocardial dysfunction and heart apoptosis. Am. J. Physiol. Heart Circ. Physiol. 280, H1608–1614.
Fauvel, H., Marchetti, P., Obert, G., Joulain, O., Chopin, C., Formstecher, P., Neviere, R., 2002. Protective effects of cyclosporin A from endotoxin-induced myocardial dysfunction and apoptosis in rats. Am. J. Respir. Crit. Care Med. 165, 449–455.
Fenton, K.E., Sable, C.A., Bell, M.J., Patel, K.M., Berger, J.T., 2004. Increases in serum levels of troponin I are associated with cardiac dysfunction and disease severity in pediatric patients with septic shock. Pediatr. Crit. Care Med. 5, 533–538.
Fillmore, N., Mori, J., Lopaschuk, G.D., 2014. Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy. Br. J. Pharmacol. 171, 2080–2090.
Fink, M.P., 2001. Cytopathic hypoxia: mitochondrial dysfunction as mechanism contributing to organ dysfunction in sepsis. Crit. Care Clin. 17, 219–237.
Fitzgerald, K.A., Palsson-McDermott, E.M., Bowie, A.G., Jefferies, C.A., Mansell, A.S., Brady, G., Brint, E., Dunne, A., Gray, P., Harte, M.T., McMurray, D., Smith, D.E., Sims, J.E., Bird, T.A., O'Neill, L.A., 2001. Mal (MyD88-adapter-like) is required for toll-like receptor-4 signal transduction. Nature 413, 78–83.
Flohe, L., Brigelius-Flohe, R., Saliou, C., Traber, M.G., Packer, L., 1997. Redox regulation of NF-kappa B activation. Free Radic. Biol. Med. 22, 1115–1126.
Galkin, A., Abramov, A.Y., Frakich, N., Duchen, M.R., Moncada, S., 2009. Lack of oxygen deactivates mitochondrial complex I: implications for ischemic injury? J. Biol. Chem. 284, 36055–36061.
Goddard, C.M., Allard, M.F., Hogg, J.C., Walley, K.R., 1996. Myocardial morphometric changes related to decreased contractility after endotoxin. Am. J. Physiol. 270, H1446–1452.
Gonzalez, A.S., Elguero, M.E., Finocchietto, P., Holod, S., Romorini, L., Miriuka, S.G., Peralta, J.G., Poderoso, J.J., Carreras, M.C., 2014. Abnormal mitochondrial fusion-fission balance contributes to the progression of experimental sepsis. Free Radic. Res. 48, 769–783.
Goris, R.J., te Boekhorst, T.P., Nuytinck, J.K., Gimbrere, J.S., 1985. Multiple-organ failure. Generalized autodestructive inflammation? Arch. Surg. 120, 1109–1115.
Gotloib, L., Shostak, A., Galdi, P., Jaichenko, J., Fudin, R., 1992. Loss of microvascular negative charges accompanied by interstitial edema in septic rats' heart. Circ. Shock 36, 45–56.
Green, D.R., Kroemer, G., 2004. The pathophysiology of mitochondrial cell death. Science 305, 626–629.
Han, D., Williams, E., Cadenas, E., 2001. Mitochondrial respiratory chain-dependent generation of superoxide anion and its release into the intermembrane space. Biochem. J 353, 411–416.
Heusch, G., Schulz, R., Rahimtoola, S.H., 2005. Myocardial hibernation: a delicate balance. Am. J. Physiol. Heart Circ. Physiol. 288, H984–999.
Hickson-Bick, D.L., Jones, C., Buja, L.M., 2008. Stimulation of mitochondrial biogenesis and autophagy by lipopolysaccharide in the neonatal rat cardiomyocyte protects against programmed cell death. J. Mol. Cell. Cardiol. 44, 411–418.
Hoshino, K., Takeuchi, O., Kawai, T., Sanjo, H., Ogawa, T., Takeda, Y., Takeda, K., Akira, S., 1999. Cutting edge: toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. J. Immunol. 162, 3749–3752.
Ince, C., Mayeux, P.R., Nguyen, T., Gomez, H., Kellum, J.A., Ospina-Tascon, G.A., Hernandez, G., Murray, P., De Backer, D., 2016. The endothelium in sepsis. Shock 45, 259–270.
Jiang, S., Zhu, W., Li, C., Zhang, X., Lu, T., Ding, Z., Cao, K., Liu, L., 2013. alpha-Lipoic acid attenuates LPS-induced cardiac dysfunction through a PI3K/Akt-dependent mechanism. Int. Immunopharmacol. 16, 100–107.
Joshi, M.S., Julian, M.W., Huff, J.E., Bauer, J.A., Xia, Y., Crouser, E.D., 2006. Calcineurin regulates myocardial function during acute endotoxemia. Am. J. Respir. Crit. Care Med. 173, 999–1007.
Kawai, T., Adachi, O., Ogawa, T., Takeda, K., Akira, S., 1999. Unresponsiveness of MyD88-deficient mice to endotoxin. Immunity 11, 115–122.
Kleinert, H., Boissel, J.P., Schwartz, P.M., Föstermann, U., 2000. Regulation of the Expression of Nitric Oxide Synthase Isoforms L.J. Ignarro NItric Oxide Biology and Pathology. San Diego, California, 105–128.
Lancel, S., Hassoun, S.M., Favory, R., Decoster, B., Motterlini, R., Neviere, R., 2009. Carbon monoxide rescues mice from lethal sepsis by supporting mitochondrial energetic metabolism and activating mitochondrial biogenesis. J. Pharmacol. Exp. Ther. 329, 641–648.
Larche, J., Lancel, S., Hassoun, S.M., Favory, R., Decoster, B., Marchetti, P., Chopin, C., Neviere, R., 2006. Inhibition of mitochondrial permeability transition prevents sepsis-induced myocardial dysfunction and mortality. J. Am. Coll. Cardiol. 48, 377–385.
Levonen, A.L., Hill, B.G., Kansanen, E., Zhang, J., Darley-Usmar, V.M., 2014. Redox regulation of antioxidants, autophagy, and the response to stress: implications for electrophile therapeutics. Free Radic. Biol. Med. 71, 196–207.
Levonen, A.L., 2014. Activation of stress signaling pathways by oxidized and nitrated lipids. Free Radic. Biol. Med. 75 (1), S8.
Levy, R.J., Piel, D.A., Acton, P.D., Zhou, R., Ferrari, V.A., Karp, J.S., Deutschman, C.S., 2005. Evidence of myocardial hibernation in the septic heart. Crit. Care Med. 33, 2752–2756.
Lo, S., Yuan, S.S., Hsu, C., Cheng, Y.J., Chang, Y.F., Hsueh, H.W., Lee, P.H., Hsieh, Y.C., 2013. Lc3 over-expression improves survival and attenuates lung injury through increasing autophagosomal clearance in septic mice. Ann. Surg. 257, 352–363.
Lopaschuk, G.D., Ussher, J.R., Folmes, C.D., Jaswal, J.S., Stanley, W.C., 2010. Myocardial fatty acid metabolism in health and disease. Physiol. Rev. 90, 207–258.
Lopez, L.C., Escames, G., Tapias, V., Utrilla, P., Leon, J., Acuna-Castroviejo, D., 2006. Identification of an inducible nitric oxide synthase in diaphragm mitochondria from septic mice: its relation with mitochondrial dysfunction and prevention by melatonin. Int. J. Biochem. Cell Biol. 38, 267–278.
Lu, Y.C., Yeh, W.C., Ohashi, P.S., 2008. LPS/TLR4 signal transduction pathway. Cytokine 42, 145–151.
Maack, C., O'Rourke, B., 2007. Excitation-contraction coupling and mitochondrial energetics. Basic Res. Cardiol. 102, 369–392.
Makazan, Z., Saini, H.K., Dhalla, N.S., 2007. Role of oxidative stress in alterations of mitochondrial function in ischemic-reperfused hearts. Am. J. Physiol. Heart Circ. Physiol. 292, H1986–1994.
McDonough, K.H., Virag, J.I., 2006. Sepsis-induced myocardial dysfunction and myocardial protection from ischemia/reperfusion injury. Front. Biosci. 11, 23–32.
Merx, M.W., Liehn, E.A., Graf, J., van de Sandt, A., Schaltenbrand, M., Schrader, J., Hanrath, P., Weber, C., 2005. Statin treatment after onset of sepsis in a murine model improves survival. Circulation 112, 117–124.
Mileykovskaya, E., Dowhan, W., 2014a. Cardiolipin-dependent formation of mitochondrial respiratory supercomplexes. Chem. Phys. Lipids 179, 42–48.
Mileykovskaya, E., Dowhan, W., 2014. Role of cardiolipin in mitochondrial supercomplex assembly, Louro, R.O., Díaz-Moreno I. Redox proteins in supercomplexes and signalosomes. Lisboa, 81–105.
Morikawa, A., Koide, N., Kato, Y., Sugiyama, T., Chakravortty, D., Yoshida, T., Yokochi, T., 2000. Augmentation of nitric oxide production by gamma interferon in a mouse vascular endothelial cell line and its modulation by tumor necrosis factor alpha and lipopolysaccharide. Infect. Immun. 68, 6209–6214.
Neviere, R., Fauvel, H., Chopin, C., Formstecher, P., Marchetti, P., 2001. Caspase inhibition prevents cardiac dysfunction and heart apoptosis in a rat model of sepsis. Am. J. Respir. Crit. Care Med. 163, 218–225.
Nisoli, E., Falcone, S., Tonello, C., Cozzi, V., Palomba, L., Fiorani, M., Pisconti, A., Brunelli, S., Cardile, A., Francolini, M., Cantoni, O., Carruba, M.O., Moncada, S., Clementi, E., 2004. Mitochondrial biogenesis by NO yields functionally active mitochondria in mammals. Proc. Natl. Acad. Sci. U. S. A. 101, 16507–16512.
Paradies, G., Petrosillo, G., Paradies, V., Ruggiero, F.M., 2010. Oxidative stress, mitochondrial bioenergetics, and cardiolipin in aging. Free Radic. Biol. Med. 48, 1286–1295.
Paradies, G., Paradies, V., De Benedictis, V., Ruggiero, F.M., Petrosillo, G., 2014. Functional role of cardiolipin in mitochondrial bioenergetics. Biochim. Biophys. Acta 1837, 408–417.
Parker, M.M., Shelhamer, J.H., Bacharach, S.L., Green, M.V., Natanson, C., Frederick, T.M., Damske, B.A., Parrillo, J.E., 1984. Profound but reversible myocardial depression in patients with septic shock. Ann. Intern. Med. 100, 483–490.
Piantadosi, C.A., Suliman, H.B., 2012a. Redox regulation of mitochondrial biogenesis. Free Radic. Biol. Med. 53, 2043–2053.
Piantadosi, C.A., Suliman, H.B., 2012b. Transcriptional control of mitochondrial biogenesis and its interface with inflammatory processes. Biochim. Biophys. Acta 1820, 532–541.
Piantadosi, C.A., Carraway, M.S., H, D.W., Suliman, H.B., 2007. Protecting the permeability pore and mitochondrial biogenesis. In: Chadwick, Derek J., Goode, Camie (Eds.), Sepsis: New Ingsights, New Therapies. Wiley, Chichester, UK, pp. 266–280.
Pinsky, M.R., 2001. Sepsis: a pro- and anti-inflammatory disequilibrium syndrome. Contrib. Nephrol., 354–366.
Poelaert, J., Declerck, C., Vogelaers, D., Colardyn, F., Visser, C.A., 1997. Left ventricular systolic and diastolic function in septic shock. Intensive Care Med. 23, 553–560.
Proulx, F., Lacroix, J., Qureshi, I.A., Nadeau, D., Gauthier, M., Lambert, M., 1997. Acquired carnitine abnormalities in critically ill children. Eur. J. Pediatr. 156, 864–869.
Randle, P.J., Garland, P.B., Hales, C.N., Newsholme, E.A., 1963. The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1, 785–789.
Ren, J., Ren, B.H., Sharma, A.C., 2002. Sepsis-induced depressed contractile function of isolated ventricular myocytes is due to altered calcium transient properties. Shock 18, 285–288.
Romero-Bermejo, F.J., Ruiz-Bailen, M., Gil-Cebrian, J., Huertos-Ranchal, M.J., 2011. Sepsis-induced cardiomyopathy. Curr Cardiol Rev 7, 163–183.
Rossi, M.A., Celes, M.R., Prado, C.M., Saggioro, F.P., 2007. Myocardial structural changes in long-term human severe sepsis/septic shock may be responsible for cardiac dysfunction. Shock 27, 10–18.
Rudiger, A., Singer, M., 2007. Mechanisms of sepsis-induced cardiac dysfunction. Crit. Care Med. 35, 1599–1608.
Ruetten, H., Thiemermann, C., 2000. Nitric Oxide and Sepsis Shock J. Ignarro Nitric Oxide, biology and pathology. San Diego, California 747–758.
Russell, L.K., Mansfield, C.M., Lehman, J.J., Kovacs, A., Courtois, M., Saffitz, J.E., Medeiros, D.M., Valencik, M.L., McDonald, J.A., Kelly, D.P., 2004. Cardiac-specific induction of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1alpha promotes mitochondrial biogenesis and reversible cardiomyopathy in a developmental stage-dependent manner. Circ. Res. 94, 525–533.
Schlame, M., 2013. Cardiolipin remodeling and the function of tafazzin. Biochim. Biophys. Acta 1831, 582–588.

Schulte, W., Bernhagen, J., Bucala, R., 2013. Cytokines in sepsis: potent immunoregulators and potential therapeutic targets–an updated view. Mediators Inflamm 2013, 165974.
Smeding, L., Plotz, F.B., Groeneveld, A.B., Kneyber, M.C., 2012. Structural changes of the heart during severe sepsis or septic shock. Shock 37, 449–456.
Su, G.L., 2002. Lipopolysaccharides in liver injury: molecular mechanisms of Kupffer cell activation. Am. J. Physiol. Gastrointest. Liver Physiol. 283, G256–265.
Suliman, H.B., Welty-Wolf, K.E., Carraway, M., Tatro, L., Piantadosi, C.A., 2004. Lipopolysaccharide induces oxidative cardiac mitochondrial damage and biogenesis. Cardiovasc. Res. 64, 279–288.
Supinski, G.S., Murphy, M.P., Callahan, L.A., 2009. MitoQ administration prevents endotoxin-induced cardiac dysfunction. Am. J. Physiol. Regul. Integr. Comp. Physiol. 297, R1095–1102.
Szabó, C., 2000. Pathophysiological role of nitric oxide in inflammation L. Ignarro Nitric Oxide, biology and pathology. San Diego, California 841–872.
Szeto, H.H., 2014. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. Br. J. Pharmacol. 171, 2029–2050.
Takeda, K., Kaisho, T., Akira, S., 2003. Toll-like receptors. Annu. Rev. Immunol. 21, 335–376.
Thiemermann, C., Vane, J., 1990. Inhibition of nitric oxide synthesis reduces the hypotension induced by bacterial lipopolysaccharides in the rat in vivo. Eur. J. Pharmacol. 182, 591–595.
Torgersen, C., Moser, P., Luckner, G., Mayr, V., Jochberger, S., Hasibeder, W.R., Dunser, M.W., 2009. Macroscopic postmortem findings in 235 surgical intensive care patients with sepsis. Anesth. Analg. 108, 1841–1847.
Turner, A., Tsamitros, M., Bellomo, R., 1999. Myocardial cell injury in septic shock. Crit. Care Med. 27, 1775–1780.
Vanasco, V., Cimolai, M.C., Evelson, P., Alvarez, S., 2008. The oxidative stress and the mitochondrial dysfunction caused by endotoxemia are prevented by alpha-lipoic acid. Free Radic. Res. 42, 815–823.
Vanasco, V., Magnani, N.D., Cimolai, M.C., Valdez, L.B., Evelson, P., Boveris, A., Alvarez, S., 2012. Endotoxemia impairs heart mitochondrial function by decreasing electron transfer, ATP synthesis and ATP content without affecting membrane potential. J. Bioenerg. Biomembr. 44, 243–252.
Vanasco, V., Saez, T., Magnani, N.D., Pereyra, L., Marchini, T., Corach, A., Vaccaro, M.I., Corach, D., Evelson, P., Alvarez, S., 2014. Cardiac mitochondrial biogenesis in endotoxemia is not accompanied by mitochondrial function recovery. Free Radic. Biol. Med. 77, 1–9.
Ventura-Clapier, R., Garnier, A., Veksler, V., Joubert, F., 2011. Bioenergetics of the failing heart. Biochim. Biophys. Acta 1813, 1360–1372.
Wan, M., Hua, X., Su, J., Thiagarajan, D., Frostegard, A.G., Haeggstrom, J.Z., Frostegard, J., 2014. Oxidized but not native cardiolipin has pro-inflammatory effects, which are inhibited by Annexin A5. Atherosclerosis 235, 592–598.
Watts, J.A., Kline, J.A., Thornton, L.R., Grattan, R.M., Brar, S.S., 2004. Metabolic dysfunction and depletion of mitochondria in hearts of septic rats. J. Mol. Cell. Cardiol. 36, 141–150.
Wu, Z., Puigserver, P., Andersson, U., Zhang, C., Adelmant, G., Mootha, V., Troy, A., Cinti, S., Lowell, B., Scarpulla, R.C., Spiegelman, B.M., 1999. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell 98, 115–124.
Yin, H., Zhu, M., 2012. Free radical oxidation of cardiolipin: chemical mechanisms, detection and implication in apoptosis, mitochondrial dysfunction and human diseases. Free Radic. Res. 46, 959–974.
Yuan, H., Perry, C.N., Huang, C., Iwai-Kanai, E., Carreira, R.S., Glembotski, C.C., Gottlieb, R.A., 2009. LPS-induced autophagy is mediated by oxidative signaling in cardiomyocytes and is associated with cytoprotection. Am. J. Physiol. Heart Circ. Physiol. 296, H470–479.
Zang, Q., Maass, D.L., Tsai, S.J., Horton, J.W., 2007. Cardiac mitochondrial damage and inflammation responses in sepsis. Surg. Infect. (Larchmt) 8, 41–54.