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Chapter 14

The Role of Altered Lipid Metabolism in Septic Myocardial Dysfunction

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Additional information is available at the end of the chapter

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1. Introduction

Despite the novel pathogenetic and therapeutic acquisitions sepsis remains the main cause of death in the critically ill patient (p.). The incidence of sepsis is increasing, with more than 750 000 cases occurring in the United States every year; sepsis is complicated by organ dysfunction giving rise to severe sepsis which causes more than 200 000 deaths each year [1]. The cardiovascular syndrome is the cause of the major part of the fatalities leading to the picture of the septic shock with 90,000 deaths annually. The myocardial dysfunction in sepsis has been widely studied and many causes of heart dysfunction have been described. The presence of a metabolic compromise is well known in chronic heart failure and has been considered as a basis for contractile failure, interestingly similar alterations have been recently described also in sepsis. The purpose of this study is to examine the current available data on this topic.

Sepsis has been defined as the systemic host reaction to an infection [2]. The typical immune response in sepsis presents a first stage, characterized by an increased production of proinflammatory interleukins (ILs) by monocytes, macrophages. lymphocytes and endothelial cells in response to a few molecules, common to all virulent pathogens, called pathogen-associated molecular patterns (PAMPs) [3]. They are recognized by receptors on the surface of the immune cells, named Pattern Recognition Receptors (PRP) the most important being the Toll-like Receptors (TLRs), existing in 13 different types each recognizing a different microbial constituent. TLR are an important component of immune activity programmed to respond quickly to the infectious challenges by recognizing PAMP. Lipopolysaccharide (LPS) in particular is recognized by the complex TLR4-CD14 in the plasma membrane and the inflammatory signal is transduced by the recruitment of the adaptor molecules that associate with the intracellular Toll/interleukin-1 receptor (TIR) domain of the TLR to initiate signal transduction. Of these adaptor molecules myeloid differentiation primary- response protein 88 (MyD88) is associated with all TLRs except TLR3 while the TIR-domain containing adaptor

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inducing interferon (IFN)-β (TRIF) is only associated to TLR3 [3]. Both of them lead to nuclear factor-κB (NF-kB) activation and induction of over 150 inflammatory and procoagulant genes with increased expression of the proinflammatory ILs tumor necrosis factor α(TNFα), IL1β, IL6, interferon γ (IFNγ), chemokines and cell adhesion molecules. This phase, named Systemic Inflammatory Reaction Syndrome (SIRS) is followed by a second phase, the compensatory anti- inflammatory response syndrome (CARS), that modulates SIRS through death by apoptosis of immune cells, gene silencing of the pro-inflammatory genes and increased production of the contra-inflammatory ILs IL10, IL4 and TGFβ [4-6] Through this biphasic reaction in the largest part of the cases the homeostasis is re-established. It is possible however that during the proinflammatory phase because of the "cytokine storm"-induced organ damage, further increased through the release by the injured tissue of the endogenous damage-associated molecular pattern (DAMPs or alarmins such as hig mobility group protein B1(HMBG1), hyaluronan, HSP, proteins S100 etc), as more frequently occurs in young and reactive people, or during the contra-inflammatory phase, due to immunosuppression and diffuse infection, death may ensue [4]. The normal biphasic reaction may be altered when sepsis is present in very old and diseased persons that frequently present a mild phase of SIRS or do not present it at all; in the later stages it seems that immunosuppression is almost always present [7]. Indeed from what has been described it seems that in both the cases sepsis is characterized by an "altered immune response", unbalanced [8] with prevalence of an excessive proinflammatory reaction in the early phase and a prevalent immunosuppression in the late phase [8.] The definition of sepsis based on the recent achievement on this topic could be reconsidered focusing more on the immune status, we propose the sequent definition: " sepsis is the altered immune response to an infectious challenge, either increased or decreased, and followed by a compromised organ function". The passage from the SIRS to the CARS is marked by the phenomenon of LPS tolerance [9]: the prolonged stimulation of TLR4, the specific receptor for endotoxin, by LPS leads to the silencing of proinflammatory genes and to the stimulation of the contra-inflammatory ones through a process of gene reprogramming [10] with increased expression of IL-10, TGF-β, and type I IFNs. Neutrophil function is seriously impaired in sepsis with the development of a decreased ability to migrate into the infection site, related to the severity of the disease [for review see 11]. During this stage macrophages exhibit an increased phagocytic ability but an altered capacity of antigen presentation due to reduced expression of several major histocompatibility complex (MHC) Class II molecules (e.g. HLA-DRs) with impaired T-cell proliferation as well as reduced production of IFNγ. This phase corresponds also to a stage of ischemic tolerance caused by the reduced production of NF-kB responsible for the amplification of the damage induced by ischemia [12]. TLRs are indeed involved in the tissue damage caused by non-infectious challenges such as ischemia-reperfusion injury (IRI), burns, surgery, trauma etc. because they mediate the inflammatory reaction to the alarmins released by these noxae: the deletion of TLR2 and TLR4 may reduce the cellular damage in these settings [13-14].The mitochondrial DNA released after tissue damage may be recognized by TLRs, behaving as a DAMP for its far origin by bacteria according to endosymbiotic theory; its experimental infusion may cause a picture similar to the ARDS [15]. TLRs are also important to explain the link between inflammation and metabolic alterations [16] and the state of low grade inflammation present for so far unknown reasons in obesity, metabolic syndrome, diabetes and in chronic

myocardial ischemia; moreover they may also be involved in the adipose tissue dysfunction described during sepsis [17,18]. One of the main problems in the study of sepsis has been its experimental reproduction: the LPS infusion method, used also at low doses in human volunteers, is not reliable because it reproduces only the proinflammatory phase and led in the past to misunderstand the complex regulation of immunity in sepsis, moreover in this model is lacking an infectious focus. The availability of successive different models such as the infusion of living bacteria and the cecal ligation and puncture (CLP), at present considered a good reproduction of human septic peritonitis, allowed further progress supplying models similar to human sepsis [19].

2. Metabolic response in sepsis and injury

The first phase of sepsis, coincident with SIRS and also called flow phase, is characterized by a state of hypercatabolism with negative nitrogen balance induced by the increase in proinflammatory ILs and stress hormones, while the anabolic ones are reduced. This phase is also marked by hyperglycemia, hyperlactatemia and increased energy expenditure varying with the nature of the injurious stress (15-20% after surgery, 20-40% in sepsis and up to 120% in burns [20]). Injury in general and sepsis in particular are associated with an increased protein breakdown (mainly derived by the muscle representing the main store of proteins in the body, up to 40% of total body proteins), protein catabolism in sepsis may reach 260 gr\day [21] corresponding to a loss of 1 Kg muscle, with negative nitrogen balance, an increased blood pool of amino acids (a.a.), used in the liver for neoglucogenesis and the production of acute phase proteins, and reduced uptake of a.a. by the muscle. The protein utilization as a fuel is opposite to the normal and rapidly depletes body lean mass. The increased production of IL-1β, IL-6 and TNFα causes protein catabolism both directly and indirectly through the stimulation of the Hypothalamus–Pituitary-Adrenal (HPA) axis [22]. The increased protein catabolism may be reproduced by counter-regulatory hormones infusion.

2.1. Glucose metabolism and insulin sensitivity in sepsis

Insulin resistance may be defined as the inability of insulin to adequately stimulate glucose uptake in the muscle or to inhibit gluconeogenesis in the liver [23]. The pathogenesis of the insulin resistance is no more interpreted on the basis of the glucocentric but of the lipocentric theory [24] stating that the excess of circulating free fatty acids (FFA), the main competitive inhibitors of glucose utilization in the cell, when present in excess in plasma because of increased lipolysis, decreased fat storing capacity of adipose tissue or reduced fatty acid oxydation (FAO) may accumulate in the organs (liver, myocardium, pancreas etc) giving origin to reduced sensitivity to insulin, increased hepatic glucose output and to the phenomenon of lipotoxicity, syndrome characterized by accumulation of FFA in the cell, increased production of reactive oxygen species (ROS), activation of apoptosis (lipoapoptosis) and organ dysfunction [25]. The etiology of insulin resistance in sepsis is related to the increase of the contra-insular substances (glucagon, TNFα, growth hormone, cortisol) and to the reduced expression of the insulin-sensitizing adiponectin while the endogenous insulin secretion in the critically ill p. is increased as occurs in the early phase of type II diabetes mellitus, on the contrary of what was suggested in the past [26]. The consequences of the

metabolic storm in sepsis are an increased hepatic production of glucose, a reduced glucose uptake by insulin-dependent tissues, increased levels of FFA- consequence of the increased lipolysis- reduced FAO and reduced insulin sensitivity at the muscular and hepatic level [27]. The high levels of blood glucose allow a high uptake by the non-insulin-dependent cells because of the increased expression of the stress- and Ils-dependent glucose transporter GLUT1 [27]. In this way a high rate of glucose oxidation through mitochondria is made possible leading to an enhanced production of ROS: the increased oxidative and nitrosative stress, chiefly in presence of a reduction in ROS scavengers, -mainly glutathione[28]- typical of the critical states, may damage mainly the Complexes I and III of the electron transport chain (ETC) initiating the mitochondrial dysfunction. Insulin is provided with an anti-inflammatory action that is missing if a reduced sensitivity to its action is present, such as in critical illness, further increasing inflammation [27]. Proinflammatory ILs interfere with insulin activity through multiple mechanisms ; 1) TNFα and other cytokines activate Jun-N-terminal kinase (JNK) responsible for serine phosphorylation of the insulin receptor substrate 1 (IRS-1) at Ser 307, so disrupting insulin signalling [29] 2) furthermore JNK activation has been showed, in LPS-induced experimental sepsis, to depress PPARα expression reducing FFA oxidation [30]; JNK inhibition prevented cardiac dysfunction, despite continued induction of inflammatory markers, demonstrating that there is a dysmetabolic basis for LPS-induced cardiac dysfunction in this experimental setting [30]. An important clinical application of the role played by the altered glucose metabolism in the critically ill p. derived from the Leuven Study [31] that showed a striking reduction from 8% to 4,6% in the mortality of critically ill surgical p. receiving mechanical ventilation by maintaining glycemia between 80 and 110 mg% with intensive insulin therapy. However in 2009 the NICE SUGAR Study showed that a blood glucose target of 180 mg% or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg range, probably by reducing the incidence of hypoglycaemia [32]. A diffuse coverage of this matter is beyond the scope of this report (for review see reference [33]).

Hyperlactatemia in sepsis has been considered as a consequence of the establishment of an hypoxic environment, this concept is however no longer tenable, except for the p. in septic shock, because in many organs an increased oxygen saturation has been showed both in clinical sepsis and after LPS infusion [34]. Currently the cause of hyperlactatemia is considered to be the increased expression of Hypoxia-inducible factor1 (HIF-1)- and of cytokines activating PDHK4, an enzyme inhibiting PDH (pyruvate dehydrogenase) through phosphorylation so preventing the transformation of pyruvate into acetyl-CoA and its oxidation through the TCA (Tricarboxilic acid Cycle); the excess of pyruvate is transformed into lactate by Lactate dehydrogenase (LDH) through a process called accelerated aerobic glycolysis [35-38]. The plasma levels of lactate seems to be related to the outcome [35].

2.2. TG and FFA utilization in the normal heart

In a physiological environment rich in oxygen but also in pathophysiological conditions (like diet rich in lipids, starvation or diabetes) the heart can utilize all metabolites but it prefers FFA oxidation, from which it gets 60-90% of the necessary energy, obtaining the remaining part from the oxidation of glucose and ketone bodies [39]. The myocardiocyte gets FFA mainly taking up tryglicerides (TG)-rich lipoproteins (LP) (chylomicrons and very

low-density lipoprotein, VLDL) through the endothelial lipoprotein lipase (LPL), enzyme present in the capillary endothelium and bound to it through a proteoglycan, the Glycosylphosphatidyl-inositol high density lipoprotein-binding protein 1 (GPIHBP1), which anchors LPL to endothelium and serves as a bridge allowing LP uptake[40]. The myocardial cells may take up FFA also from the albumin-bound pool (10 time less abundant). FFA obtained from hydrolysis of TG by LPL or transported by albumin are then taken up by the myocardiocyte, through transporters, mainly FAT\CD36 (50-60%) but also by fatty acid binding protein (FABP) and fatty acid transport plasma membrane (FATPpm), only a very small part is taken up by diffusion [41]. Once transported into the cytosol, FFAs are esterified to long chain acyl CoA by fatty acyl CoA synthase (FACS) and transported for FFA oxidation(FAO) across mitochondrial membrane. This process is carried out in three steps: at first acyl-CoA is metabolized into acyl-carnitine by the enzyme carnitine palmitoyl transferase-1 (CPT-1), located on the outer mitochondrial membrane. Acyl-carnitine is hence transported across the inner mitochondrial membrane by carnitine translocase (CAT) and again transformed into long chain Acyl-CoA and carnitine by CPT- 2 (carnitine shuttle) [42]. The step catalyzed by CPT-1 is the rate-limiting reaction of FAO and the activity of this enzyme is strictly regulated by malonyl-CoA (the product of carboxylation of acetyl-CoA), whose levels are controlled by a balance between the activity of the enzymes involved in its metabolism, the acetyl CoA carboxylase (ACC) and malonyl CoA decarboxylase. AMP-activated protein kinase (AMPK), a fundamental energy sensor in the cell, controls this reaction phosphorylating and inhibiting ACC whenever it senses a decrease in the ATP\AMP ratio [42]. In the normal heart, 75% of the fatty acids taken up are immediately oxidized. Acetyl-CoA has a central role in the regulation of the utilization of the substrates: it is the metabolic product of both glucose (through pyruvate) and fatty acid utilization. It may be utilized for oxidation in the Krebs cycle or, if the cellular level of ATP is high, used for FFA synthesis. Acetyl-CoA may also be transformed into pyruvate and lactate by LDH in the presence of hypoxia but also when it is produced in huge quantities. More than 40 years ago Randle described the reciprocal inhibition exercised by glucose and FFA utilization [43]. He displayed in the isolated heart and in a skeletal muscle preparation that the oxidation of one substrate inhibited directly, without hormonal intermediation, the use of the other (Randle cycle). So an increase in FAO causes a proportional decrease in glucose oxidation and uptake leading to hyperglycemia. The actual interpretation of Randle cycle is that an increase in serum concentration and uptake of FFA activates FAO and causes accumulation of its byproducts as ROS, ceramides, diacylglycerol, acyl-carnitine and fatty acyl-CoAs inside the skeletal muscle so depressing glucose uptake, whereas in the liver they inhibit insulin-mediated suppression of glycogenolysis and gluconeogenesis [44-45]. Also the increased lipolysis present in many conditions (fasting, exercise, inflammatory conditions, diabetes and obesity) leading to an increased FAO may downregulate glucose utilization through increased serum FFA and reduced insulin sensitivity. All these signals, particularly diacylglycerol, interfere with insulin signalling activating PKC novel isoforms ($\delta,\varepsilon,\eta,\theta$) causing a reduced tyrosine phosphorylation of the IRS-1 which is normally responsible for the activation through phosphatidyl inositol 3-kinase (PI3K) and Akt of the membrane translocation of the insulin-dependent glucose transporter 4 (GLUT4)[46]. So an

increase in FAO causes a proportional decrease in glucose uptake and oxidation with hyperglycemia. This mechanism has been considered important in the pathophysiology of diabetes mellitus type2 (T2DM). Conversely glucose uptake and oxidation to acetyl CoA and pyruvate involves the conversion to malonylCoA by ACC leading to inhibition of CPT-1 and consequently of FAO; moreover insulin decreases lipolysis and the level of FFA. During starvation increased lipolysis raises FFA uptake and oxidation inhibiting glucose oxidation and favouring accumulation of pyruvate and lactate redirected to glycogen synthesis allowing also glucose sparing for the brain. Conversely after a glucose rich meal the increased uptake and utilization of glucose inhibit the utilization of FFA through the accumulation of malonylCoA. The normal heart responds to an increase in workload by switching from FFA to preferential glucose utilization. The Randle cycle explains how the heart regulates the fuel selection in the short term to face physiologic challenges however the long-term adaptation to physiologic and pathophysiologic conditions is mediated by translational and post-translational modifications rather than by the metabolic ones. A fitting example is the metabolic switch occurring after birth. During the fetal life the heart, probably because of the relatively hypoxic medium, relies more on carbohydrate metabolism, whereas in the adult myocardiocyte glycogen occupies less than 2% of the cell volume, in the fetal cells it represents more than 30% of the cell volume [47]. After birth the heart, due probably to the increased availability of oxygen, prefers FFA oxidation because of the discontinuous availability of metabolites and the elevated fat content of mother's milk; the metabolic shift is accompanied by increased expression of the enzymes involved in FAO. The utilization of both lipid and carbohydrates has advantages and drawbacks: the complete oxidation of a molecule of palmitic acid (molecular mass 256,43) yields more ATP (105 molecules vs 31) but consumes much more oxygen (46 atoms vs 12) than the oxidation of a molecule of glucose. Moreover the oxidation of lipid produces more oxidative stress, a drawback partially corrected by the increased production of the uncoupling protein 3(UCP3) and differently from anaerobic glycolysis it is not available in hypoxic or ischemic settings. Such long term substrate modifications are transcriptionally regulated and the switch to carbohydrate utilization is due to a downregulation of the nuclear receptors PPARα involved in the transcription of the enzymes of FFA transport and utilization.

The key enzyme in the regulation of pyruvate metabolism is the PDH. The activity of cardiac PDH is mainly modulated by the PDH kinase (PDHK4), an isoform of the kinase phosphorylating and transforming PDH from the active to the inactive form. Short-term metabolic inhibition of PDHK4 is affected by pyruvate while its activation is affected by acetyl CoA and NADH. The long-term regulation is determined by many conditions characterized by insulin deficiency (diabetes) or resistance (starvation, high-fat diet, and hyperthyroidism) that increase PDHK expression, while insulin suppresses its production [35,36,38].

3. The metabolic myocardial switch

In pathological conditions a long term modification in substrate preference may be present: the diabetic heart relies almost exclusively on FAO [48], on the contrary the myocardium submitted to mechanical, ischemic\hypoxic or inflammatory stress switches to the anaerobic glycolysis,

which can also continue in an environment poor in oxygen. Even though glycolysis allows a much lesser production of energy (2 molecules of ATP instead of 36 per molecule of glucose oxidized) through the transformation of pyruvate into lactate by LDH it presents the advantage to go on also in a hypoxic setting; however this process, which in the short-term is adaptive, in the long-term becomes maladaptive because of the reduced energy production [49]. The better the heart defends itself in the presence of stressful events, the more easily it is able to switch to the type of metabolism more efficient in that situation and the more it is provided with metabolic flexibility. Thus the survival of the myocardium depends, in these conditions, on an increased supply of glucose that is assured by the augmentation of the main transmembrane glucose transporters, GLUT1 and GLUT4. GLUT1 is present ubiquitously, augments in presence of reduced glucose levels and during inflammatory, metabolic and osmotic stress [50]; GLUT4 is present in the adipose tissue, heart, liver and in the striated muscle and is the typical insulin-dependent transporter. The increase in glucose transporters, mainly in GLUT1, has an adaptive meaning in the stressed heart; its overexpression protects against experimental ventricular hypertrophy, at least until cardiac failure appears, causing its downregulation [51].

This metabolic remodelling seems to be controlled by the fetal gene program, so called because it is present in the fetal environment, relatively hypoxic, and is reactivated whenever a stressful situation is present [47,52]. It modifies the expression of contractile proteins switching the expression of heavy myosin chain (HMC) from the more efficient but more energy expensive alpha to the slower but less energy consuming beta isoform, and increases the production of some humoral factors (brain natriuretic peptide, BNP) and of several protective proteins (heat shock proteins, HSP). The cardioprotective pathway of the PI3K and Akt, activated during pre- and post-conditioning, is also activated by the fetal gene program supplying an antiapoptotic protection and leading to an overlapping between cardioprotection in chronic ischemia and ischemic preconditioning [52]. The metabolic component is mainly regulated by the enzyme pyruvate deydrogenase kinase (PDHK4) phosphorylating and inactivating pyruvate deydrogenase (PDH) and inhibiting the transformation into Acetyl-CoA that could enter the TCA; it is instead transformed into lactate by LDH allowing a continued production of ATP also in low oxygen settings. This activation of glycolysis, such as the dependent increase in GLUT1,4, in LDH and glycolytic enzymes is mainly controlled by the transcription factor HIF-1 that is upregulated in the settings of ischemia\hypoxia but also in non-hypoxic conditions such as during inflammatory states and tumours because its expression is increased through a cross-talk with NF-kB [53]. On the other hand hypoxia and inflammation are not completely separated conditions as showed by the induction of TLR4 and TLR6 by HIF-1 during hypoxia [54]. HIF-1 is composed by a constitutively expressed HIF-1β subunit and an oxygen-sensitive HIF-1α subunit, target under normoxic conditions of three prolyl hydroxilases 1,2,3(PDH1,2,3), the hydroxylation allows the binding of the von Hippel-Lindau protein (VHL) and the consequent ubiquitination and proteasome degradation of HIF-1α. On the contrary during hypoxia PDH2 activity is reduced with accumulation of HIF-1α, its dimerization with HIF-1β and the expression of many target genes [55].

The increased expression of HIF-1 causes at the same time a downregulation of mitochondrial lipid oxidation depressing the expression of the transcription factor PPARα

(possessing a DNA consensus motif for HIF-1)[56] and an upregulation of PPARγ activating fatty acid uptake and glycerolipid biosynthesis so leading to lipotoxicity [57]. HIF-1 stimulates also mitochondrial autophagy to rebalance the reduced oxidation with mitochondrial mass[58]. The stimulation of glycolysis by HIF-1 has an important role in sepsis because the phagocytes use huge quantities of glucose through glycolysis in the hypoxic environment of the inflamed tissues either for cell migration either for phagocytosis and bacterial killing [59]. The activity of HIF-1 is regulated by acetylation performed by CBP\p300 and inhibited by deacetylation by SIRT1. The inverse shift to mitochondrial lipid oxidation is controlled by SIRT1 which increases the expression of PGC-1α with simultaneous activation of both mitochondrial biogenesis and lipid oxidation through PPARα upregulation. SIRT1 and HIF-1 are reciprocally regulated so that in the hypoxic\inflammatory setting HIF-1α is activated while Sirt1 is decreased due to NAD^+ scarcity so inhibiting HIF-1α deacetylation and inactivation while in normoxic environment HIF-1α is inactivated by oxygen-dependent prolyl hydroxylases PHD2 activated by SIRT1.

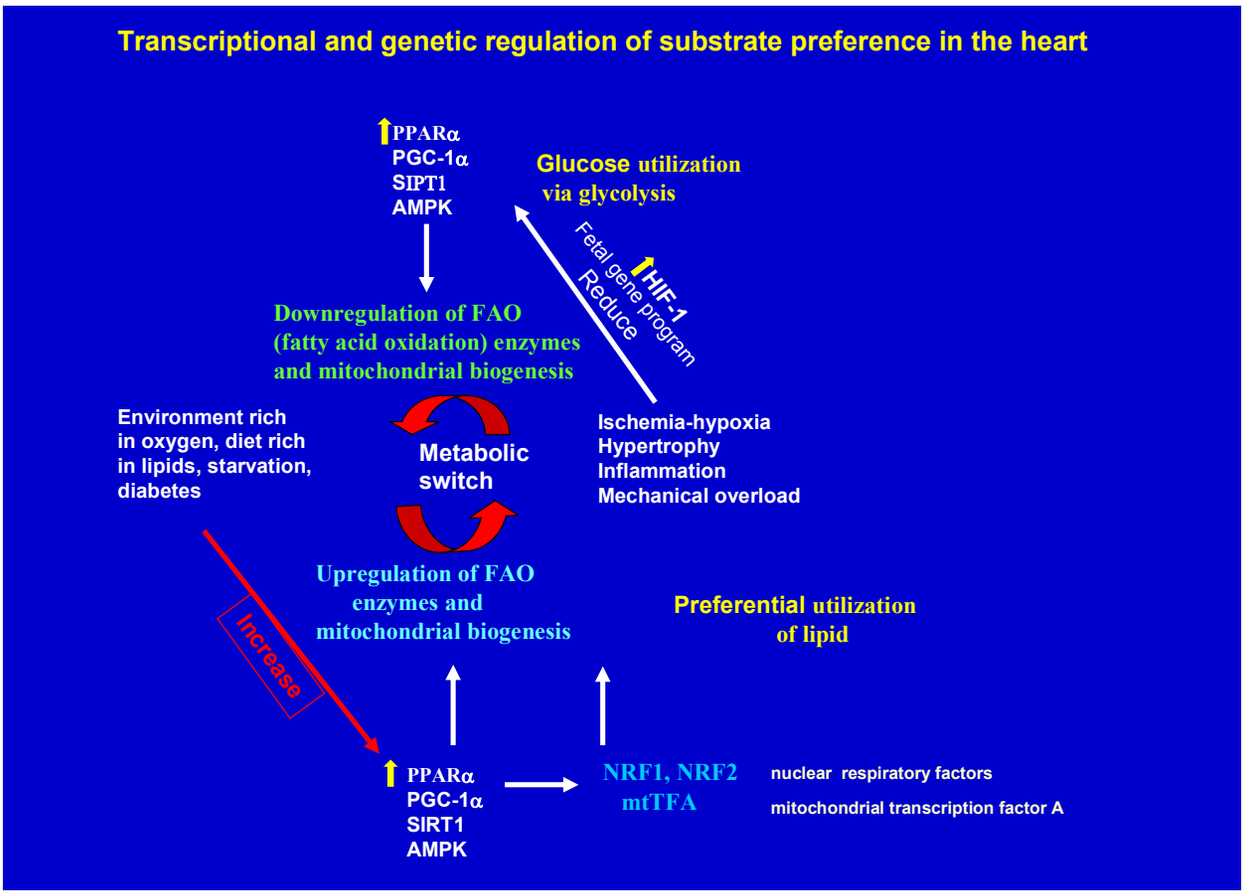

Figure 1. Metabolic switch. See text for explanation.

Sirtuins are class III NAD^+-dependant histone deacetylases (HDAC) targeting histones, transcription factors and enzymes regulating in this way gene expression and metabolic function in relation to the energy status of the cell [60-64]. They have been related to the regulation of metabolism, apoptosis and inflammation, to extending life span and to the

healthy aging. Sirtuins exist in seven forms with different subcellular localization: SIRT1,6,7 present in nucleus, SIRT2 in cytoplasm, SIRT3,4,5 in the mitochondria. Because they are mainly regulated by the levels of NAD^+, the AMPK that increases its concentration upregulates their expression while the DNA-repairing enzyme poly(ADP-ribose) polymerase 1 (PARP), activated whenever there is an oxidative stress and consuming for its activity high quantities of NAD^+, downregulates sirtuin expression . SIRT1 is able to deacetylate and activate a series of transcription factors involved in many steps of metabolism (AMPK, FOXO, HIF-1, PGC-1α, p53, NF-κB, PPARα and β, LXR,FXR,ERR). Mitochondrial sirtuins are in a critical location to regulate metabolism and biogenesis of the organelles controlling oxidative phosphorylation (OXPHOS), intracellular Calcium and the production of ROS [65]. SIRT1 is also regulated via microRNA: microRNA34a downregulates its expression metabolically and microRNA199a in the hypoxic setting [66,67]. Statins have been showed to upregulate SIRT1 expression in endothelial cells contributing possibly to improve clinically endothelial function [68].

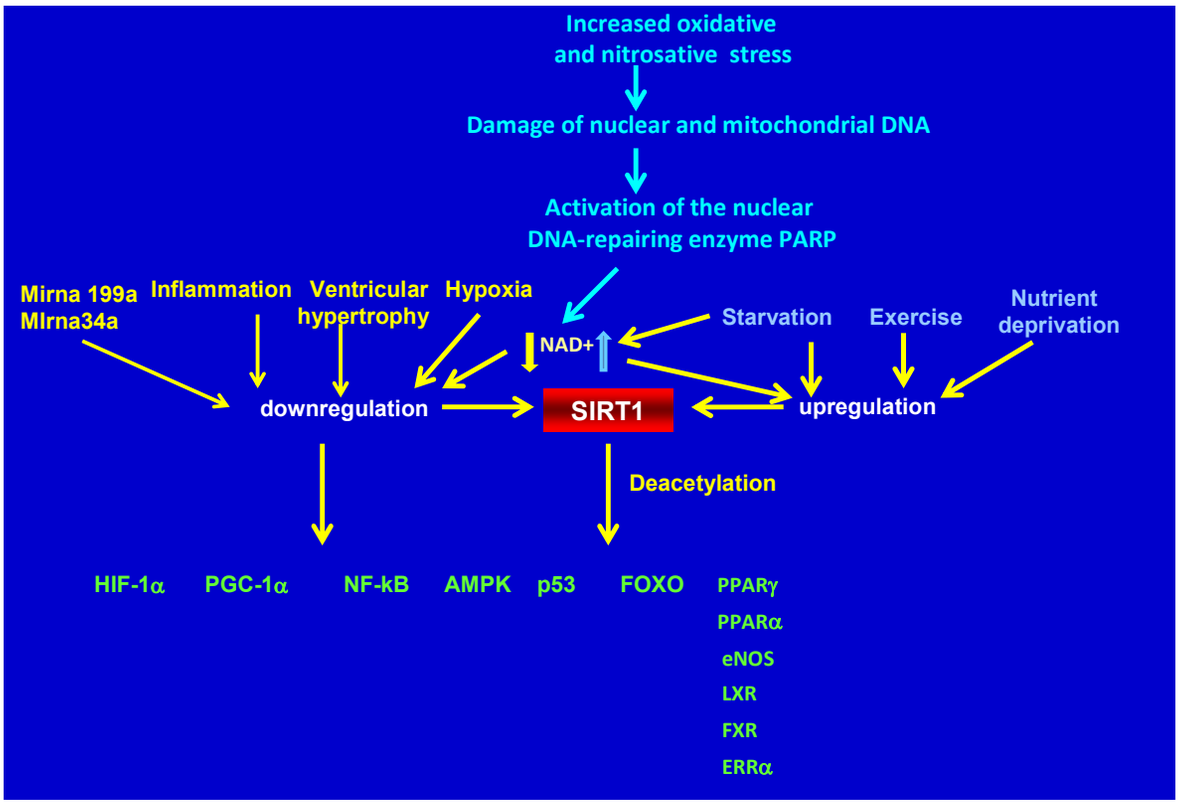

Figure 2. Regulation of SIRT1 expression. See text for explanation.

4. Transcriptional regulation of FFA transport, uptake and oxidation

Transport, uptake and oxidation of FFA in the cell is a process tightly regulated by several transcription factors belonging to the nuclear hormone receptor superfamily. The nuclear receptors involved include the peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), farnesoid X receptor (FXR) and ERR (estrogen related receptor), which

bind and are activated by lipids, acting as sensors of endocrine signals and of dietary components and planners of the physiological response to nutrients. PPARs, the most important of them, are present in three types (alpha, beta and gamma), besides their action as lipids sensors, they are involved in the regulation of lipid and glucose metabolism, insulin sensitivity and modulation of inflammation (for review see [69-71]); their actions are partially overlapping with a certain degree of redundancy but they are not coincident. In elucidating the function of PPARs an important role has been played by the studies in genetically modified mice with overexpression or deletion of these nuclear receptors. PPARs are activated by endogenous ligands, FFA or their derivatives (arachidonic acid, eicosanoids, leukotrienes and oxidized lipoproteins) but there are also known exogenous ligands, used as drugs, for PPARα (fibrates) and PPARγ (thiazolidinediones) or for both PPARα and γ (muraglitazar) [72].

The PPARs form heterodimers with retinoid X receptors (RXR) and bind to consensus DNA sequences in the promoter of the target genes, the PPAR response binding element (PPRE), formed by two hexameric nucleotides sequences separated by one base pair. In the absence of ligands the heterodimer binds with the co-repressors, blocking gene transcription; when activated by ligands, the complex, because of a change of conformation, releases the co-repressors and recruits the co-activators and the RNA polymerase giving rise to transcription. PPARα are expressed mainly in tissues with high oxidative metabolism such as heart, muscle and liver. PPARγ are expressed at high levels only in adipose tissue where they regulate the maturation and fat deposition in adipocytes so indirectly regulating, through the plasma level of FFA, the insulin sensitivity; they are however expressed at low level in many organs among which the heart [73]. Whereas PPARα and γ share the ability to activate the transcription of proteins involved in FFA uptake, storage and oxidation, PPARβ only activate the proteins involved in FFA oxidation. Also different are the effects on glucose metabolism: PPARα depress glucose oxidation whereas PPARβ activate glycolysis (through PDHK4 activation) and glucose uptake; PPARγ activate only glucose uptake [69,74].

PPARβ\δ are expressed in various tissues where they regulate lipid but even glucose metabolism. PPARγ also regulate mitochondrial biogenesis through interaction with the PPARγ coactivator 1 (PGC-1) network (see below)[74]. Because FAO takes mainly place in mitochondria (only the breakdown of very long chain fatty acids, subsequently converted to medium chain fatty acids and shuttled to mitochondria, takes place in the peroxisomes) there is a common regulatory mechanism for FAO and mitochondrial biogenesis controlled by PPARs and by the network of PGC-1. The PPARγ mainly but also the PPARα, have been showed, in several model systems, to modulate inflammation by transrepressing target genes of the transcription factors NF-κB, nuclear factor of activated T cells (NFAT), activator protein 1 (AP1) and signal transducers and activators of transcription (STATs) through a process called transrepression [75-77] so modulating the action of lymphocytes, macrophages and dendritic cells. This process has twofold importance, on the one side it may regulate the inflammation induced by tissue

macrophages, involved in the low grade inflammation and important in dysmetabolic conditions such as reduced insulin sensitivity, metabolic syndrome and atherosclerosis on the other side it may be of critical interest in regulating inflammatory reaction in sepsis [78]. LXRs and FXR heterodimerize also with RXR and are activated respectively by oxysterol and bile acids: both exist in the isoforms α and β, contribute to lipid and lipoprotein regulation and modulate inflammation. In the regulation of FAO a fundamental role is also played by the orphan receptor (transcription factors without an identified endogenous ligand) ERR (estrogen related receptor) involved also in the regulation of mitochondrial biogenesis, gluconeogenesis and oxidative phosphorylation by interacting with PPARα and γ and PGC-1 [79].

5. TG delivery: Lipolysis

The amount of lipid in the myocardial cell is regulated by the balance between TG delivery to the heart through the VLDL- regulated by lipolysis- and the oxidation of TG in the myocardiocyte. Considering their importance in cellular signalling, lipid synthesis and as energy substrates, the level of circulating TG and FFA is tightly regulated [80]. Adipocytes are the only cells able to hydrolize TG giving rise to FFA and glycerol utilized by other tissues. This process is initiated by the adipose triglyceride lipase (ATGL) catalysing the hydrolysis of triglycerides to diglycerides followed by the hydrolysis of diglycerides to monoglycerides by the hormone-sensitive lipase (HSL) able also to catalyse the first phase and of monoglycerides to TG and glycerol by the monoglyceride lipase (MGL)[81-83]. ATGL deficiency is associated with fat deposition in all tissues indicating that ATGL is rate limiting in the catabolism of cellular fat depots [84]. Lipolysis is also regulated by perilipin , a protein coating the lipid droplets, that exposes TG of a lipid droplet to the action of the lipases [85].

Many substances may activate physiologically and in diseases HSL, the more important enzyme for its sensitivity to the hormonal regulation but also for its action modulating adipogenesis and adipose metabolism [86]. Catecholamines acting through β_1, β_2 and also β_3 receptors coupled to a G stimulating (G_s) protein are the main stimulators of HSL; the alpha$_2$ receptors inhibit instead lipolysis through a G inhibitory (G_i) protein, this effect may be antagonized by administration of beta-blockers. Also natriuretic peptides are able to enhance lipolysis by activating guanylyl cyclase and increasing cGMP [83]. TNFα, IL1β and IL6 increase HSL activity through the stimulation of several kinases of the MAP kinase cascade (janus kinases (JNK), p44\42 and extracellular signal-regulated kinase-1/2 (ERK1/2) and the consequent increase in cAMP [87,88]. These kinases phosphorylate perilipin allowing HSL and ATGL to access and hydrolyse TG; this effect was prevented by metformin [89].

LPS may activate lipolysis by increasing ILs level, the demonstration however that the inhibition of TNF-alpha, IL1 and cathecolamines could not prevent lipolysis in endotoxemic rats, led to show a direct lipolytic action carried out by low-dose endotoxin [90].This action is not mediated by an increase in cAMP, activation of PKA or PKC or inhibition of NFkB but through phosphorylation of perilipin by LTR4 and ERK1/2.

The main inhibitor of lipolysis is insulin through the insulin-like receptor substrates 1and 2(IRS-1and 2) that activate the phosphadityl inositol 3-kinase(PI3K) complex and phosphorylate and activate the phosphodiesterase 3(PDE-3) [80]. Insulin acts also via an Akt-Independent PI3K-dependent signalling pathway which modifies PKA phosphorylation of perilipin [91]. The reduction in insulin activity is responsible for increased lipolysis in diabetes and obesity together with the reduction in the insulin-sensitizing activity of adiponectin [92] probably linked to the adipose tissue dysfunction described in sepsis [17,18]. Moreover adiponectin may reduce fat deposition in visceral adipose tissue increasing the deposit in the subcutaneous compartment through PPARγ upregulation [18]. The lipolytic activity is differently regulated in subcutaneous and visceral fat: the former, more important for the basal activity, is more sensitive to the antilipolytic action of insulin, the latter is mainly activated during hormonal stimulation and provides FFA directly to the liver through the portal circulation in physiological and pathophysiological situations. In sepsis seems to be present a failure of adipocytes differentiation leading to a decreased storage ability of the subcutaneous tissue allowing FFA to be accumulated in visceral fat (with an increase in the metabolic and cardiovascular risk) and in organs giving rise to lipotoxicity for the concomitant reduction of FAO [18]. Lipolysis is increased in sepsis [14] due to a raised activity of the lipases of the adipose tissue, mainly the HSL, because of the increased plasma level of catecholamines, ILs and natriuretic peptides and the reduced activity of insulin and adiponectin (fig 3).

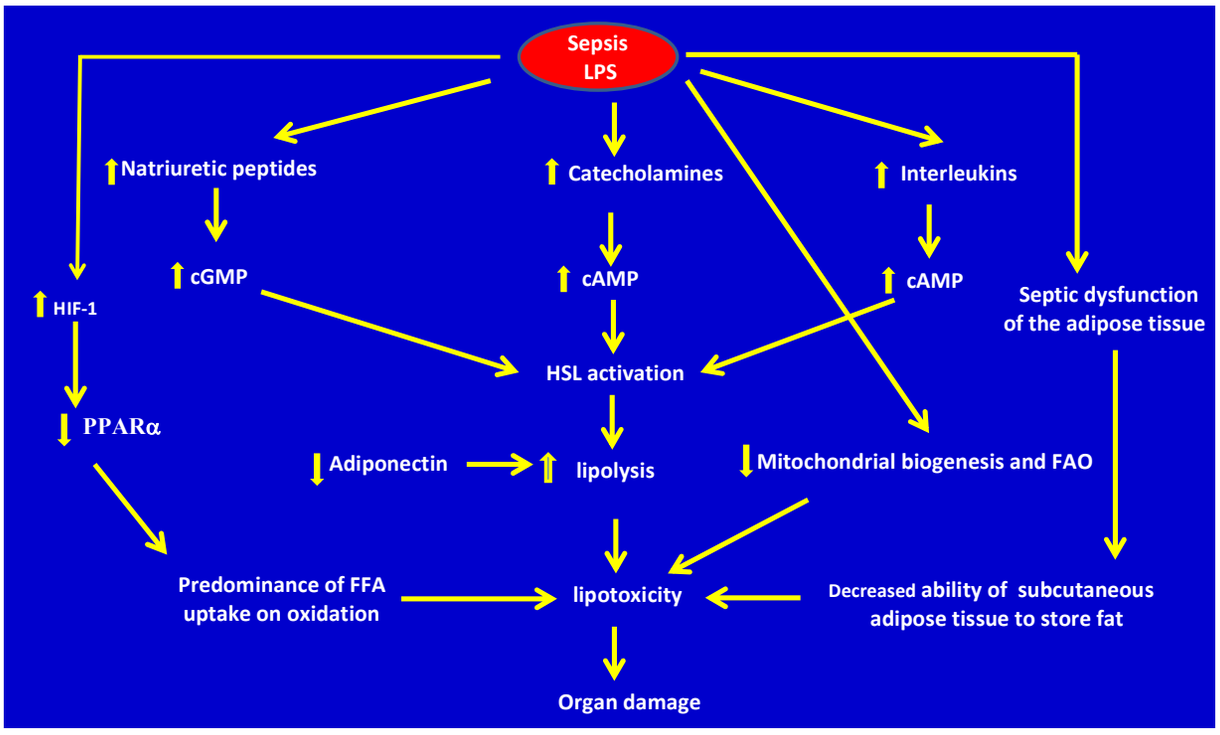

Figure 3. Lipolysis in sepsis. See text for explanation.

5.1. Lipoprotein metabolism in sepsis

Sepsis and inflammation reproduce an atherogenic picture of serum lipoproteins [93] with an early reduction -preceding even the change in leukocytes- of total HDL- and LDL-cholesterol, an increase in VLDL and TG justified by augmented liver synthesis and lipolysis, a reduction in HDL phospholipids compensated by an increase in VLDL phospholipids.

5.2. HDL in sepsis

Until recently HDL were considered as devoted only to reverse cholesterol transport (RCT), a process through which the cholesterol is transferred from the cells to the acceptor apolipoproteinA-1 by the specific transporter A binding cassette 1(ABC1) and delivered to the liver where it is finally secreted and eliminated in the bile, the only way of its removal from the body. The recent application in this field of the Gel Filtration Chromatography based proteomics revealed that HDL contain not only apo-A1, apo-A2 and some enzymatic and transfer protein involved in cholesterol transport but more than 50 other associated proteins [94]. Many of the proteins isolated carry out functions completely different from RCT belonging to the complement proteins (C3,C1 inhibitor, factor H) and to serine protease inhibitors (SERPIN) [95-97]. The recent attainments point to an important role of HDL in immunity and in the modulation of the inflammatory response but they are also involved in a lot of disparate functions ranging from glucose metabolism to endothelial protection displaying also an antithrombotic action (for review see [98,99]). Of main importance in sepsis is the property of HDL to bind and neutralize LPS, mediated through its content in phospholipids.

HDLs may carry out anti-inflammatory actions in many ways: they downregulate the proinflammatory transcription factor NF-kB through a not yet completely understood mechanism -probably by the reduced degradation of Inhibitor kappa-B-a (IkB-a) [100]-, moreover they reduce the expression of the adhesion molecules CD11b and MCP-1 on human monocytes [97] and may curtail TNF-alpha production and upregulate IL-10 production by lymphocytes. The normal anti-inflammatory function of HDLs turns into a proinflammatory one during the acute phase reaction (APR) when they become dysfunctional [101]. The reasons for this change are manifold: there is a reduction in ApoA-1 levels, partially substituted by serum amyloid A apolipoprotein (Apo-SAA), their size is smaller because of a reduced activity of lecytin cholesterol acyl transferase (LCAT), enzyme deputed to esterification of cholesterol that allows the enlargement of HDL, HDLs become poorer in the antioxidant enzymes paraoxanase [102,103].

The interference with the function of the inflammatory cells may be direct or mediated by the effect of the HDL on the reduction of cellular cholesterol and of cholesterol-enriched microdomains or rafts of their plasma membrane; this is also showed by the increased lethality and inflammatory response observed during sepsis in transgenic null mice for critical receptors involved in cholesterol efflux as SR-BI and ACBA1 [104].

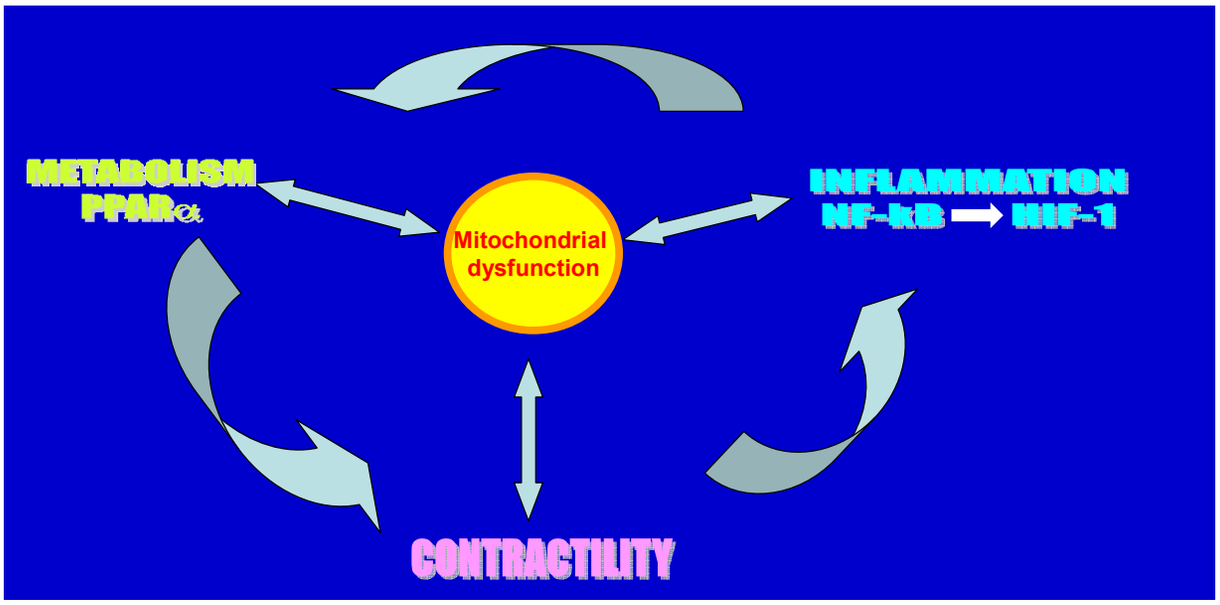

Figure 4. Relationships among mitochondrial dysfunction, metabolism, and contractility. See text for explanation.

HDL may bind and inactivate LPS mainly through their phospholipid component [105,106], in sepsis and inflammation because of the HDL reduction their LPS inhibiting function is assumed by the VLDL phospholipids.

Also the endothelial function is modified through an increased production of nitric oxide (NO) by the stimulation of endothelial nitric oxide synthase (eNOS) mediated by the activation of the protective PI3K\Akt pathway leading to vasodilation, antiadhesion and anti-inflammatory effects [107]. A similar cardioprotective and antiapoptotic action of HDL have been shown through the activation of Stat3 mediated by sphingosine 1 phosphate (S1P), one of their common component [108]. The recombinant HDL(rHDL) or HDL mimetics, currently under clinical trial, are provided with the same actions attributed to the HDL [109,110]. The level of total, HDL- and LDL-cholesterol is decreased in septic and critically ill patients, as well as in experimental animals infused with LPS and proinflammatory cytokines and the decrease is negatively related to IL6 and TNFa concentrations [111]; HDL reduction is also related to mortality and severity of the disease [105,106].

The reduced level of serum HDL and cholesterol in sepsis is explained by a reduced RCT [112] mediated by the LPS-induced downregulation of the scavenger receptors SR-B1 and ABCA1 [113]. The sequestration of the cholesterol into the cell may be useful in the short term, due to the increased delivery to the immune cells, but harmful in the long run because of the decreased delivery to the steroidogenetic and liver cells and to the atherogenic picture it induces.

5.3. VLDL

VLDL are a circulant reservoir of TG and FFA able to activate PPARα and γ [114]. In clinical sepsis and experimental endotoxemia the serum level of VLDL, FFA and TG is increased

due to the upregulation of the hepatic synthesis of TG, FFA and apoB, to the increased lipolysis, decreased lipid oxidation and inhibition of LPL [103]. The increased lipolysis in sepsis is due to the activation of the hormone-sensitive lipase (HSL) by catecholamines acting through PKA stimulation and cAMP increase. To the increased lipolysis contribute also the increased level of ILs, of natriuretic peptides and the reduction in insulin and adiponectin activity (see paragraph on lipolysis).

Feingold, in mice, showed that LPS reduced in the heart, diaphragm and kidneys [115-117] the levels of many enzymes involved in the fatty acid metabolism (FATP1,MCAD, CD36, CPT1β etc) through the reduced expression of many transcription factors: PPARα and γ, LXRα, FXRα, pregnane X receptors and their coactivators PPARγ coactivator 1α and β (PGC-1α and β), steroid coactivator receptor 1 and 2 (SRC1-2) and ERRα. The downregulation of the nuclear receptors can be reproduced by IL-1 and TNFα administration. Maitra and colleagues described an important role for IRAK1, a signalling component downstream of TLR4, in the downregulation of these transcription factors in sepsis showing that IRAK1 $^{-/-}$ mice were protected against alterations in lipid metabolism [118]. Because all these factors are deacetylated and activated by SIRT1 their downregulation in sepsis may play an important causative role [68] (see the paragraphs on metabolic switch and mitochondrial dysfunction).

The increase in VLDL during sepsis, traditionally considered as a reaction mobilizing lipid stores to delivery an increased amount to the immune cells, may also have a protective meaning: the increased level of serum VLDL and of their content in phospholipids can substitute for the HDL in binding and neutralizing LPS [119,120].

6. Mitochondrial dysfunction play an important role in septic cardiomyopathy

Mitochondrial dysfunction -present in sepsis but also in many other pathological states such as chronic heart failure, diabetes mellitus, metabolic syndrome and several neurodegenerative diseases- is a syndrome characterized by a picture of reduced oxygen consumption, ineffective ATP production, increased accumulation of ROS and calcium in the organelle leading to the opening in the internal mitochondrial membrane of a high conduction pore allowing the entry of solutes until a molecular weight of 1.500, with mitochondrial swelling, collapse of the electron gradient, release of proapoptotic proteins and death of the organelle (mitoptosis) followed by mitophagy: this phenomenon called mitochondrial permeability transition pore (MPTP) has an important role in sepsis and its inhibition may experimentally improve septic myocardial dysfunction [28,121-123].

Mitochondrial functionality is regulated by the equilibrium between de novo mitochondrial formation (mitochondrial biogenesis) and mitochondrial autophagy (mitophagy), frequently preceding whole cell autophagy. This latter process, taking place only in deenergized organelles, is very important for cell survival because it allows the elimination of dysfunctional mitochondria, producing too much radical oxygen species(ROS) and assures

the high quality of the mitochondria provided with a high membrane potential and resistant to MPTP [124]. Moreover autophagy has been shown to be protective in ischemia-reperfusion injury (IRI) and inflammation by inhibiting the exposition of mtDNA and the consequent activation of the inflammasome NALP3 [125]. Autophagy involves a complex molecular machinery including more than 30 Atg (AutophaGy-related) proteins and 50 lysosomal hydrolases [126].

The mitochondrial biogenesis is orchestrated by PPARα and β\δ, by the ERRα and above all by the network PGC-1α, PGC1– β and PGC-1 related coactivator (PRC), factors enriched in tissues with high oxidative capacity (heart, muscle, brown adipose tissue and kidneys) and highly inducible by starvation, exercise and cold acclimation (126-128); PGC1-β is also induced by Ils [129]. Mice with single deficiency in PGC-1α or PGC1-β display only minimal alteration under nonstressed conditions and have a normal mitochondrial mass [130,131] whereas mice with double deletion of both PGC-1 forms died shortly after birth with small hearts, bradycardia, intermittent heart block, and a markedly reduced cardiac output [132], allowing to think that one isoform may compensate for the other. Mitochondrial biogenesis to take place needs the transcription of the genes controlled by mitochondrial DNA, a process activated by the mitochondrial transcription factor A (Tfam), a nuclear-encoded transcription factor essential for replication, maintenance and transcription of mitochondrial DNA [133]. The majority of the genes codifying mitochondrial proteins are however present in nuclear DNA and are activated, such as Tfam, by the nuclear respiratory factors 1 and 2 (NRF1 and NRF2). PGC-1 coordinates the function of NRF1, NRF2 and Tfam, regulating mitochondrial biogenesis and, through the complex PPARs-ERRs, controls FAO such that a prompt adaptive response to physiological events as cold acclimation, exercise, starvation etc may be possible with selection of the most suitable level of FFA oxidation needed in the particular situation.

Cardiac contractile activity is linked to the mitochondrial biogenesis because an increase in intracellular calcium increases the expression of PGC-1 via calcineurin (CaN) -activating also PPARα promoter and FAO- and Ca-calmodulin dependent kinase (CaMK), a process requiring cAMP response element-binding protein (CREB)(126,133): in this way the contractile activity is strictly linked to the metabolism and to the mitochondrial oxidative function.

PGC-1 expression is also controlled hormonally by tyroid hormones (TH), metabolically via adrenergic system and cAMP, by AMPK and p38 MAPK through phosphorylation [126,133] and by eNOS-produced NO. The cellular mitochondrial content is proportional to the energy requirement [75], mitochondrial biogenesis is therefore controlled by the two main energy sensors in the cell: Sirt1(silent mating type information regulator 2 homolog 1) and AMPK act coordinately to control PGC-1 activity respectively through deacetylation and phosphorylation. Sirtuins are class III histone deacetylating enzymes supplied by AMPK with the adequate level of the NAD^+, essential activator of Sirt1 that in turn deacetylates PGC-1 and activates its gene expression [75]. Sirt1 is also an important in vivo regulator of mitophagy by deacetylation of the autophagy genes Atg5, Atg7 and Atg8 [134], linking this protective mechanism, devoted to the clearance of depotentiated mitochondria, with PGC-

1a mediated biogenesis. For biogenesis to occur it is necessary mitochondria undergo the processes of fusion and fission regulated respectively by mitofusins (Mfn1-2) and by dynamin-related protein(DRP1 and OPA1) [126].

The first description of mitochondrial dysfunction in sepsis dates back to 1970' [135,136], but the initial studies were not reliable due to inadequate techniques to test mitochondrial function. More recent studies however linked the altered oxygen utilization and ATP production in sepsis to mitochondrial dysfunction (137,138), even though there are substantial differences among the sepsis model induced by LPS administration in which is present a widespread mitochondrial damage and the CLP model characterized by a less evident mitochondrial pathology because damaged organelles undergo autolysis and autophagy [139]. Several alterations have been described in mitochondria in experimental and human sepsis both morphological (swelling, destruction of cristae, decreased electron density, breaks in membrane and altered outer membrane integrity) and biochemical (release of cytochrome c, decreased mtDNA copy number, reduced activity of Complexes I and III) [28,140,141]; their extent has been related to outcome [142]. Several studies showed an initial increase of mitochondrial activity in sepsis, followed by a reduction. Singer [132] hypothesized that, after a metabolic stimulation of mitochondrial function. caused by the excessive inflammatory response, in the successive phase there is a metabolic downregulation determined by the mitochondrial dysfunction. In this latter phase a stimulation of oxygen consumption (VO2) would be harmful because it forces mitochondria, adapted to a reduction of metabolism, to overwork without being prepared for it. The restorative phase of sepsis is linked to the activation of mitochondrial biogenesis; also LPS may have a role in inducing this process [140,143]. The absence of relevant cell death by apoptosis or necrosis in parenchymatous organs and the ability also of the tissues with less regenerative capacity to recover led to think that multiple organ dysfunction syndrome (MODS) were related mainly to a functional compromise mediated by endocrine and metabolic alterations and provided with a protective role [144-146]. In sepsis a paradoxical increase has been observed, in some tissue, in blood oxygen saturation [147], related to outcome and linked to an altered mitochondrial oxygen utilization (cytopathic hypoxia) [148], which has been attributed to nitric oxide (NO) overproduction by mitochondrial nitric oxide synthase (mtNOS) [149,150] or other NOS isoforms: NO competitively inhibits oxygen binding to cytochrome c oxydase (COX) determining a tonic inhibition of mitochondrial oxygen consumption, reversible on inhibiting its excessive production [151]. The exact role of NO inhibition by COX in vivo in physiologic and pathologic conditions is however an unsettled problem [152]. Other gaseous molecules share with NO the ability to interact with COX, to inhibit it competitively and to regulate at this level the body oxygen consumption [153,154]; they are called gasotransmitters and include carbon monoxide (CO) and Hydrogen Sulphide (H_2S), this latter molecule was first shown able to induce experimentally in mice, but not in pigs and superior mammals, a particular state of depression of the metabolism and of the resistance to hypoxia, called "suspended animation" (155]. A similar observation has been made with NO and CO in Drosophila [156,157]. Exploiting this property of gasotransmitters in the treatment of myocardial and cerebral hypoxia\ischemia is tempting, considered also the limitations of the current treatment

with hypothermia of the hypoxic organ injury, even though they also have a high toxicity [158]. To the picture of metabolic hibernation may contribute, besides NO, also CO and H_2S increased during sepsis [159-161].

In addition to the antagonism against COX the higher levels of NO, in presence of an increased oxidative stress, by reacting with superoxide, may further injure mitochondria determining the formation of the toxic peroxynitrite able to damage the Complex I and III of the ETC, the membrane lipid and mitochondrial and nuclear DNA. The available data however cannot be explained only by this mechanism; the metabolic ebb phase, coincident with CARS and silencing of proinflammatory genes, is characterized by a profound state of mitochondrial depression, reduced oxidative metabolism and oxygen consumption leading to a state of metabolic hibernation responsible for the depressed cell function during MODS in sepsis; mitochondrial depression is however completely reversible on recovery from sepsis. Recently Schilling and colleagues showed that LPS administration through TLR4 stimulation may induce a fuel switch from preferential myocardial use of lipid to glycolysis, similar to the one observed in the failing heart, with decreased mitochondrial oxidation, lipid accumulation within them and a suppression of the genes encoding PGC-1α and β: the genetic overexpression of PGC-1β may restore mitochondrial function independently of the inflammatory response [162]. Smeding and colleagues [163], on the other hand, observed that the sirtuin activator resveratrol protect mitochondria in a mice model of CLP improving myocardial dysfunction, preserving energy production but without improving survival. At this point some question should be raised: could we think that the mitochondrial dysfunction is a reversible event even in the presence of a continuing sepsis? Which may be the correct link and the ordinated succession among all the alterations described?

We try to reconstruct the successive steps leading to mitochondrial dysfunction and to metabolic hibernation in sepsis (fig. 5). The first step is the hypercatabolic phase with the transient activation of mitochondrial oxidative phosphorylation (OXPHOS) activated by the acute hormonal stress response in the very early phase, with increased oxidative and nitrosative stress damaging ETC and inducing a downregulation of many of its proteins. Immediately after, in the inflammatory setting of sepsis, occurs the shift to glycolysis and the activation of mito autophagy. SIRT1 is rapidly deactivated by the reduced function of AMPK, the decreased NAD^+ levels due to the activation of PARP and by the increased expression of miR199a [66]. The stimulation of this enzyme in sepsis was first showed by Fink [148]; recently Zhang and colleagues, after LPS administration in mice, observed that the plasma levels of ATP, SIRT1 and AMPK decline precipitously after 10' and remain below the detection level for up to 12 h while HIF-1 increases contemporarily along with an increase in mitochondrial autophagy. Importantly all these effects are absent in wild type mice treated with resveratrol but not in Sirt1 liver knockout mice [164]. This study further confirm the critical role of SIRT1 that would be downregulated in sepsis for many causes: increased HIF-1 expression, increased miR199a expression, drastic reduction of NAD^+ by activation of PARP consuming it and reduced activity of AMPK supplying it. The main consequence of these modifications are the reduced deacetylation by SIRT1 and phosphorylation by AMPK of PGC-1α, also PGC1− β seems to be reduced in muscle during sepsis [162,165] making impossible a compensation. The

role of PARP has also been showed by Soriano in the setting of human septic myocardiopathy [166], where the degree of myocardial compromise related well with the staining for the product of activated PARP [poly(ADP-ribose) (PAR)], and in many experimental model of cardiovascular diseases[167] in which PARP inhibitors provide significant benefits. Interestingly the metabolic hibernation in sepsis according to our hypothesis has a different starting point from the true mammals hibernation in which the scarcity of nutrients leads to increased levels of NAD+ and AMP with AMPK and SIRT1 activation and deacetylation of clock protein BMAL1 and the opposite switch from glucose to lipid metabolism [168]. The connection between bioenergetics impairment and inflammation in sepsis has also been studied by Liu and colleagues [169-170] that underline the role of Sirt1 in reprogramming immune response through the silencing of the proinflammatory genes and the coordination of the metabolic response. In the experimental setting many attempts have been made to treat mitochondrial dysfunction by supplying substrates, cofactors, mitochondrial-targeted antioxidants, scavengers of mitochondrial ROS and membrane stabilizers displaying improvements at many levels: ATP production, reduced production of ROS in mitochondrial ETC, reduction of apoptosis and prevention of MPTP opening [171-174]. Apoptosis may also have a role in septic mitochondrial dysfunction as it has in CHF. Lancel and colleagues demonstrated in cardiomyocytes isolated 4 hours after endotoxin injection in rats, an increase in the release of caspase-3, -8, and -9-like activities, associated with destruction of the sarcomeric structure and cleavage of components of the cardiac myofilament [175]. Simvastatin, whose use has been proposed in sepsis, may protect against apoptosis induced by Staphylococcus aureus alpha-toxin [176].

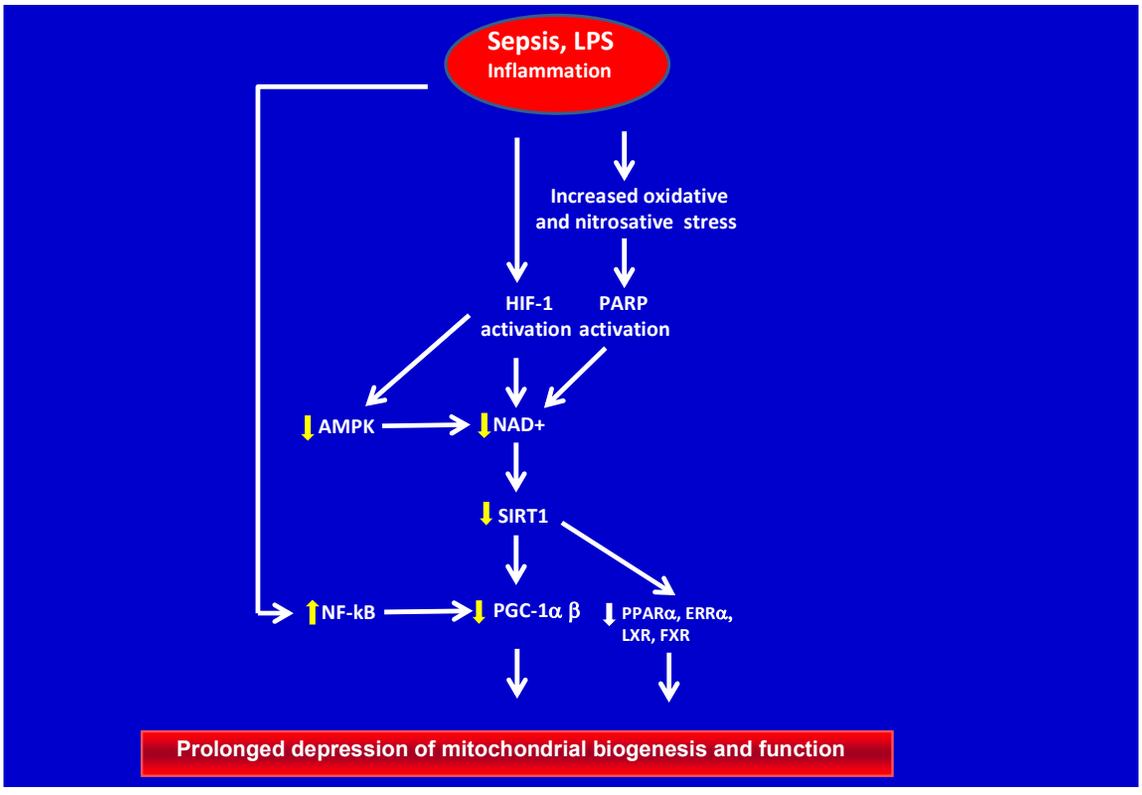

Figure 5. Mitochondrial dysfunction in sepsis. See text for explanation

6.1. Cardiac function in sepsis

The pathogenesis of the myocardial dysfunction in sepsis is not definitively explained and is probably caused by a myriad of alterations. The morphological picture recognized in sepsis was formerly considered unspecific but more recently many interesting alterations have been described even though certainly some of them are not the cause but the consequence of the acute cardiac damage. Beside not specific alterations such as cell edema, the already described mitochondrial lesions, damage of cytoplasmic membrane and myofibrils, inflammatory cells infiltration [139,177], more definite biochemical and microscopic changes have been observed with lipid infiltration [178], increased deposits of glycogen and increased levels of glucose uptake, GLUT1 and GLUT4 [141], increased sarcolemmal permeability [179], disruption of sarcolemmal dystrophin and beta-dystroglycan [180].

6.2. Hemodynamic pattern

Parker and colleagues in 20 p. in septic shock [181], adequately resuscitated, with the combined use of radionuclide-gated cardiac cineangiography and thermodilution observed important differences in the hemodynamic pattern of survivors and non survivors. Both groups had a hyperdynamic pattern with high cardiac index (CI) and low systemic vascular resistance (SVR) but survivors had an important LV dilatation and a reduced left ventricle ejection fraction (LVEF) normalizing in 7-10 days while non survivors paradoxically showed higher LVEF but did not show ventricular dilatation. On the basis of these data Parker thought that LV dilatation were an adaptive mechanism apt to increase systolic stroke through a better utilization of Starling mechanism (early preload adaptation). Successive studies by echocardiography have not confirmed however a significant LV dilatation while observing an altered biventricular relaxation and a systolic dysfunction of the right ventricle in 41% of the p, isolated or in conjunction with a LV dysfunction [182-185].The apparently better cardiac function in non survivors is currently perceived as a consequence of the persistent septic hemodynamic pattern with decreased SVR causing higher CI and LVEF, both being heavily load-dependent indexes [186]. A LV depressed contractile performance is constant in human and experimental sepsis [187] if related to pre and after-load, it is explained by the global ventricular hypokinesia observed in 60% of the p. in septic shock [188]: the impairment of LV contractility may be unravelled also by the reduction of CI in response to norepinephrine infusion [181]. A feature of septic myocardiopathy is the absence of the increased LV filling pressure, characteristic of cardiogenic shock, due to the dysfunction of the right ventricle [189] and to the slightly increased LV compliance [190]

Currently the hyperkinetic syndrome (small left ventricle, supranormal ejection fraction, tachycardia, high cardiac index) had a 100% mortality rate [186]. In contrast with the majority of other reports Jianhui and colleagues (describe in mice infused with intraperitoneal LPS and studied with left ventricular (LV) pressure-volume catheters significant drop in LV stroke volume with a significant decrease in LVEF with no apparent change in LV afterload. load-dependent indexes of LV function were markedly reduced at 6 h, including EF, stroke work, and dP/dtmax. In contrast, there was no reduction of load-

independent indexes of LV contractility leading the authors to think that the depressed contractility after LPS infusion was due only to loading conditions [191].

6.3. Pathophysiological mechanism

The infusion of small doses of LPS in healthy volunteers may reproduce the features of the septic circulatory dysfunction with low systemic resistances and a depressed myocardial function [187]. The mechanism of the altered myocardial function, at first attributed to a myocardial depressant factor (MDF) [192], began to be understood when in 1985 Parrillo [193] showed that the serum of septic humans during the acute phase may depress the contractile function of isolated myocardiocytes; this effect may be prevented, as subsequently demonstrated by Kumar, by immunoadsorption of IL-1β and TNFα [194]. Ils may cause myocardial depression both directly or through the NO produced by the induction of iNOS [195]. In the recent years the focus of the research has been turned on the upstream mediators of ILs, the TLRs, that have been shown to be main mediators of myocardial damage in sepsis models of both LPS infusion and CLP and in human sepsis [196]. Their effect as already seen is due to the release, consequent to the inflammatory reaction and to the tissue damage, of DAMP further increasing tissue injury. The main TLRs types expressed in the heart are TLR2 (recognizing lipoteichoic acid) and TLR4 (LPS receptor) but also TLR 3 and 9 are present [196]. Both TLR2 and TLR4 have been demonstrated as essential mediators of the septic myocardial damage: in mice with their genetic deficiency there was a better preservation of cardiac function and a decreased mortality[14,197,198]. Also TLR5, receptor for bacterial flagellin, TLR9 (endocellular recognizing bacterial DNA) and very recently TLR3, endocellular receptor recognizing viral double stranded RNA, have been showed to play a deleterious role in mediating cardiac dysfunction in sepsis [199,200]. This depression of myocardial function is linked to the response of myocardiocytes to the release of alarmins with increased production of pro- and anti-inflammatory ILs, of chemokines and cell adhesion molecules [196]. The connection with the reduced contractile function is represented by the increased production of the 2 small calcium regulated molecules (S100A8 and S100A9) that have been showed with coimmunoprecipitation, able to suppress calcium flux interacting with the RAGE receptor [201]. TLRs lead to iNOS stimulation, NF-kB upregulation and to increased expression of TNFα, IL1β, IL6, IFNγ, chemokines and cell adhesion molecules responsible for the cellular damage but also for the initiation of the reparative process [202]. The inflammatory reaction, as already seen, is modulated by the appearance of LPS tolerance and proinflammatory genes silencing. As already said, a long term stimulation with LPS or a TLR4 ligand (such as HMBG1) may induce preconditioning [9] and in decreased brain infarct size in mice that were subjected to focal cerebral ischaemia/reperfusion injury [10].

In sepsis there is an increased production of NO by inflammatory cells infiltrating myocardium but also by endothelial and smooth muscle vascular cells due to stimulation of iNOS. The increased NO production causes an impressive vasodilation, a reduced sensitivity to the vasoconstrictors and an increase in capillary permeability. NO has also a depressive action upon the myocardium mediated by the production of cGMP. In fact NO

behaves as a double-edged sword because if on one hand depresses myocardial contractility increasing cGMP production, reduces oxygen consumption by antagonizing COX and may induce apoptosis on the other hand it supports relaxation normalizing the stiffness of the septic myocardium, antagonizes the action of the increased endothelin and has a cardioprotective effect through the induction of preconditioning [203]: unselective antagonism of NOS with NNMA is harmful in sepsis because even though it raises blood pressure it decreases cardiac, hepatic and renal blood flow [204]. Many other alterations have been described in septic myocardium: an altered phosphorylation of Troponin I (TnI) in serin 23-24 by Protein Kinase A (PKA), activated by β receptors or an upregulation of Protein Phosphatase 2A (PP2A). dephosphorylating TnI [205,206]. The cause of the increased phosphorylation of Tn seems to be the increased β-adrenergic activity during the early phases of sepsis followed by a reduction during the late phase characterized by the hypodynamic cardiac pattern. A calcium leak from sarcoplasmic reticulum has been also described in sepsis similar to that observed in CHF and determined also by PKA activation and increased phosphorylation of the calstabin, a protein maintaining in its stable form the sarcoplasmic ATPase assigned to the re-entry of Calcium in sarcoplasmic reticulum after systole [207,208]. Such an alteration could justify both diastolic dysfunction due to the diastolic calcium leak and the systolic dysfunction showing itself in the late phase as expression of depletion of Calcium reserves. An altered autonomic tone with increased in sympathetic activity in the early phases of sepsis and decreased heart rate variability has been described [209].

Levy and colleagues [141], as already seen, showed in the septic myocardium important alterations (reduced cardiac performances, increased glucose uptake, increased myocardial glucose transmembrane transporters GLUT1 and GLUT4, increased deposits of glycogen). Because these modifications have been described as typical of the myocardial hibernation, Levy proposed that this latter may take part in the septic cardiac dysfunction. It is however debatable that the "true" ischemic myocardial hibernation is responsible for cardiac dysfunction in sepsis for several reasons: 1)myocardial hibernation is no longer considered as a down-regulation of the contractile and metabolic activity aiming at reducing the oxygen consumption and at adapting it to the reduced blood supply (smart heart hypothesis). It is instead attributed to repetitive episodes of myocardial stunning [210] 2) reduced myocardial perfusion has never been demonstrated in sepsis [211], the biochemical modifications showed in septic myocardium are not features of hibernating myocardium, they are instead present in the fetal heart and also in the stressed myocardium as expressions of the reactivation of the fetal gene program [47,52]. The alterations described in septic myocardium would therefore be unspecific and their presence could be explained in sepsis by the inflammatory state that characterizes it. The picture of metabolic hibernation present in sepsis should therefore be separated from that of the true myocardial ischemic hibernation whose existence, in our opinion, has not been convincingly demonstrated in sepsis.

Myocardial injury in sepsis is also shown by the increase of many markers such as troponin (Tn) and natriuretic peptides. Whereas Tn I and TnT levels are good indicators

for cardiac function in sepsis relating well with left ventricular dysfunction and a poor prognosis, BNP is related to the outcome but only weakly with cardiac filling pressures [212]. A high level of BNP >144 pg/ml predicts cardiac dysfunction with high sensitivity (92%) and high specificity (86%)[213]. BNP upregulation takes part in the reactivation of the fetal gene program and its production has been shown to be increased during inflammatory processes related to the ability of inflammatory ILs and of p38MAPK to increase its secretion increasing its promoter activity [214]. Differently from the regulation of the similar molecule ANP, BNP secretion is regulated more by inflammation than by hemodynamic compromise.

7. Metabolic dysfunction in chronic heart failure

The chronically failing heart is certainly energy-deprived [215], as has been ascertained by studies with ^{31}P magnetic resonance (MR) spectroscopy [216] showing the reduced phosphocreatine: ATP ratio, important index of the energetic state of the heart correlated with the indexes of systolic and diastolic function [217]. The cardiac contractile function is inextricably linked to the metabolic function so that the alterations of cardiac metabolism observed in chronic heart failure must affect also the contractile function. As heart failure progresses mithocondrial respiration is gradually compromised preventing that a normal level of FAO may take place. In samples taken from explanted hearts, during transplantation in patients with advanced heart failure, the level of the enzymes of FAO was low compared to the non-failing hearts [218]. The reduction of mitochondrial biogenesis and of FFA oxidation in the advanced phase of CHF is, as already seen, caused by the reactivation of the fetal gene program through the upregulation of HIF-1 and the downregulation of PPARα, β\δ, ERRα, , of SIRT1 and of the PGC-1α network demonstrated in myocardial samples of patients with end-stage heart failure compared with explanted non failing hearts [219]. The expression of these transcription factors and coactivators is reduced in pathological hypertrophy and heart failure whereas it is upregulated in physiological forms of hypertrophy related to postnatal growth or exercise training [220] so furnishing a precise boundary between physiologic and pathologic cardiac growth. Interestingly also a constitutive cardiospecific overexpression of PGC-1α in mice (MHC–PGC-1α mice) may damage the heart leading to myocardiopathy with uncontrolled mitochondrial proliferation but only in the neonatal period, whereas the overexpression in adult mice provoked only modest mitochondrial proliferation [221,222]. PGC-1α -\- mice show a reduced capacity both of exercising and of acclimating to cold temperature [223].

The fetal gene program is mediated by an incompletely known but modified expression of various microRNA [224-226]: Sucharov described that changes in the expression level of miR 100 and 133b contribute to the regulation of the fetal gene program [225]. The reduced expression of SIRT1 underlies the depressed mitochondrial biogenesis and FAO in the chronically failing heart. SIRT1 seems to be expressed at higher levels in the first phases of hypertrophy, the first physiologic response to the overload of the heart, as a

response to the stressing event inducing it but begins to be downregulated when PARP activation takes place, due to the increased oxidative stress [227], reducing NAD^+ availability. The reduction in SIRT1, provided with an antiapoptotic function, and the compromised mitochondrial activity may contribute to the increased cellular death in chronically failing myocardium [228,229]. Overall we may conclude that some similarities exist between the metabolic and morphological alterations observed in sepsis and CHF.

8. Cardiac lipotoxicity in chronic heart failure and sepsis

In 1858 Virchow first reported intramyocyte lipid accumulation in patients with congestive heart failure, he referred to it as "lipid atrophy" of the myocardium [230]. At present the presence in the myocardial cell of neutral lipid droplets is ascribed to the altered glucose and lipid metabolism and to a mismatch between lipid delivery and oxidation. In normal conditions TG are stored only in adipocytes, under the control of PPARγ, with minimal presence of lipids in other tissues [231,232]; in this way adipocytes play indirectly a key role in the control of systemic glucose, lipid homeostasis and insulin sensitivity through the regulation of the serum level of FFA. In congenital lipodystrophy, a disease characterized by a decreased capacity of lipid storage in adipose tissue, the non-adipose organs accumulate TG and there is a premature cardiomyopathy [233]. When an overload of cellular FFA takes place caused by increased lipolysis or increased uptake (evident in clinical settings as in diabetes, in the experimental CD36 and LPL overexpression [234,235] or in settings of reduced FAO), lipid deposits in the myocardium and other organs may occur giving rise to the already seen phenomenon of lipotoxicity [236]. The contractile dysfunction caused by intramyocardial lipid accumulation is mediated at least partly by an altered expression of Sarco/Endoplasmic Reticulum Calcium ATPasi (SERCA2) as showed in specimen taken intraoperatively in patients with aortic stenosis and metabolic syndrome [237]. A diastolic dysfunction is also present, frequently preceding the systolic derangement and associated with interstitial fibrosis. Lipid accumulation is present in the heart of patients with CHF mainly in people with obesity, diabetes and metabolic syndrome. The relationship is bidirectional, insulin resistance predisposes to CHF and CHF increases insulin resistance. A reduced insulin sensitivity is observed in many patients with CHF, moreover its presence represents a risk factor for the eventual development of heart failure. Therefore the lipid accumulation alone without a reduced insulin sensitivity, obesity or metabolic syndrome can cause lipotoxicity. The importance of the cardiac isolated steatosis has been showed in the experimental context by demonstrating that myocardial overexpression of both PPARα and γ is associated with lipid accumulation and contractile dysfunction [238,239] probably because they stimulate more the uptake than the oxidation of FFA; moreover the PPARα activator fenofibrate can prevent the contractile dysfunction and the reduced calcium sensitivity in a rat model of LPS infusion further demonstrating the tight relationships between metabolic and contractile compromise [240]. Lipid deposits in the cardiomyocytes as TG in CHF is only a marker of an imbalance between the uptake and oxidation of FFA and not necessarily relates

to toxic lipid byproducts formation. The chronic accumulation of neutral lipids is probably not, per se, immediately harmful for the myocardial cell in CHF but represents a mechanism of defence against the excess of the FFAs, more metabolically reactive, reaching it [241]. In the long term however lipid store may behaves as a time bomb because when a critical point is reached, either by accumulation of excessive quantity of lipid or by some event triggering an increased FAO, the accumulation of toxic byproducts such as ceramides, diacylglycerol, fatty acyl-CoAs and acyl-carnitine ensues damaging the myocardial cell.

The lipid accumulation in the heart during infections has been described since the '90 of the last century [242] however the only complete study in sepsis is the article by Rossi and colleagues [169]. They showed in septic myocardium an increased staining by the dye oil red O, specific for lipid, and attributed it to an altered metabolism of the myocardium.

These alterations are the morphological expression of the switch from lipid to glucose utilization in a setting in which lipolysis is increased and FAO reduced by PPARα downregulation and by acute mitochondrial dysfunction.

Very little is known about the significance of lipid accumulation in the septic myocardium; initially interpreted as a degenerative marker in infectious diseases it could have in the setting of the acute septic myocardiopathy a meaning considerably different from the chronic lipid accumulation in CHF even though the microscopic aspect is similar.

Certainly a lipidomic approach to the problem may be of great help.

In conclusion notwithstanding similar morphological aspects and the involvement of many common biochemical pathways the cardiac dysfunction in sepsis and in CHF may have different meanings and consequences.

9. Conclusions

In the recent years the strict relationships between myocardial contractility and metabolism have been ascertained and a metabolic basis for cardiac contractile dysfunction verified in many clinical and experimental settings. Several metabolic alterations have been showed in CHF and septic myocardial dysfunction, their relationship with cardiac contractile dysfunction is not completely understood. They are probably a marker of the complex transcriptional and posttranscriptional alterations induced by the inflammatory, mechanical and metabolic stress the heart undergoes in both conditions and particularly of the coordinated compromise of mitochondrial function and of lipid oxidation but they represent also a direct inducer and amplifier of cellular damage. The significance of the morphological and metabolic alterations could be remarkably different in the slowly-evolving setting of CHF and in the acute one of the septic myocardial dysfunction, moreover the malignancy of the noxae underlying similar microscopic aspects may be very dissimilar. To understand in deep this aspect more thorough studies are needed. We currently do not know if they may represent a target for therapy because of the uncertain efficacy of the drugs until now used for this purpose but perhaps the light shed on the pathophysiological mechanism may give us an important help in the search for a future effective treatment.

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10. References

[1] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care. Crit Care Med. 2001;29:1303–1310.
[2] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; SCCM/ESICM/ACCP/ATS/SIS: 2001 SCCM/ESICM/ACCP /ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003 Apr;31(4):1250-6.
[3] Cinel I, Opal SM: Molecular biology of inflammation and sepsis: a primer. Crit Care Med. 2009 Jan;37(1):291-304.
[4] Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton AH, Bricker TL, Jarman SD 2nd, Kreisel D, Krupnick AS, Srivastava A, Swanson PE, Green JM, Hotchkiss RS: Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA. 2011 Dec 21;306(23):2594-605.
[5] Skrupky LP, Kerby PW, Hotchkiss RS: Advances in the management of sepsis and the understanding of key immunologic defects. Anesthesiology. 2011 Dec;115(6):1349-62
[6] Shubin NJ, Monaghan SF, Ayala A: Anti-inflammatory mechanisms of sepsis. Contrib Microbiol. 2011;17:108-24.
[7] Lorne E, Dupont H, Abraham E: Toll-like receptors 2 and 4: initiators of non-septic inflammation in critical care medicine? Intensive Care Med. 2010 Nov;36(11):1826-35.
[8] Skrupky LP, Kerby PW, Hotchkiss RS: Advances in the management of sepsis and the understanding of key immunologic defects. Anesthesiology. 2011 Dec;115(6):1349-62.
[9] van der Poll T, van Zoelen MA, Wiersinga WJ: Regulation of pro-and anti-inflammatory host responses. Contrib Microbiol. 2011;17:125-36.
[10] Biswas SK, Lopez-Collazo E: Endotoxin tolerance: new mechanisms, molecules and clinical significance. Trends Immunol. 2009 Oct;30(10):475-87.
[11] McCall CE, Yoza B, Liu T, El Gazzar M: Gene-specific epigenetic regulation in serious infections with systemic inflammation. J Innate Immun. 2010;2(5):395-405
[12] Alves-Filho JC, Spiller F, Cunha FQ: Neutrophil paralysis in sepsis. Shock. 2010 Sep;34 Suppl 1:15-21.
[13] Vartanian K, Stenzel-Poore M: Toll-like receptor tolerance as a mechanism for neuroprotection. Transl Stroke Res. 2010 Dec 1;1(4):252-260.
[14] Frantz S, Ertl G, Bauersachs J: Mechanisms of disease: Toll-like receptors in cardiovascular disease. Nat Clin Pract Cardiovasc Med. 2007 Aug;4(8):444-54.

* Corresponding Author

[15] Zhao P, Wang J, He L, Ma H, Zhang X, Zhu X, et al: Deficiency in TLR4 signal transduction ameliorates cardiac injury and cardiomyocyte contractile dysfunction during ischemia. J Cell Mol Med 2009;13:1513–25.
[16] Calfee CS, Matthay MA: Clinical immunology: Culprits with evolutionary ties. Nature. 2010 Mar 4;464(7285):41-2.
[17] Könner AC, Brüning JC: Toll-like receptors: linking inflammation to metabolism. Trends Endocrinol Metab. 2011 Jan;22(1):16-23.
[18] Langouche L, Perre SV, Thiessen S, Gunst J, Hermans G, D'Hoore A, Kola B, Korbonits M, Van den Berghe G: Alterations in adipose tissue during critical illness: An adaptive and protective response? Am J Respir Crit Care Med. 2010 Aug.
[19] Siracusano L, Girasole V: Sepsis and Adiponectin. In: Masayoshi Y (Ed): Adiponectin: Production, Regulation and Roles in Disease. Nova Publishers At Press.
[20] van der Poll T: Experimental human sepsis models. Drug Discovery Today: Disease Models, 2012:9;e3-e9.
[21] Weissman C: The metabolic response to stress: an overview and update. Anesthesiology. 1990 Aug;73(2):308-27.
[22] Biolo G, Toigo G, Ciocchi B, Situlin R, Iscra F, Gullo A, Guarnieri G: Metabolic response to injury and sepsis: changes in protein metabolism. Nutrition. 1997 Sep;13(9 Suppl):52S-57S.
[23] Tappy L, Chioléro R: Substrate utilization in sepsis and multiple organ failure. Crit Care Med 2007; 35[Suppl.]:S531–S534.
[24] Li L, Messina JL: Acute insulin resistance following injury. Trends Endocrinol Metab. 2009 Nov;20(9):429-35.
[25] Mittra S, Bansal VS, Bhatnagar PK: From a glucocentric to a lipocentric approach towards metabolic syndrome. Drug Discov Today. 2008 Mar;13(5-6):211-8.
[26] Unger RH, Clark GO, Scherer PE, Orci L: Lipid homeostasis, lipotoxicity and the metabolic syndrome. Biochim Biophys Acta. 2010 Mar;1801(3):209-14.
[27] Duska F, Andel M: Intensive blood glucose control in acute and prolonged critical illness: endogenous secretion contributes more to plasma insulin than exogenous insulin infusion. Metabolism. 2008 May;57(5):669-71.
[28] Van den Berghe G: How does blood glucose control with insulin save lives in intensive care? J Clin Invest 2004; 114:1187–1195.
[29] Crouser ED: Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. Mitochondrion. 2004 ; 4:729-41.
[30] Karpac J, Jasper H: Insulin and JNK: optimizing metabolic homeostasis and lifespan. Trends Endocrinol Metab. 2009 Apr;20(3):100-6.
[31] Drosatos K, Drosatos-Tampakaki Z, Khan R, Homma S, Schulze PC, Zannis VI, Goldberg IJ: Inhibition of c-Jun-N-terminal kinase increases cardiac peroxisome proliferator-activated receptor alpha expression and fatty acid oxidation and prevents lipopolysaccharide-induced heart dysfunction. J Biol Chem. 2011 Oct 21;286(42):36331-9.
[32] van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in critically ill patients. N Engl J Med. 2001 Nov 8;345(19):1359-67.

[33] NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ: Intensive versus conventional glucose control in critically ill patients.
[34] N Engl J Med. 2009 Mar 26;360(13):1283-97.
[35] Egi M, Finfer S, Bellomo R: Glycemic control in the ICU. Chest. 2011 Jul;140(1):212-20.
[36] Dyson A, Stidwill R, Taylor V, Singer M: Tissue oxygen monitoring in rodent models of shock. Am J Physiol Heart Circ Physiol. 2007 Jul;293(1):H526-33.
[37] Levy B: Lactate and shock state: the metabolic view. Curr Opin Crit Care. 2006 ;12:315-21.
[38] Holness MJ, Sugden MC: Regulation of pyruvate dehydrogenase complex activity by reversible phosphorylation. Biochem Soc Trans. 2003 ;31 :1143-51.
[39] Alamdari N, Constantin-Teodosiu D, Murton AJ, Gardiner SM, Bennett T, Layfield R, Greenhaff PL: Temporal changes in the involvement of pyruvate dehydrogenase complex in muscle lactate accumulation during lipopolysaccharide infusion in rats. J Physiol. 2008 15;586:1767-75.
[40] Siracusano L, Girasole V: Glucose and lipid metabolism in sepsis and endotoxemia. Acta Anaesthesiol Scand. 2009 Mar;53(3):413-14.
[41] Stanley WC, Recchia F, Lopaschuk GD: Myocardial Substrate Metabolism in the Normal and Failing Heart. Physiol Rev 2005; 85:1093–1129.
[42] Davies BS, Beigneux AP, Fong LG, Young SG: New wrinkles in lipoprotein lipase biology. Curr Opin Lipidol. 2012 Feb;23(1):35-42.
[43] Koonen, D.P., Glatz, J.F., Bonen, A., Luiken, J: Long-chain fatty acid uptake and FAT/CD36 translocation in heart and skeletal muscle. Biochim. Biophys. Acta, Mol. Cell Biol. Lipids2005: 1736;163–180.
[44] Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC: Myocardial fatty acid metabolism in health and disease. Physiol Rev. 2010 Jan;90(1):207-58.
[45] Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose-fatty acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963; 1:785–789.
[46] Hue L, Taegtmeyer H. The Randle cycle revisited: a new head for an old hat. Am J Physiol Endocrinol Metab. 2009;297:E578–E591.
[47] Shuldiner AR, McLenithan JC: Genes and pathophysiology of type 2 diabetes: more than just the Randle cycle all over again. J Clin Invest 2004;114: 1414–1417.
[48] Watson RT, Pessin JE: Bridging the GAP between insulin signaling and GLUT4 translocation. Trends Biochem Sci. 2006 Apr;31(4):215-22.
[49] Rajabi M, Kassiotis EC, Razeghi P, Taegtmeyer H: Return to the fetal gene program protects the stressed heart: a strong hypothesis. Heart Fail Rev 2007; 12:331–343.
[50] van de Weijer T, Schrauwen-Hinderling VB, Schrauwen P: Lipotoxicity in type 2 diabetic cardiomyopathy. Cardiovasc Res. 2011 Oct 1;92(1):10-8.
[51] Taegtmeyer H, Wilson CR, Razeghi P, Sharma S: Metabolic energetics and genetics in the heart. Ann NY Acad Sci 2005; 1047:208-18.

[52] Sheperd PR, Kahn BB: Glucose transporters and insulin action. Implications for Insulin Resistance and Diabetes Mellitus. N Engl J Med 2003; 341:248–257.
[53] Friehs I, Moran AM, Stamm C, Colan SD, Takeuchi K, Cao-Danh H, Rader CM, McGowan FX, del Nido PJ: Impaired glucose transporter activity in pressure-overload hypertrophy is an early indicator of progression to failure.
[54] Circulation 1999; 100:II187–II193.
[55] Taegtmeyer H, Sen S, Vela D: Return to the fetal gene program: a suggested metabolic link to gene expression in the heart. Ann N Y Acad Sci. 2010 Feb; 1188:191-8.
[56] van Uden P, Kenneth NS, Rocha S: Regulation of hypoxia-inducible factor-1alpha by NF-kappaB. Biochem J. 2008 Jun 15;412(3):477-84.
[57] Kuhlicke J, Frick JS, Morote-Garcia JC, Rosenberger P, Eltzschig HK: Hypoxia inducible factor (HIF)-1 coordinates induction of Toll-like receptors TLR2 and TLR6 during hypoxia. PLoS One. 2007 Dec 26;2(12):e1364.
[58] Semenza GL. Regulation of oxygen homeostasis by hypoxia-inducible factor 1. Physiology (Bethesda) 2009;24:97–106.
[59] Narravula S, Colgan SP: Hypoxia-inducible factor 1-mediated inhibition of peroxisome proliferator-activated receptor alpha expression during hypoxia. J Immunol. 2001 Jun 15;166(12):7543-8.
[60] Krishnan J, Suter M, Windak R, Krebs T, Felley A, Montessuit C, Tokarska-Schlattner M, Aasum E, Bogdanova A, Perriard E, Perriard JC, Larsen T, Pedrazzini T, Krek W: Activation of a HIF1alpha-PPARgamma axis underlies the integration of glycolytic and lipid anabolic pathways in pathologic cardiac hypertrophy. Cell Metab. 2009 Jun;9(6):512-24.
[61] Cadenas S, Aragonés J, Landázuri MO: Mitochondrial reprogramming through cardiac oxygen sensors in ischaemic heart disease. Cardiovasc Res. 2010 Nov 1;88(2):219-28.
[62] Kominsky DJ, Campbell EL, Colgan SP: Metabolic shifts in immunity and inflammation. J Immunol. 2010 Apr 15;184(8):4062-8.
[63] Haigis MC, Sinclair DA: Mammalian sirtuins: biological insights and disease relevance. Annu Rev Pathol. 2010;5:253-95.
[64] Rahman S, Islam R: Mammalian Sirt1: insights on its biological functions. Cell Commun Signal. 2011 May 8;9:11.
[65] Cantó C, Auwerx J: Targeting sirtuin 1 to improve metabolism: all you need is NAD(+)? Pharmacol Rev. 2012 Jan;64(1):166-87.
[66] Cantó C, Auwerx J: PGC-1alpha, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. Curr Opin Lipidol. 2009 Apr;20(2):98-105.
[67] Borradaile NM, Pickering JG: NAD(+), sirtuins, and cardiovascular disease. Curr Pharm Des. 2009;15(1):110-7.
[68] Menzies KJ, Hood DA: The role of SirT1 in muscle mitochondrial turnover. Mitochondrion. 2012 Jan;12(1):5-13.
[69] Rane S, He M, Sayed D, Vashistha H, Malhotra A, Sadoshima J, Vatner DE, Vatner SF, Abdellatif M: Downregulation of miR-199a derepresses hypoxia-inducible factor-1alpha and Sirtuin 1 and recapitulates hypoxia preconditioning in cardiac myocytes. Circ Res. 2009 Apr 10;104(7):879-86.

[70] Lee J, Kemper JK: Controlling SIRT1 expression by microRNAs in health and metabolic disease. Aging (Albany NY). 2010 Aug;2(8):527-34.
[71] Tabuchi T, Satoh M, Itoh T, Nakamura M: MicroRNA-34a regulates the longevity-associated protein SIRT1 in coronary artery disease: effect of statins on SIRT1 and microRNA-34a expression. Clin Sci (Lond). 2012 Aug 1;123(3):161-71.
[72] Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. Physiol Rev. 2010 Jan;90(1):207-58.
[73] Desvergne B, Michalik L, Wahli W: Transcriptional regulation of metabolism. Physiol Rev 86: 465–514, 2006.
[74] Huss JM, Kelly DP: Nuclear receptor signaling and cardiac energetics. Circ Res 95: 568–578, 2004.
[75] Schupp M, Lazar MA: Endogenous ligands for nuclear receptors: digging deeper. J Biol Chem. 2010 Dec 24; 285(52):40409-15.
[76] Grimaldi PA: Metabolic and nonmetabolic regulatory functions of peroxisome proliferator-activated receptor beta. Curr Opin Lipidol. 2010 Jun;21(3):186-91.
[77] Finck BN, Kelly DP. Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) regulatory cascade in cardiac physiology and disease. Circulation 2007;115:2540–2548.
[78] Huang W, Glass CK: Nuclear receptors and inflammation control: molecular mechanisms and pathophysiological relevance. Arterioscler Thromb Vasc Biol. 2010 Aug;30(8):1542-9.
[79] Glass CK, Ogawa S: Combinatorial roles of nuclear receptors in inflammation and immunity. Nature Rev. Immunol. 2006;6,44–55.
[80] Bensinger SJ, Tontonoz P: Integration of metabolism and inflammation by lipid-activated nuclear receptors. Nature. 2008 Jul 24;454(7203):470-7.
[81] von Knethen A, Soller M, Brüne B: Peroxisome proliferator-activated receptor gamma (PPAR gamma) and sepsis. Arch Immunol Ther Exp 2007; 55:19-25.
[82] Eichner LJ, Giguère V: Estrogen related receptors (ERRs): a new dawn in transcriptional control of mitochondrial gene networks. Mitochondrion. 2011 Jul;11(4):544-52.
[83] Arner P: Human fat cell lipolysis: biochemistry, regulation and clinical role. Best Pract Res Clin Endocrinol Metab. 2005;19:471-82.
[84] Lass A, Zimmermann R, Oberer M, Zechner R: Lipolysis - a highly regulated multi-enzyme complex mediates the catabolism of cellular fat stores. Prog Lipid Res. 2011 Jan;50(1):14-27.
[85] Ahmadian M, Wang Y, SulHS: Lipolysis in adipocytes. Int J Biochem Cell Biol. 2010 May;42(5):555-9.
[86] Lafontan M, Langin D: Lipolysis and lipid mobilization in human adipose tissue. Prog Lipid Res. 2009;48:275-97.
[87] Haemmerle G, Lass A, Zimmermann R, Gorkiewicz G, Meyer C, Rozman J, Heldmaier G, Maier R, Theussl C, Eder S, Kratky D, Wagner EF, Klingenspor M, Hoefler G, Zechner R: Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. Science. 2006 May 5;312(5774):734-7.

[88] Lampidonis AD, Rogdakis E, Voutsinas GE, Stravopodis DJ: The resurgence of Hormone-Sensitive Lipase (HSL) in mammalian lipolysis. Gene. 2011 May 15;477(1-2):1-11.
[89] Shen WJ, Yu Z, Patel S, Jue D, Liu LF, Kraemer FB: Hormone-sensitive lipase modulates adipose metabolism through PPARγ. Biochim Biophys Acta. 2011 Jan;1811(1):9-16.
[90] Chen X, Xun K, Chen L, Wang Y. TNF-alpha, a potent lipid metabolism regulator. Cell Biochem. Funct. 2009;27:407–416.
[91] Cawthorn WP, Sethi JK: TNF-alpha and adipocyte biology. FEBS Lett. 2008 Jan 9;582(1):117-31.
[92] Zhang T, He J, Xu C, Zu L, Jiang H, Pu S, Guo X, Xu G: Mechanisms of metformin inhibiting lipolytic response to isoproterenol in primary rat adipocytes. J Mol Endocrinol. 2009 Jan;42(1):57-66.
[93] Zu L, He J, Jiang H, Xu C, Pu S, Xu G: Bacterial endotoxin stimulates adipose lipolysis via toll-like receptor 4 and extracellular signal-regulated kinase pathway. J Biol Chem. 2009 Feb 27;284(9):5915-26.
[94] Choi SM, Tucker DF, Gross DN, Easton RM, DiPilato LM, Dean AS, Monks BR, Birnbaum MJ: Insulin regulates adipocyte lipolysis via an Akt-independent signaling pathway. Mol Cell Biol. 2010 Nov;30(21):5009-20.
[95] Qiao L, Kinney B, Schaack J, Shao J: Adiponectin inhibits lipolysis in mouse adipocytes. Diabetes. 2011 May;60(5):1519-27.
[96] W. Khovidhunkit, R.A. Memon, K.R. Feingold, C. Grunfeld, Infection and inflammation-induced proatherogenic changes of lipoproteins, J. Infect.Dis. 181 (2000) 462–472.80
[97] Davidsson P, Hulthe J, Fagerberg B, Camejo G. Proteomics of apolipoproteins and associated proteins from plasma high-density lipoproteins. Arterioscler Thromb Vasc Biol 2010;30:156–63.
[98] Gordon,S.M. et al.:Proteomic characterization of human plasma high density lipoprotein fractionated by gel filtration chromatography. 2010:J. Proteome.Res. 9, 5239–5249 68.
[99] Gordon S, Deng J, Lu LJ, Davidson WS: High-density lipoprotein proteomics: Identifying new drug targets and biomarkers by understanding functionality. Curr. Cardio.RiskRep. 2010:4, 1–8.
[100] Murphy,A.J. et al. High-density lipoprotein reduces the human monocyte inflammatory response. Arterioscler. Thromb. Vasc. Biol. 2008;28, 2071–2077.
[101] Gordon SM, Hofmann S, Askew DS, Davidson WS: High density lipoprotein: it's not just about lipid transport anymore. Trends Endocrinol Metab. 2011;22:9-15.
[102] Säemann MD, Poglitsch M, Kopecky C, Haidinger M, Hörl WH, Weichhart T:The versatility of HDL: a crucial anti-inflammatory regulator. Eur J Clin Invest. 2010 ;40(12):1131-43.
[103] Galbois A, Thabut D, Tazi KA, Rudler M, Mohammadi MS, Bonnefont- Rousselot D et al: Ex vivo effects of high-density lipoprotein exposure on the lipopolysaccharide-induced inflammatory response in patients with severe cirrhosis. Hepatology 2009;49:175–84.

[104] Hima Bindu G, Rao VS, Kakkar VV: Friend Turns Foe: Transformation of Anti-Inflammatory HDL to Proinflammatory HDL during Acute-Phase Response. Cholesterol, vol. 2011, no. 19, Article ID 274629, 6 pages, 2011.

[105] Esteve E, Ricart W, Fernández-Real JM: Dyslipidemia and inflammation: an evolutionary conserved mechanism. Clin Nutr. 2005 Feb;24(1):16-31.

[106] Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C: Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res 45 : 1169 –1196,2004.

[107] Zhu X, Lee JY, Timmins JM, Brown JM, Boudyguina E, Mulya A et al: Increased cellular free cholesterol in macrophage-specific Abca1 knock-out mice enhances pro-inflammatory response of macrophages. J Biol Chem 2008;283:22930–41.

[108] Murch O, Collin M, Hinds CJ, Thiemermann C: Lipoproteins in inflammation and sepsis. I. Basic science. Intensive Care Med. 2007;33:13-24.

[109] Wendel M, Paul R, Heller AR: Lipoproteins in inflammation and sepsis. II. Clinical aspects. Intensive Care Med. 2007 Jan;33(1):25-35.

[110] Mineo C, Shaul PW: HDL stimulation of endothelial nitric oxide synthase: a novel mechanism of HDL action. Trends Cardiovasc Med. 2003 Aug;13(6):226-31.

[111] Theilmeier,G. et al. (2006) High-density lipoproteins and their constituent, sphingosine-1-phosphate, directly protect the heart against ischemia/reperfusion injury in vivo via the S1P3 lysophospholipid receptor. Circulation 114,1403–1409.

[112] Frias MA., Lang U, Gerber-Wicht C, James RW: Native and reconstituted HDL protect cardiomyocytes from doxorubicin-induced apoptosis. Cardiovasc. Res. (2010):85, 118–126 51.

[113] Frias MA, Lang U, Gerber-Wicht C, James RW: Emerging high-density lipoprotein infusion therapies: fulfilling the promise of epidemiology? J Clin Lipidol. 2010 Sep-Oct;4(5):399-404.

[114] Chien JY, Jerng JS, Yu CJ, Yang PC: Low serum level of high-density lipoprotein is a poor prognostic factor for severe sepsis. 2005 Crit Care Med 33:1688–1693.

[115] Feingold KR, Grunfeld C: The acute phase response inhibits reverse cholesterol transport. J Lipid Res. 2010 Apr;51(4):682-4. Epub 2010 Jan 13.

[116] Baranova I, Vishnyakova T, Bocharov A, Chen Z, Remaley AT, Stonik J, Eggerman TL, Patterson AP: Lipopolysaccharide down regulates both scavenger receptor B1 and ATP binding cassette transporter A1 in RAW cells. Infect Immun. 2002 Jun;70(6):2995-3003.

[117] Ziouzenkova O, Perrey S, Asatryan L, Hwang J, MacNaul KL, Moller DE, Rader DJ, Sevanian A, Zechner R, Hoefler G, Plutzky J: Lipolysis of triglyceride-rich lipoproteins generates PPAR ligands: evidence for an antiinflammatory role for lipoprotein lipase. Proc Natl Acad Sci U S A. 2003 Mar 4;100(5):2730-5

[118] Feingold K, Kim MS, Shigenaga J, Moser A, Grunfeld C: Altered expression of nuclear hormone receptors and coactivators in mouse heart during the acute-phase response. Am J Physiol Endocrinol Metab. 2004;286(2):E201-7.

[119] Feingold KR, Wang Y, Moser A, Shigenaga JK, Grunfeld C: LPS decreases fatty acid oxidation and nuclear hormone receptors in the kidney. J Lipid Res.2008; 49:2179-87.

[120] Feingold KR, Moser A, Patzek SM, Shigenaga JK, Grunfeld C: Infection decreases fatty acid oxidation and nuclear hormone receptors in the diaphragm. J Lipid Res. 2009;50:2055-63.

[121] Maitra U, Chang S, Singh N, Li L: Molecular mechanism underlying the suppression of lipid oxidation during endotoxemia. Mol Immunol. 2009;47:420-5.

[122] Halestrap AP: What is the mitochondrial permeability transition pore? J Mol Cell Cardiol. 2009 Jun;46(6):821-31.

[123] Andrews DT, Royse C, Royse AG: The mitochondrial permeability transition pore and its role in anaesthesia-triggered cellular protection during ischaemia-reperfusion injury. Anaesth Intensive Care. 2012 Jan;40(1):46-70.

[124] Larche J, Lancel S, Hassoun SM, Favory R, Decoster B, Marchetti P, Chopin C, Neviere R: Inhibition of mitochondrial permeability transition prevents sepsis-induced myocardial dysfunction and mortality. J Am Coll Cardiol. 2006 Jul 18;48(2):377-85.

[125] Lee J, Giordano S, Zhang J: Autophagy, mitochondria and oxidative stress: cross-talk and redox signalling. Biochem J. 2012 Jan 15;441(2):523-40.

[126] Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, Englert JA, Rabinovitch M, Cernadas M, Kim HP, Fitzgerald KA, Ryter SW, Choi AM: Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol. 2011 Mar;12(3):222-30.

[127] Ventura-Clapier R, Garnier A, Veksler V: Transcriptional control of mitochondrial biogenesis: the central role of PGC-1alpha. Cardiovasc Res. 2008 Jul 15;79(2):208-17.

[128] Scarpulla RC: Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. Biochim Biophys Acta. 2011 Jul;1813(7):1269-78.

[129] Scarpulla RC: Transcriptional paradigms in mammalian mitochondrial biogenesis and function. Physiol Rev. 2008 Apr;88(2):611-38.

[130] Vats D, Mukundan L, Odegaard JI, Zhang L, Smith KL, Morel CR, et al. Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. Cell Metab: 2006;4:13–24.

[131] Lin J, Wu P-H, Tarr PT, Lindenberg KS, St-Pierre J,Zhang C-Y, Mootha VK, Jãger S, Vianna, CR, Reznick, R.M., et al. 2004. Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1 null mice. Cell119: 121–135.

[132] Leone, T.C., Lehman, J.J., Finck, B.N., Schaeffer, P.J., Wende, A.R., Boudina, S., Courtois, M., Wozniak, D.F., Sambandam, N., Bernal-Mizrachi, C., et al. PGC-1 deficient mice exhibit multi-system energy metabolic derangements: Muscle dysfunction, abnormal weight control, and hepatic steatosis. PLoS Biol. 2005 3: 672–687.

[133] Lai L, Leone TC, Zechner C, Schaeffer PJ, Kelly SM, Flanagan DP, Medeiros DM, Kovacs A, Kelly DP: Transcriptional coactivators PGC-1alpha and PGC-lbeta control overlapping programs required for perinatal maturation of the heart. Genes Dev. 2008 Jul 15;22(14):1948-61.

[134] Rimbaud S, Garnier A, Ventura-Clapier R. Mitochondrial biogenesis in cardiac pathophysiology. Pharmacol Rep. 2009;61:131-138.

[135] Lee IH, Cao L, Mostoslavsky R, Lombard DB, Liu J, Bruns NE, Tsokos M, Alt FW, Finkel T: A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. Proc. Natl Acad. Sci. USA 105, 3374–3379 (2008).
[136] Schumer W, Das Gupta TK, Moss GS, Nyhus LM: Effect of endotoxemia on liver cell mitochondria in man. Ann Surg. 1970 ; 171:875-82.
[137] Mela L, Bacalzo LV Jr, Miller LD: Defective oxidative metabolism of rat liver mitochondria in hemorrhagic and endotoxin shock. Am J Physiol. 1971; 220:571-7.
[138] Exline MC, Crouser ED: Mitochondrial mechanisms of sepsis-induced organ failure. Mitochondria in Sepsis. Front Biosci. 2008 ;13:5030-41.
[139] Singer M: Mitochondrial function in sepsis: Acute phase versus multiple organ failure. Crit Care Med 2007; 35[Suppl.]:S441–S448.
[140] Smeding L, Plötz FB, Groeneveld AB, Kneyber MC: Structural changes of the heart during severe sepsis or septic shock. Shock. 2012 May;37(5):449-56.
[141] Suliman HB, Welty-Wolf KE, Carraway M, Tatro L, Piantadosi CA: Lipopolysaccharide induces oxidative cardiac mitochondrial damage and biogenesis. Cardiovasc Res 64:279Y288, 2004.
[142] Levy RJ, Piel DA, Acton PD, Zhou R, Ferrari VA, Karp JS, Deutschman CS: Evidence of myocardial hibernation in the septic heart. Crit Care Med 33:2752Y2756, 2005.
[143] Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M: Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002 Jul 20;360(9328):219-23.
[144] Carré JE, Orban JC, Re L, Felsmann K, Iffert W, Bauer M, Suliman HB, Piantadosi CA, Mayhew TM, Breen P, Stotz M, Singer M: Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am J Respir Crit Care Med. 2010 Sep 15;182(6):745-51.
[145] Singer M, De Santis V, Vitale D, Jeffcoate W: Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet 2004; 364:545-8.
[146] Levy RJ: Mitochondrial dysfunction, bioenergetic impairment and metabolic down-regulation in sepsis. Shock 2007; 28:24-28.
[147] Azevedo LC: Mitochondrial dysfunction during sepsis. Endocr Metab Immune Disord Drug Targets. 2010 Sep;10(3):214-23.
[148] Dyson A, Stidwill R, Taylor V, Singer M: Tissue oxygen monitoring in rodent models of shock. Am J Physiol Heart Circ Physiol. 2007 Jul;293(1):H526-33.
[149] Fink MP: Bench-to-bedside review: Cytopathic hypoxia. Critical Care 2002;6:491–499.
[150] Kato K, Giulivi C: Critical overview of mitochondrial nitric-oxide synthase. Front Biosci. 2006 ; 11:2725-38.
[151] Valdez LB, Boveris A: Mitochondrial nitric oxide synthase, a voltage-dependent enzyme, is responsible for nitric oxide diffusion to cytosol. Front Biosci 2007; 12:1210-9.
[152] Bateman RM, Sharpe MD, Goldman D, Lidington D, Ellis CG: Inhibiting nitric oxide overproduction during hypotensive sepsis increases local oxygen consumption in rat skeletal muscle. Crit Care Med 2008; 36:225-23.
[153] Brown GC: Nitric oxide and mitochondria. Front Biosci. 2007; 12:1024-33.

[154] Pun PB, Lu J, Kan EM, Moochhala S: Gases in the mitochondria. Mitochondrion: 2010 Mar;10(2):83-93.
[155] Cooper CE, Brown GC: The inhibition of mitochondrial cytochrome oxidase by the gases carbon monoxide, nitric oxide, hydrogen cyanide and hydrogen sulfide: chemical mechanism and physiological significance. J Bioenerg Biomembr. 2008 Oct;40(5):533-9.
[156] Blackstone E, Morrison M, Roth MB: H2S induces a suspended animation-like state in mice. Science 2005 Apr 22;308(5721):518.
[157] Nystul TG, Roth MB: Carbon monoxide-induced suspended animation protects against hypoxic damage in Caenorhabditis elegans. Proc Natl Acad Sci U S A. 2004 Jun 15;101(24):9133-6.
[158] Aslami H, Juffermans NP: Induction of a hypometabolic state during critical illness - a new concept in the ICU? Neth J Med. 2010 May;68(5):190-8.
[159] Baumgart K, Radermacher P, Wagner F: Applying gases for microcirculatory and cellular oxygenation in sepsis: effects of nitric oxide, carbon monoxide, and hydrogen sulfide. Curr Opin Anaesthesiol. 2009 Apr;22(2):168-76.
[160] Zegdi R, Perrin D, Burdin M, Boiteau R, Tenaillon A. Increased endogenous carbon monoxide production in severe sepsis. Intensive Care Med. 2002;28:793–796.
[161] Hoetzel A, Dolinay T, Schmidt R, Choi AM, Ryter SW: Carbon monoxide in sepsis. Antioxid Redox Signal. 2007 Nov;9(11):2013-26
[162] Hui Y, Du J, Tang C, Bin G, Jiang H: Changes in arterial hydrogen sulfide (H2S) content during septic shock and endotoxin shock in rats. J Infect. 2003 Aug;47(2):155-60.
[163] Schilling J, Lai L, Sambandam N, Dey CE, Leone TC, Kelly DP. Toll-like receptor-mediated inflammatory signaling reprograms cardiac energy metabolism by repressing peroxisome proliferator-activated receptor coactivator- 1 signaling. Circ Heart Fail. 2011;4:474–482.
[164] Smeding : Salutary effect of resveratrol on sepsis-induced myocardial depression. Crit Care Med. 2012
[165] Schrauwen P, Schrauwen-Hinderling V, Hoeks J, Hesselink MK. Mitochondrial dysfunction and lipotoxicity. Biochim Biophys Acta. 2010;1801:266–271.
[166] Zhang Z, Lowry SF, Guarente L, Haimovich B: Roles of SIRT1 in the acute and restorative phases following induction of inflammation. J Biol Chem. 2010 Dec 31;285(53):41391-401.
[167] Menconi MJ, Arany ZP, Alamdari N, Aversa Z, Gonnella P, O'Neal P, Smith IJ, Tizio S, Hasselgren PO: Sepsis and glucocorticoids downregulate the expression of the nuclear cofactor PGC-1beta in skeletal muscle. Am J Physiol Endocrinol Metab. 2010 Oct;299(4):E533-43.
[168] Soriano FG, Nogueira AC, Caldini EG, Lins MH, Teixeira AC, Cappi SB, Lotufo PA, Bernik MM, Zsengellér Z, Chen M, Szabó C: Potential role of poly(adenosine 5'-diphosphate-ribose) polymerase activation in the pathogenesis of myocardial contractile dysfunction associated with human septic shock. Crit Care Med. 2006 Apr;34(4):1073-9.

[169] Pacher P, Szabó C: Role of poly(ADP-ribose) polymerase 1 (PARP-1) in cardiovascular diseases: the therapeutic potential of PARP inhibitors. Cardiovasc Drug Rev. 2007 Fall;25(3):235-60.

[170] Melvin RG, Andrews MT: Torpor induction in mammals: recent discoveries fueling new ideas. Trends Endocrinol Metab. 2009 Dec;20(10):490-8.

[171] Liu TF, Brown CM, El Gazzar M, McPhail L, Millet P, Rao A, Vachharajani VT, Yoza BK, McCall CE: Fueling the flame: bioenergy couples metabolism and inflammation. J Leukoc Biol. 2012 May 9. [Epub ahead of print].

[172] Liu TF, Yoza BK, El Gazzar M, Vachharajani VT, McCall CE: NAD+-dependent SIRT1 deacetylase participates in epigenetic reprogramming during endotoxin tolerance. J Biol Chem. 2011 Mar 18;286(11):9856-64.

[173] Dare AJ, Phillips AR, Hickey AJ, Mittal A, Loveday B, Thompson N, Windsor JA: A systematic review of experimental treatments for mitochondrial dysfunction in sepsis and multiple organ dysfunction syndrome. Free Radic Biol Med. 2009 Dec 1;47(11):1517-25.

[174] Ruggieri AJ, Levy RJ, Deutschman CS: Mitochondrial dysfunction and resuscitation in sepsis. Crit Care Clin. 2010 Jul;26(3):567-75, x-xi.

[175] Protti A, Singer M: Bench-to-bedside review: potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure. Crit Care. 2006;10(5):228.

[176] Kozlov AV, Bahrami S, Calzia E, Dungel P, Gille L, Kuznetsov AV, Troppmair J: Mitochondrial dysfunction and biogenesis: do ICU patients die from mitochondrial failure? Ann Intensive Care. 2011 Sep 26;1(1):41.

[177] Lancel S, Joulin O, Favory R, Goossens JF, Kluza J, Chopin C, Formstecher P, Marchetti P, Neviere R: Ventricular myocyte caspases are directly responsible for endotoxin-induced cardiac dysfunction. Circulation. 2005 May 24;111(20):2596-604.

[178] Buerke U, Carter JM, Schlitt A, Russ M, Schmidt H, Sibelius U, Grandel U, Grimminger F, Seeger W, Mueller-Werdan U, Werdan K, Buerke M: Apoptosis contributes to septic cardiomyopathy and is improved by simvastatin therapy. Shock. 2008 Apr;29(4):497-503.

[179] Balija TM, Lowry SF: Lipopolysaccharide and sepsis-associated myocardial dysfunction. Curr Opin Infect Dis. 2011 Jun;24(3):248-53.

[180] Rossi MA, Celes MR, Prado CM: Myocardial structural changes in long term human severe sepsis\septic shock may be responsible for cardiac dysfunction. Shock 2007; 27:10-18.

[181] Celes MR, Torres-Duenas D, Prado CM, et al. Increased sarcolemmal permeability as an early event in experimental septic cardiomyopathy: a potential role for oxidative damage to lipids and proteins. Shock 2010; 33:322–331.

[182] Celes MR, Torres-Duenas D, Malvestio LM, et al. Disruption of sarcolemmal dystrophin and beta-dystroglycan may be a potential mechanism for myocardial dysfunction in severe sepsis. Lab Invest 2010; 90:531–542.

[183] Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, et al: Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984;/100:/483 90.

[184] G Redl , P Germann , H Plattner e Al: Right ventricular function in early septic shock states. Intensive Care Med 1993;19:3–7.

[185] Bouhemad B, Nicolas-Robin A, Arbelot C, Arthaud M, Féger F, Rouby JJ: Acute left ventricular dilatation and shock-induced myocardial dysfunction. Crit Care Med 2009, 37: 441-447.

[186] J Poelaert, C Declerck, D Vogelaers e Al: Left ventricular systolic and diastolic function in septic shock. Intensive Care Med 1997;23:553–60.

[187] Vieillard Baron A, Schmitt JM, Beauchet A et Al: Early preload adaptation in septic shock? A transesophageal echocardiographic study. Anesthesiology 2001;94:400–6.

[188] Vieillard-Baron A: Septic cardiomyopathy. Ann Intensive Care. 2011 Apr 13;1(1):6.

[189] Suffredini A, Fromm RE, Parker MM, Brenner M, Kovacs JA, Wesley RA,Parrillo JE: The cardiovascular response of normal humans to the administration of endotoxin. N Engl J Med 1989, 321: 280-287.

[190] Vieillard-Baron A, Caille V, Charron C, et al. Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 2008; 36:1701–1706.

[191] Vincent JL, Reuse C, Frank N, Contempré B, Kahn RJ: Right ventricular dysfunction in septic shock: assessment by measurements of right ventricular ejection fraction using thermodilution technique. Acta Anaesthesiol Scand 1989, 33: 34-38.

[192] Etchecopar-Chevreuil C, François B, Clavel M, Pichon N, Gastinne H, Vignon P: Cardiac morphological and functional changes during early septic shock: a transesophageal echocardiographic study. Intensive Care Med 2008, 34: 250-256.

[193] Jianhui L, Rosenblatt-Velin N, Loukili N, Pacher P, Feihl F, Waeber B, Liaudet L: Endotoxin impairs cardiac hemodynamics by affecting loading conditions but not by reducing cardiac inotropism. Am J Physiol Heart Circ Physiol. 2010 Aug;299(2):H492-501.192)Wiggers CJ. Myocardial depression in shock: a survey of cardiodynamic studies. Am Heart J. 1947;33:633– 650.

[194] Parrillo JE, Burch C, Shelhamer JH, Parker MM, Natanson C, Schuette W: A circulating myocardial depressant substance in humans with septic shock. Septic shock patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. J Clin Invest. 1985 Oct;76(4):1539-53.

[195] Kumar A, Thota V, Dee L, Olson J, Uretz E, Parrillo JE: Tumor necrosis factor alpha and interleukin 1beta are responsible for in vitro myocardial cell depression induced by human septic shock serum. J Exp Med 183(3):949Y958, 1996.

[196] Flynn A, Chokkalingam Mani B, Mather PJ: Sepsis-induced cardiomyopathy: a review of pathophysiologic mechanisms. Heart Fail Rev. 2010 Nov;15(6):605-11.

[197] Marchant DJ, Boyd JH, Lin DC, Granville DJ, Garmaroudi FS, McManus BM: Inflammation in myocardial diseases. Circ Res. 2012 Jan 6;110(1):126-44.

[198] Fallach R, Shainberg A, Avlas O, Fainblut M, Chepurko Y, Porat E, Hochhauser E: Cardiomyocyte Toll-like receptor 4 is involved in heart dysfunction following septic shock or myocardial ischemia. J Mol Cell Cardiol. 2010 Jun;48(6):1236-44.

[199] Zou L, Feng Y, Chen YJ, Si R, Shen S, Zhou Q, Ichinose F, Scherrer-Crosbie M, Chao W: Toll-like receptor 2 plays a critical role in cardiac dysfunction during polymicrobial sepsis. Crit Care Med. 2010 May;38(5):1335-42.

[200] Gao M, Ha T, Zhang X, Liu L, Wang X, Kelley J, Singh K, Kao R, Gao X, Williams D, Li C: Toll-like receptor 3 plays a central role in cardiac dysfunction during polymicrobial sepsis. Crit Care Med. 2012 May 24. [Epub ahead of print] J. [200] Rolli, N. Rosenblatt-Velin, J. Li et al: "Bacterial flagellin triggers cardiac innate immune responses and acute contractile dysfunction,". PLoS ONE, vol. 5, no. 9, Article ID e12687, 1–13, 2010.

[201] Boyd JH, Kan B, Roberts H, Wang Y, Walley KR. S100a8 and s100a9 mediate endotoxin-induced cardiomyocyte dysfunction via the receptor for advanced glycation end products. Circ Res. 2008;102:1239 –1246.

[202] Zhang Z, Schluesener HJ: Mammalian toll-like receptors: from endogenous ligands to tissue regeneration. Cell Mol Life Sci. 2006 Dec;63(24):2901-7.

[203] SP Jones, R Bolli: The ubiquitous role of nitric oxide in cardioprotection Journal of Molecular Cellul Cardiol 2006;40:16–23.

[204] De Backer D: Nitric oxide inhibition in septic shock. Reanimation 2006;15;145-149.

[205] LL Wu, C Tang, MS Liu: Altered phosphorylation and calcium sensitivity of cardiac myofibrillar proteins during sepsis . Am J Physiol Regul Integr Comp Physiol 281:408-416, 2001.

[206] Tavernier B, Li JM, El-Omar MM, Lanone S, Yang ZK, Trayer IP, Mebazaa A, Shah AM: Cardiac contractility impairment associated with increased phosphorylation of troponin I in endotoxemic rats. Faseb J 2001, 15:294-296.

[207] Hassoun SM, Marechal X, Montaigne D, et al. Prevention of endotoxin-induced sarcoplasmic reticulum calcium leak improves mitochondrial and myocardial dysfunction. Crit Care Med 2008; 36:2590–2596.

[208] Lehnart SE: Novel targets for treating heart and muscle disease: stabilizing ryanodine receptors and preventing intracellular calcium leak. Curr Opin Pharmacol. 2007 Apr;7(2):225-32.

[209] Huang J, Wang Y, Jiang D, Zhou J, Huang X: The sympathetic-vagal balance against endotoxemia. J Neural Transm. 2010 Jun;117(6):729-35.

[210] Slezak J, Tribulova N, Okruhlicova L, Dhingra R, Bajaj A, Freed D, Singal P: Hibernating myocardium: pathophysiology, diagnosis, and treatment. Can J Physiol Pharmacol. 2009;874:252-65.

[211] Hunter JD, Doddi M: Sepsis and the heart. Br J Anaesth. 2010;104: 3-11.

[212] Maeder M, Fehr T, Rickli H e Al: Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. Chest. 2006 May;129:1349-66.

[213] McLean AS, Tang B, Nalos M, Huang SJ, Stewart DE: Increased B-type natriuretic peptide (BNP) level is a strong predictor for cardiac dysfunction in intensive care unit patients. Anaesth Intensive Care 2003, 31:21-27.

[214] de Bold AJ: Cardiac natriuretic peptides gene expression and secretion in inflammation. J Investig Med. 2009 Jan;57(1):29-32.

[215] Neubauer S: The failing heart--an engine out of fuel.N Engl J Med. 2007 Mar 15;356(11):1140-5.1.

[216] Neubauer S, Horn M, Cramer M, et al: Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. Circulation 1997;96:2190-6.

[217] Neubauer S, Horn M, Pabst T, et al: Contributions of ^{31}P-magnetic resonance spectroscopy to the understanding of dilated heart muscle disease. Eur Heart J 1995;16:Suppl O:115-8.

[218] Sack MN, Rader TA, Park S, Bastin J, McCune SA, Kelly DP: Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. Circulation. 1996 Dec 1;94(11):2837-42.

[219] Sihag S, Cresci S, Li AY, Sucharov CC, Lehman JJ. PGC-1alpha and ERRalpha target gene downregulation is a signature of the failing human heart. J Mol Cell Cardiol 46: 201–212, 2009.

[220] Abel ED, Doenst T: Mitochondrial adaptations to physiological vs. pathological cardiac hypertrophy. Cardiovasc Res. 2011 May 1;90(2):234-42.

[221] Lehman JJ, Barger PM, Kovacs A, Saffitz JE, Medeiros DM, Kelly DP: Peroxisome proliferator-activated receptor gamma coactivator-1 promotes cardiac mitochondrial biogenesis. J Clin Invest. 2000;106:847–856.

[222] L. K. Russell, C. M. Mansfield, J. J. Lehman, et al., "Cardiac specific induction of the transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator-1α promotes mitochondrial biogenesis and reversible cardiomyopathy in a developmental stage-dependent manner," Circulation Research 2004; 94: 525–533.

[223] Leone TC, Lehman JJ, FinckBN et al: "PGC-1α deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis," PLoS Biology, vol. 3, no. 4, p. e101, 2005.

[224] Thum T, Galuppo P, Wolf C, Fiedler J, Kneitz S, van Laake LW, Doevendans PA, Mummery CL, Borlak J, Haverich A, Gross C, Engelhardt S, Ertl G, Bauersachs J: MicroRNAs in the human heart: a clue to fetal gene reprogramming in heart failure. Circulation. 2007 Jul 17;116(3):258-67.

[225] Sucharov C, Bristow MR, Port JD: miRNA expression in the failing human heart: functional correlates. J Mol Cell Cardiol. 2008 Aug;45(2):185-92.

[226] Divakaran V, Mann DL: The emerging role of microRNAs in cardiac remodeling and heart failure. Circ Res. 2008 Nov 7;103(10):1072-83.

[227] Molnár A, Tóth A, Bagi Z, Papp Z, Edes I, Vaszily M, Galajda Z, Papp JG, Varró A, Szüts V, Lacza Z, Gerö D, Szabó C: Activation of the poly(ADP-ribose) polymerase pathway in human heart failure. Mol Med. 2006 Jul-Aug;12(7-8):143-52.

[228] Sundaresan NR, Pillai VB, Gupta MP: Emerging roles of SIRT1 deacetylase in regulating cardiomyocyte survival and hypertrophy. J Mol Cell Cardiol. 2011 Oct;51(4):614-8.

[229] Rajamohan SB, Pillai VB, Gupta M, Sundaresan NR, Birukov KG, Samant S, Hottiger MO, Gupta MP: SIRT1 promotes cell survival under stress by deacetylation-dependent deactivation of poly(ADP-ribose) polymerase 1. Mol Cell Biol. 2009 Aug;29(15):4116-29.

[230] Virchow R. Cellular Pathology as Based Upon Physiological and Pathological Histology. London: John Churchill, 1860:325.

[231] Tontonoz P, Spiegelman BM. Fat and beyond: The diverse biology of PPARgamma. Annu Rev Biochem. 2008;77: 289-312.

[232] Medina-Gomez G, Gray S, Vidal-Puig A: Adipogenesis and lipotoxicity: role of peroxisome proliferator-activated receptor gamma (PPARgamma) and PPARgammacoactivator-1 (PGC1). Public Health Nutr. 2007 Oct;10(10A):1132-7.

[233] Bhayana S, Siu VM, Joubert GI, Clarson CL, Cao H, Hegele RA: Cardiomyopathy in congenital complete lipodystrophy. Clin Genet. 2002 Apr;61(4):283-7.

[234] Sharma S, Adrogue JV, Golfman L, Uray I, Lemm J, Youker K, Noon GP, Frazier OH, Taegtmeyer H: Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. FASEB J. 2004 Nov;18(14):1692-700.

[235] Yagyu H, Chen G, Yokoyama M, Hirata K, Augustus A, Kako Y, Seo T, Hu Y, Lutz EP, Merkel M, Bensadoun A, Homma S, Goldberg IJ: Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cadiomyopathy. J Clin Invest. 2003 Feb;111(3):419-26.

[236] Unger RH, Clark GO, Scherer PE, Orci L. 2010. Lipid homeostasis, lipotoxicity and the metabolic syndrome. Biochim Biophys Acta 1801:209–214.

[237] Marfella R, Di Filippo C, Portoghese M, Barbieri M, Ferraraccio F, Siniscalchi M, Cacciapuoti F, Rossi F, D'Amico M, Paolisso G: Myocardial lipid accumulation in patients with pressure-overloaded heart and metabolic syndrome. J Lipid Res. 2009 Nov;50(11):2314-23.

[238] Finck BN, Han X, Courtois M, Aimond F, Nerbonne J, Kovacs A, Gross RW, Kelly DP: A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. Proc. Natl. Acad. Sci. USA 2003;100: 1226–1231.

[239] Son NH, Park TS, Yamashita H, Yokoyama M, Huggins LA, Okajima K, Homma S, Szabolcs MJ, Huang LS, Goldberg IJ: Cardiomyocyte expression of PPARgamma leads to cardiac dysfunction in mice. J Clin Invest. 2007 Oct;117(10):2791-801.

[240] Jozefowicz E, Brisson H, Rozenberg Mebazaa A, Gelé P, Callebert J, Lebuffe G, Vallet B, Bordet R, Tavernier B: Activation of peroxisome proliferatoractivated receptor-alpha by fenofibrate prevents myocardial dysfunction during endotoxemia in rats. Crit Care Med 2007; 35:856-63.

[241] Brindley DN, Kok BP, Kienesberger PC, Lehner R, Dyck JR: Shedding light on the enigma of myocardial lipotoxicity: the involvement of known and putative regulators of fatty acid storage and mobilization. Am J Physiol Endocrinol Metab. 2010 May;298(5):E897-908.

[242] Ilbäck NG, Mohammed A, Fohlman J, Friman G: 1990. Cardiovascular lipid accumulation with Coxsackie B virus infection in mice. Am. J. Pathol. 136: 159–167.