Biochimica et Biophysica Acta 1813 (2011) 1360–1372

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Bioenergetics of the failing heart ☆

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ARTICLE INFO

Article history:
Received 23 June 2010
Received in revised form 24 August 2010
Accepted 14 September 2010
Available online 24 September 2010

Keywords:
Cardiac energy metabolism
Mitochondria
Creatine kinase
Compartmentation
Cytoarchitecture

ABSTRACT

The heart is responsible for pumping blood throughout the blood vessels to the periphery by repeated, rhythmic contractions at variable intensity. As such the heart should permanently adjust energy production to energy utilization and is a high-energy consumer. For this the heart mainly depends on oxidative metabolism for adequate energy production and on efficient energy transfer systems. In heart failure, there is disequilibrium between the work the heart has to perform and the energy it is able to produce to fulfill its needs. This has led to the concept of energy starvation of the failing heart. This includes decreased oxygen and substrate supply, altered substrate utilization, decreased energy production by mitochondria and glycolysis, altered energy transfer and inefficient energy utilization. Mitochondrial biogenesis and its transcription cascade are down-regulated. Disorganization of the cytoarchitecture of the failing cardiomyocyte also participates in energy wastage. Finally, the failing of the cardiac pump, by decreasing oxygen and substrate supply, leads to a systemic energy starvation. Metabolic therapy has thus emerged as an original and promising approach in the treatment heart failure. This article is part of a Special Issue entitled: Mitochondria and Cardioprotection.

1. Introduction

The heart is among the largest energy consumer organ in the body. Energy is stored in the form of ATP and phosphocreatine (PCr) which is formed by the phosphorylation of creatine from ATP by creatine kinase (CK). The heart consumes around 1 mM ATP/s. This means that all ATP and PCr content should be renewed every ≈20 s. Because heart muscle produces more than 90% of its energy from mitochondrial respiration, it is a highly oxidative tissue. As a consequence, there is a strict correlation between cardiac oxygen consumption and cardiac work showing that the bioenergetic of the heart is of the tight flux mode (Fig. 1).

Among cardiac pathologies, heart failure has increasing prevalence in industrialized countries. Heart failure (HF) is a clinical syndrome that is characterized by progressive deterioration of the pump function leading to the incapacity of the heart to meet the body requirements. Heart failure patients also suffer from decreased exercise capacity increased fatigability, as well as dyspnea. Decreased fatigue resistance is intricately linked to energetic failure of the skeletal and respiratory muscles.

Heart failure originates from a mismatch between the demand of the organism and the capacity of the heart to fulfill its pump function. This mismatch may result from decreased oxygen and substrate delivery caused by chronic hypoxia, atherosclerosis, coronary artery disease, or mitochondrial defects induced by genetic or toxic factors. It may also result from increased workload to the myocardium following hypertension, for example, or from altered cardiac structure, or inefficient ATP utilization leading to decreased efficiency of energy utilization. As a consequence of the pump failure, oxygen and substrates are not adequately delivered to the periphery and metabolic products are not effectively cleaned up creating a state of energy deficiency in the organism and for the heart itself. One of the consequences of cardiac failure is thus to decrease oxygen and substrates availability for the organism.

Chronic stress to the myocardium initiates an adaptive process that comprises left ventricular hypertrophy, and functional and metabolic remodeling. However, when the stress exceeds the adaptive capacity or is prolonged, it can be followed by excessive maladaptive hypertrophy, progressive ventricular dilatation, contractile dysfunction, and, ultimately, heart failure. Progression to failure involves neuroendocrine overdrive, activation of intracellular

Abbreviations: ACE, angiotensin converting enzyme; AK, adenylate kinase; ADP, adenosine di-phosphate; AMPK, adenosine monophosphate activated protein kinase; ANT, adenine nucleotide translocase; ATP, adenosine tri-phosphate; CK, creatine kinase; CRT, cardiac resynchronization therapy; Drp1, dynamin-related protein 1; ERR, estrogen receptor related receptor; FAO, fatty acid oxidation; HF, heart failure; Mfn, mitofusin; mtDNA, mitochondrial deoxyribonucleic acid; NMR, nuclear magnetic resonance; NRF, nuclear respiratory factor; OPA1, optic atrophic type 1 protein; PCr, phosphocreatine; PGC-1, peroxisome proliferator-activated receptor-γ coactivator-1; PPAR, peroxisome proliferator-activated receptor; PRC, PGC-1 related coactivator; PTP, permeability transition pore; RAAS, renin angiotensin aldosterone system; RXR, retinoid X receptor; SERCA, sarcoplasmic reticulum Ca^{2+}-ATPase; TFAM, mitochondrial transcription factor A*; TFB1or 2M, mitochondrial transcription factor B 1 or 2

☆ This article is part of a Special Issue entitled: Mitochondria and Cardioprotection.

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doi:10.1016/j.bbamcr.2010.09.006

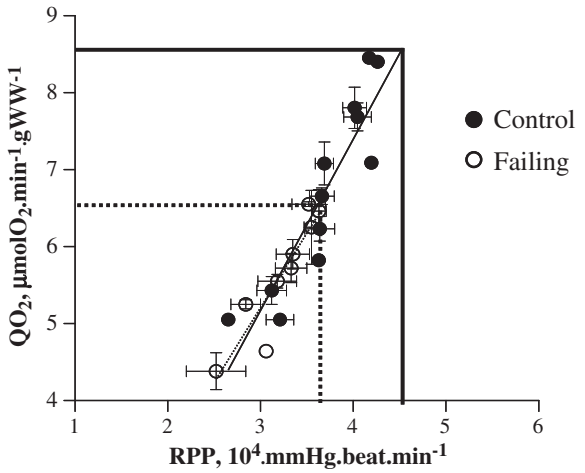

Fig. 1. Relationship between cardiac work and oxygen consumption in normal and failing rat hearts. RPP, rate pressure product, QO_2, oxygen consumption (drawn from De Sousa et al. [15]).

signaling cascades, extracellular remodeling, and mechanical load. Many of these contributing factors induce increased energy demand and thus a progressive imbalance between energy supply and demand. This leads to energy starvation that has been postulated as a central and potentially important factor contributing to heart failure development [1–6]. Energy starvation is manifest at different levels of cardiac energy metabolism. It could be taken as a unifying mechanism leading to cardiac contractile failure, and ultimately resulting in skeletal muscle energetic failure, exercise fatigue and death [6].

2. Substrates utilization

The heart is generally considered as a substrate omnivore with the capacity to oxidize fatty acids, carbohydrates, ketone bodies, lactate and even amino acids, the preferred substrate being fatty acids. Metabolic flexibility of the heart is its ability to respond to changing workload, substrate availability, circulating hormones, coronary flow, fuel metabolism by choosing the right substrate at the right moment (see [7,8] for reviews).

Studies of substrate utilization in the normal and failing heart have yielded conflicting results and interpretations and is the subject of recent extensive reviews elsewhere [8,9] and in this special issue of the journal and will be briefly summarized here.

It is generally reported that very early during the adaptive phase of hypertrophy, the myocardial energy source switches from fatty acid to glucose oxidation. However, metabolic adaptation may depend more on the nature of the stimulus inducing hypertrophy than on hypertrophy itself. These stimuli could be of physiological (exercise training, pregnancy) or pathological (hypertension) origin. Although exercise training increases mitochondrial fatty acid oxidation capacity, and hypertension decreases it, neither pregnancy or later stages of hypertension significantly affected it, showing that there is no unique metabolic signature in the hypertrophied heart [10].

In human heart, in the early stages of HF there is a normal (or slightly elevated) rate of fatty acid utilization, with a dramatic downregulation of fatty acid oxidation in advanced or end-stage HF [8]. Downregulation of fatty acid oxidation (FAO) pathway is linked to a metabolic remodeling involving downregulation of the PPARα/RXRα pathway [9,11–13] (see below). An increase in glycolysis and in glycolytic enzymes can be observed in hypertrophy but rapidly, rates of glucose oxidation are reduced as well as expression of proteins and transporters of glycolysis and carbohydrate oxidation [11,13–17]. As the process of remodeling progresses towards uncompensated state, metabolic adaptation becomes insufficient with a lower capacity to oxidize glucose leading to decreased efficiency [18] and loss of metabolic flexibility [19].

There is thus evidence that impaired substrate metabolism contributes to contractile dysfunction and cardiac remodeling characteristic of heart failure.

3. Mitochondrial capacity and function

3.1. Regulation of mitochondrial function in normal heart

Mitochondria occupy more than 30% of the cardiomyocyte volume. They are densely packed, organized under the sarcolemma and in rows between myofilaments such that a constant diffusion distance exists between mitochondria and the core of myofilaments. This type of organization provides a bioenergetic basis for contraction comprising cytoskeletal protein, mitochondria and sarcoplasmic reticulum at the level of a sarcomere within Intracellular Energetic Units [20].

During high-intensity exercise, the heart uses more than 90% of its maximal oxidative capacity [21], showing that there is no excess capacity of energy production over energy utilization. The strict linear relationship between oxygen consumption and cardiac work occurs at constant global cellular ATP and phosphocreatine (PCr) concentrations. This signs the peculiarity of the heart that is to work at metabolic homeostasis, expressed as constancy in concentrations of ATP, PCr and creatine, despite large variations in workload and oxygen consumption, or vice et versa [22,23]. Small metabolite oscillations during the cardiac cycle that may contribute to feedback metabolic regulation of respiration on a beat-to-beat basis, have been observed experimentally [24] and described by mathematical modeling [25]. The need for global metabolic homeostasis during changing energy demands imposes a major constraint on all cells. The mechanisms underlying this homeostasis are still highly debated, and few studies have carefully addressed the problem [22,25,37].

Therefore, strong energy signaling pathways should exist to ensure the close match between oxygen consumption and energy utilization. At present, the nature and function of such signals are still under debate and oxygen and substrates supply, ATP, ADP, PCr and Pi changes, calcium, redox state, phosphotransfer systems have all been considered to play a role. Their relative contribution to energy metabolism homeostasis if any will depend on the mechanical load and the metabolic conditions the heart has to respond to. Among these factors, two of them have been extensively considered. One of the candidates for coupling aerobic metabolism and cardiac work is calcium as it regulates myosin and sarcoplasmic reticulum ATPases on one hand, and the major mitochondrial dehydrogenases and F0/F1 ATPase on the other [26–28]. However, the assumption that respiration and contraction are simultaneously regulated by Ca^{2+}-ions is not completely satisfactory, as parallel increase in cardiac work and oxygen consumption with increase in length (Frank-Starling mechanism) occurs at constant intracellular Ca^{2+} concentration [22,29].

Another mechanism of regulation relies on the existence of energetic microdomains at sites of energy production and utilization, where the concentrations of ATP and ADP can be different from the rest of the cell. These microdomains are interconnected by phosphotransfer kinases and cell architecture. Indeed, the cardiomyocyte is not a well-mixed bag [30] and the reactions involved in ATP generation and utilization are not governed by stochastic events, but are rather integrated within structural and functional entities, spatially and temporarily coordinated. Glycolytic enzymes are arranged in supramolecular complexes bound to intracellular structures such as myofilaments and sarcoplasmic reticulum, where they participate in local energy production, more readily used by ion pumps and other membrane structures [31]. Mitochondria are embedded in the cytoskeleton in close interaction with surrounding organelles like sarcoplasmic reticulum, myofilaments and nucleus. This supramolecular arrangement induces specific regulatory

properties. For example, the ADP sensitivity of mitochondria *in situ* is far lower than in isolated mitochondria [32,33]. Low sensitivity to bulk ADP allows adenine nucleotide channeling and fine control of oxygen consumption by ATPases. The restricted access of cytosolic ADP to the mitochondrial compartment is possibly due to interaction of mitochondria with cytoskeletal proteins and molecular crowding [34]. Indeed, recently, tubulin has been shown to interact with porin and to decrease the permeability of porin and regulate respiration [35]. Disruption of the cytoskeleton increases the sensitivity to ADP and blunts the fine control of mitochondrial respiration [36]. The system of compartmentalized creatine kinase isoenzymes (see below) coupled to adenine nucleotide translocase (ANT) or ATPases allows the interconnection between ATP production and utilization due to the non-equilibrium state of the CK reaction. The mechanisms underlying the feedback regulation of respiration and energy fluxes are now analyzed on the framework of systems biology and includes small cyclic fluctuations of cytosolic metabolites [25]. The readers should refer to the excellent reviews by V. Saks and his coworkers for more comprehensive analysis of regulation of energy fluxes in muscle cells [22,25,37].

3.2. Mitochondrial function in heart failure

One important determinant of the capacity to oxidize different substrates is the oxidative capacity of the failing heart. In failing myocardium, it is unclear whether peak O_2 utilization is limited by maximal oxidative ATP synthetic capacity or by the maximal capacities of the ATPases to utilize ATP. Inadequate intracellular oxygen availability does not seem to be a limiting factor of oxygen consumption [38]. On the other hand, at high workloads, O_2 consumption rate by the failing myocardium can reach a maximum and becomes limited [38]. The maximal capacity to utilize oxygen is determined by the mass of mitochondria and by their intrinsic activity. Maximal oxidative capacity of the heart can be estimated by measuring the activity of key enzymes like citrate synthase, or cytochrome oxidase. In human and experimental HF, decreases in the activity of complexes of the respiratory chain or Krebs cycle enzymes or F(0)F(1)-ATPase protein expression have been largely reported [15,16,39–44] that correlate with cardiac function [45]. In addition, large scale proteomic and transcriptomic studies have confirmed that alteration in energy production and mitochondrial dysfunction is involved in the development of heart failure [46–48]. Of uppermost interest is the observation that the genomic HF profile observed in a model of pacing-induced heart failure in dogs is characterized by predominant downregulation of metabolic processes as early as 3 days after the initiation of rapid ventricular pacing evidencing that metabolic alteration is an early event in the pathophysiology of heart failure [49,50]. Thus not only alterations of metabolic processes are central in heart failure but they also represent early events in the pathophysiological process.

Moreover, mitochondria can also exhibit changes in properties. Decreased ADP/O ratio has been observed that is reflected in a 14% decrease in efficiency of the failing hearts [51]. A role for the supramolecular assembly rather than for the individual components of the electron transport chain has also been proposed [52]. Moreover, alterations in transport capacity of the ANT, and changes in isoform expression was observed in CHF patients [39,53]. In addition, an increased susceptibility of mitochondria to calcium and reactive oxygen species has been described in failing hearts. The mitochondrial permeability transition defines a sudden increase in the permeability of the inner mitochondrial membrane that is attributed to the opening of a high-conductance channel that is termed permeability transition pore (PTP) [54]. Increased susceptibility of the PTP to calcium and reactive oxygen species is involved in apoptosis and necrosis of the cardiomyocyte. However, some data argue for an early increase in PTP susceptibility in hypertrophy and heart failure [55,56]. These changes occur before any changes in mitochondrial respiration properties, evidencing a stage of preclinical mitochondrial dysfunction.

Isolated mitochondria allow assessment of the specific activity of mitochondria but not of the overall oxidative capacity of the tissue. The low yield of cardiac mitochondria isolation, the selection bias during isolation and the changes in mitochondrial regulation limit the extrapolation of isolated mitochondria studies to the living heart. More directly, oxidative capacity can be approached by recording maximal oxygen consumption rate normalized to dry weight in permeabilized cardiac fibers. A general decrease in oxidative capacity has been reported in different models of heart failure [15,57–62] as well as in humans [59,63]. This decrease in oxidative capacity was evident for all substrates but was larger with fatty acids (Rimbaud et al. unpublished data). This shows that in heart failure, fatty acid oxidation is impaired by two mechanisms, a decrease in mitochondrial activity and in addition a specific decrease in mitochondrial fatty acid oxidation capacity.

In addition to an overall decrease in the capacity to utilize oxygen, the failing heart exhibits alterations in the regulation of respiration by the phosphate acceptors AMP, ADP and creatine [15,57–59]. Interestingly the decreased sensitivity to ADP is accompanied by cytoskeleton remodeling and increased content of tubulin [64,65] although the cause and effect relationship needs to be established. The decreased sensitivity to creatine is explained by the decreased expression and content of mitochondrial creatine kinase which largely exceeds the decrease in oxidative capacity [15]. A similar defect in coupling between mitochondrial respiration and myokinase could be shown [15]. This is responsible for a lower and less efficient myocardial energy production via oxidative phosphorylation in HF. Decreased oxidative capacity on one hand and blunted servoing of mitochondria to excitation–contraction coupling on the other, will precipitate the heart in starvation.

Due to the strict correlation between oxygen consumption and work, the decreased oxidative capacity of the failing myocardium and the loss of functional coupling with sites of energy utilization will limit work and participate in cardiac dysfunction.

4. Mitochondrial biogenesis

Decreased oxidative capacity of the failing myocardium can arise from an unbalance between mitochondrial biogenesis and degradation. In the recent years, mitochondrial biogenesis has emerged as an important point among the multi-site control of mitochondria [66].

Mitochondrial biogenesis can be defined as the processes and events resulting from the growth and division of pre-existing organelles. It includes mitochondrial protein expression and its molecular control, phospholipids synthesis, import of mitochondrial proteins and mitochondrial network dynamics. Due to their ancient bacterial origin, mitochondria possess their own genome which encodes for 13 proteins whereas more than 98% of the mitochondrial protein requirement is encoded by the nuclear genome. Hence, to ensure a proper mitochondrial biogenesis, this requires a spatiotemporal coordination between protein synthesis, nuclear-encoded protein import and assembly with mitochondrial-encoded proteins. In addition, mitochondrial DNA replication and mitochondrial fusion and fission mechanisms must also be coordinated [67]. Thus, a defect in these multiple processes that constitute mitochondrial biogenesis could lead to impaired mitochondrial function and contribute to cardiac contractile failure. The discovery that alterations in mitochondrial biogenesis contribute to cardiac pathologies such as hypertrophy or failure have increased the interest of the scientific community in this process and its regulation.

4.1. Molecular control of mitochondrial protein expression

4.1.1. Mitochondrial biogenesis in the normal heart

Metabolic control of mitochondrial biogenesis will be developed elsewhere in this issue. This chapter will thus briefly review the

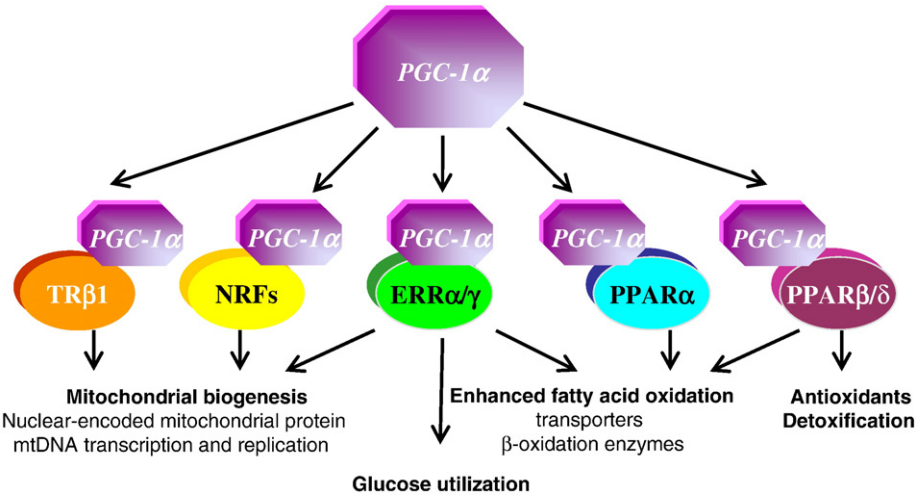

Fig. 2. PGC1α regulatory cascade. PGC-1α co-activates transcription factors such as nuclear respiratory factors (NRFs), estrogen-related-receptors (ERRs) and PPARs, known to regulate different aspects of energy metabolism including mitochondrial biogenesis, fatty acid oxidation and antioxidant.

different processes involved in mitochondrial biogenesis and mainly focus on the alterations that occur during heart failure.

The tuning of the mitochondrial protein expression is largely achieved at the level of transcriptional regulation. It depends on a highly interconnected network between coregulators and various DNA-binding transcription factors that regulate a broad set of nuclear genes encoding mitochondrial proteins having a functional or a regulatory role for the mitochondria (Fig. 2). The transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a master regulator of energy metabolism at the level of gene transcription. Through its interaction with multiple transcription factors such as peroxisome proliferator-activated receptors (PPARs), estrogen receptor related receptor (ERRs) or nuclear respiratory factor (NRFs), PGC-1α enhances mitochondrial capacity for fatty acid oxidation and oxidative phosphorylation and triggers the coordinate expression of nuclear and mitochondrial-encoded genes driving mitochondrial biogenesis [67–70]. Indeed, PGC-1α also activates the transcription and replication of mitochondrial DNA by transcriptionally activating and co-activating NRFs, which activate the transcription of the nuclear-encoded mitochondrial transcription factor A (TFAM), and of two proteins that interact with the mammalian mitochondrial RNA polymerase and TFAM, TFB1M and TFB2M (for review see [67,71,72]).

PGC-1α activates other nuclear receptors and transcription factors that are involved in mitochondrial biogenesis (Fig. 2). The principal transcriptional regulators of FAO enzyme genes are PPARα and δ, members of the ligand-activated nuclear receptor superfamily. Activation of PPARα by long-chain fatty induces a transcriptional response leading to increased expression of FAO enzymes [73]. PPARδ is an essential transcriptional regulator for mitochondrial protection and biogenesis in adult heart [74]. ERRα upregulates a subset of PGC-1alpha target genes involved in multiple energy production pathways, including cellular fatty acid transport, mitochondrial and peroxisomal fatty acid oxidation, and mitochondrial respiration [75].

PGC-1α belongs to a small family of coactivators including PGC-1β and PGC-1 related coactivator (PRC) [71]. As depicted in Fig. 3, only PGC-1α and PGC-1β gene expression strictly follows the muscle mitochondrial oxidative capacity, suggesting an important role of these two coactivators in setting the tissue-specific oxidative capacity. PRC gene expression is considerably lower than the expression of PGC-1α and PGC-1β in healthy muscles and does not seem to be expressed in a tissue-specific manner. Studies of loss of function leading to a defect of PGC-1α or PGC-1β in mice showed no profound alterations in basal cardiac phenotype, suggesting that these two coactivators partly compensate for each other's loss *in vivo* (see references in [72]). The recent generation of double PGC-1α/PGC-1β null mice has confirmed this notion as these mice die shortly after birth as a result of heart failure related to an arrest in cardiac maturation including a block in mitochondrial biogenesis [76], despite the presence of PRC.

Additionally, mitochondrial biogenesis involves fusion/fission and requires protein import and processing and cardiolipin biosynthesis. Mitochondrial shape is determined by fission and fusion of mitochondrial membranes, mediated by proteins bearing a GTPase activity in their N-terminal domain. Fission involves the dynamin-related protein 1 (Drp1) and its receptor Fis1 while fusion is mediated by two dynamin-related proteins, mitofusin (Mfn1 and 2) involved in outer membrane fusion, and OPA1 (Optic atrophic type 1 protein) that is closely related to the inner membrane (for reviews see [77,78] and dedicated chapter in this issue). Mitochondrial fusion and fission are

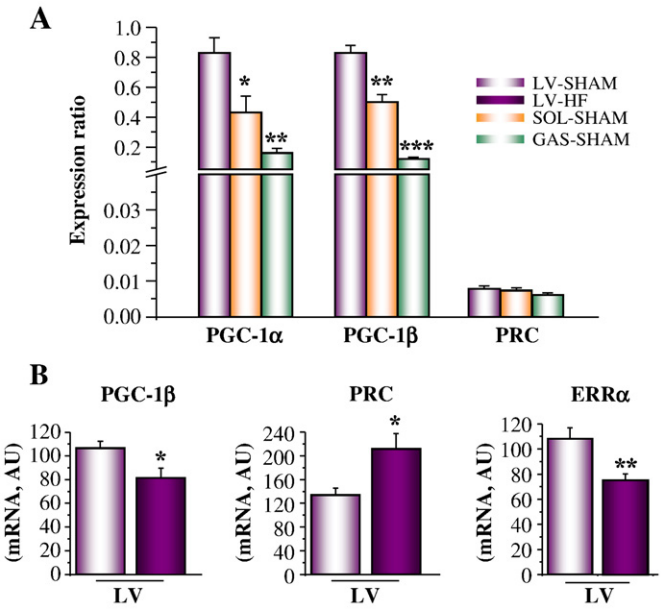

Fig. 3. Transcriptional cascade of mitochondrial biogenesis. Gene expression levels of PPARγ coactivator-1α (PGC-1α), PPARγ coactivator-1β (PGC-1β), and PGC-1 related coactivator (PRC) in left ventricle (LV), oxidative soleus muscle (SOL) and glycolytic part of gastrocnemius muscle (GAS) of sham-operated (SHAM) rats (A) and rats with chronic heart failure (HF) induced by aortic banding [85] (B). mRNA expression was measured by real-time RT-PCR according to [85], and were normalized to ribosomal protein A and TATA box binding protein levels using GeNorm software. Results are given as means ± SEM, *p<0.05, **p<0.01 and ***p<0.001 versus SHAM-LV group (A) or respective SHAM group (B).

tightly balanced processes and a shift in this balance can cause mitochondrial network disorganization and dysfunction.

Mitochondrial dynamics has been well described for differentiating and cancer cells, but such fast fusion/fission mechanisms do not seem to occur in adult cardiomyocytes [79]. Fusion and fission proteins are highly expressed in the heart and it is not excluded that this phenomenon could be involved in much slower processes and for example plays an important role during mitochondrial biogenesis during cardiac growth and postnatal cell maturation. It may also intervene in response to stress like ischemia, hypertrophy and heart failure [80–82]. This emerging field needs further investigation in mature cardiac cells.

Whether the transcriptional regulation of these processes involves the same or similar transcription cascades is still largely unknown. However, in skeletal muscle, PGC-1α and mitochondrial content correlate strongly with expression of proteins involved in mitochondrial dynamics and protein processing [83]. Moreover, evidence for a mitochondrial regulatory pathway defined by PGC-1α/ERRα and mitofusin 2 has been described [84] suggesting that partners of mitochondrial dynamic could also be regulated by PGC-1α.

4.1.2. Mitochondrial biogenesis in heart failure

Addressing the origin of decreased cardiac muscle oxidative capacity in the pathogenesis of heart failure, we previously showed in a rat model of CHF induced by pressure overload that the decrease in mitochondrial function in both cardiac and skeletal muscles is linked to altered expression of mitochondrial proteins associated with decreased expression of PGC-1α, and its downstream transcription factors NRFs and TFAM [85]. Decreased cardiac PGC-1α was subsequently described in numerous models of heart failure [86–90], strongly suggesting that downregulation of this PGC-1α transcriptional cascade is a real metabolic signature of heart failure, leading to reduced mitochondrial protein expression encoded either by nuclear or mitochondrial genome and defective oxidative capacity [67].

Recent studies have examined the PGC-1α transcriptional cascade in human heart failure and the results are quite controversial and suggest that PGC-1α downregulation is not uniformly present in human failing hearts [63,91–93]. This discrepancy between animal models and human diseases could be linked to the nature and/or the severity of the disease, the lack of age-matched control group, the sex differences between groups, and the treatment used for patients. Nevertheless, decreased expression of the key PGC-1α regulatory partner ERRα, as well as ERRα target genes will participate in the downregulation of mitochondrial metabolic capacity in human failing heart [92].

Only few studies have explored expression of PGC-1β in heart failure. A decrease in PGC-1β was reported in human dilated cardiomyopathy but not in ischemic heart disease [91]. We explored the gene expression of PGC-1β, PRC and ERRα in our rat model of heart failure induced by aortic banding. As for PGC-1α and NRFs [85] we observed a significant decrease in PGC-1β and ERRα expression in HF (Fig. 3). Thus, this concomitant downregulation of PGC-1α and PGC-1β gene expression in the failing myocardium reinforce the importance of the mitochondrial biogenesis defect in this pathology. In an opposite way, although expressed at a much lower level, PRC gene expression is increased in failing rat hearts but its precise biological function in mitochondrial biogenesis awaits further characterization. As ERRα is required for the adaptive bioenergetic response to hemodynamic stressors known to cause heart failure [94], the decreased expression of ERRα may participate in the energetic failure of the myocardium. To conclude, heart failure is characterized by an overall downregulation of energy metabolism involving the PGCs/PPARs/ERRs axis.

At present the transcriptional control of the CK system is poorly understood. In muscle cells, M-CK activity is inversely related to the mitochondrial content, while mi-CK activity increases with oxidative capacities [95]. To our knowledge, whether the expression of the mitochondrial protein mi-CK could be controlled by the classical mitochondrial biogenesis transcription cascade has not been extensively studied. However, downregulation of mi-CK have been observed in skeletal muscle [96] and heart [97] of PGC-1α KO mice suggesting that it is indeed the case. Moreover, mi-CK appears to be regulated by both ERRα and γ [98].

Nevertheless, all these results converge to an impairment of mitochondrial biogenesis in failing heart through a deactivation of the PGC-1α transcriptional cascade and a reduced mtDNA replication and depletion.

4.2. Qualitative and quantitative defects in mtDNA

The decline in mtDNA-encoded proteins observed in failing hearts could be also attributable to qualitative and/or quantitative defects in mtDNA content. However, results obtained either in experimental heart failure or in human heart failure are still under debate. A decrease in mtDNA copy number was described in a murine model of myocardial infarction [99], although our results did not reveal a significant difference in the mtDNA content between healthy and HF cardiac muscles of rats [85]. Several studies have reported maintained mtDNA content in patients with idiopathic dilated or ischemic cardiomyopathy [11,44,91,100]. A recent report from the group of R. Tian evidenced an impairment of mitochondrial biogenesis in human heart failure via a reduced mtDNA replication and depletion of mtDNA in the human failing heart [93].

Recent experimental and clinical studies have suggested that oxidative stress is enhanced in heart failure. This chronic increase in oxygen radical production in the mitochondria can induce mitochondrial DNA damage, which leads to defects of mtDNA-encoded gene expression, dysfunction of the respiratory chain complexes and thus may contribute to the progression of heart failure [99,101,102]. This mtDNA damage as well as left ventricular remodeling and failure after MI could be prevented by mitochondria-targeted antioxidants [103].

TFAM is essential for mtDNA transcription and replication and a decrease in its expression is observed in cardiac failure. Studies of loss or gain of function demonstrate that TFAM can function as a limiting determinant of mtDNA copy number and that copy number control by TFAM is independent of its transcriptional function [71]. In addition, it was shown by varying mtDNA amounts that oxidative phosphorylation activities are tightly controlled by the amount of mtDNA in the cell [104]. Interestingly, an overexpression of TFAM could ameliorate the decline in mtDNA copy number in failing hearts, mitochondrial deficiencies and cardiac failure after myocardial infarction [105,106]. In addition, a defect in the replication mechanism of the mtDNA could impair mitochondrial biogenesis and function in human failing hearts [93]. Thus, depletion of the mitochondrial DNA copy number could also be an important “actor” to the mitochondrial defects underlying human heart failure.

4.3. Import of mitochondrial protein

The targeting, import and assembly of nuclear-encoded mitochondrial proteins are essential processes of mitochondrial biogenesis. They involve a complex series of events which are dependent on the information encoded in the imported protein, the mitochondrial translocation machinery and the chaperones involved in the proper folding and assembly of proteins once they are imported (for review see [107,108]). It has been shown that errors in these events either by protein mutation or deficiency can result in a protein not reaching its final destination, ultimately leading to a disease state in humans often associated with characteristic features of cardiac myopathy and neurodegeneration (for review see [109]). A decrease in inner mitochondrial membrane proteins including mitochondrial protein

import machinery has been evidenced in failing type 2 diabetic hearts [110] but data are lacking in heart failure.

4.4. Mitochondrial phospholipid synthesis

Mitochondrial biogenesis also involves the proliferation of mitochondrial membranes. Phospholipids are important structural and functional components of mitochondrial membranes [111], and are implicated in the regulation of various processes including apoptosis, electron transport, and mitochondrial lipid and protein import. Cardiolipin is a unique phospholipid which is almost exclusively located in the inner mitochondrial membrane where it is biosynthesized. This phospholipid is known to play a key role in the activity of several inner membrane proteins and in the binding of mitochondrial creatine kinase in the vicinity of translocase. Defects in cardiolipin structure, content and acyl chain composition have been associated with mitochondrial dysfunction in multiple tissues in several physiopathological conditions including heart failure (for review [112,113]).

The mechanism(s) of alterations in cardiolipin biosynthesis and/or remodeling in the failing heart are not well known. Prior studies have argued against a role of chronic adrenergic stimulation whereas a role for mitochondrial calcium-independent phospholipase A(2) has been proposed (reviewed in [112]). Thyroid hormones and AMPKα2 are also involved in the control of mitochondrial respiration through cardiolipin homeostasis [111,114]. Further studies are needed to identify the mechanisms involved in the regulation of mitochondrial phospholipids synthesis in heart failure.

4.5. Turnover of mitochondria, and mitophagy

Mitochondria possess excellent protein quality-control systems. The only way which provides a mechanism for selective removal of deteriorating mitochondria is mitochondrial autophagy or mitophagy. The mitochondrial quality-control hypothesis was first advanced by the Shirihai's group [115]. They propose a mechanism by which the integration of mitochondrial fusion, fission and autophagy forms a quality maintenance system. Mitochondrial fusion and fission are paired, fusion triggers fission, allowing a redistribution of damaged mitochondrial components into daughter mitochondria that is targeted for autophagic destruction. So, the deregulation in mitochondrial network dynamics and morphology in failing myocardium, could thus lead to alteration in mitophagy and to dysfunctional mitochondria, but this remains to be explored.

5. Energy reserves

PCr/ATP ratio, which can be followed owing to the development of ^{31}P Nuclear Magnetic Resonance (NMR) on the whole heart *in vivo*, is considered as a powerful index of the energetic state of the heart. Depending on the species, the PCr/ATP ranges from 1.7 to 2.1. It reflects both the mitochondrial ATP production and the efficacy of energy transfer by creatine kinase. The failing heart is unable to maintain its energetic reserve. Alterations in myocardial high-energy phosphates were identified in animal models and human hearts with left ventricular hypertrophy or heart failure. A decrease in PCr/ATP ratio and an increase in calculated ADP is consistently reported in animal models of pressure overload and heart failure [38,43,116–120] and in hypertrophied and failing human hearts [121–127] (for recent reviews see [4,128]). PCr decrease is mainly responsible for this observation since its concentration is decreased from 50 to 70% in the early stages, whereas [ATP] is almost preserved [124,127] or slightly diminished by at most 30% [117,126]. Interestingly, in studies where left ventricular hypertrophy and HF are compared, the PCr/ATP ratio already drops during the phase of severe hypertrophy and before HF [118,119,127]. A loss of total creatine content and of purines is also observed and is considered adaptive as it allows to preserve the free energy of ATP hydrolysis [128,129]. Importantly, PCr/ATP ratio correlates with hemodynamic factors [130] and is of predictive value in heart failure [131]. Moreover, compromised energetics is also evident in hypertrophic cardiomyopathy [128,132] suggesting a central role for altered energetics in cardiac hypertrophy and failure [133]. The precise cellular mechanisms linking compromised high-energy phosphate levels and contractility are not well understood. However, for the reasons discussed above, the decrease in PCr/ATP ratio is more a reflection of altered energy fluxes rather than a cause. Certainly of major importance, PCr/ATP decline is accompanied by a local increase in ADP concentration that will affect both thermodynamically and kinetically the ATPases involved in excitation–contraction coupling [15,134].

6. Energy phosphotransfer

6.1. Energy phosphotransfer in normal heart

The presence of high-energy phosphotransfer systems is another essential feature of striated muscle energy metabolism. Early in the seventies, Bessman identified the creatine kinase (CK) and adenylate kinase (AK) systems as energy shuttles [135]. Since that time, considerable pieces of evidence have been accumulating to understand high-energy transfer in cardiac and muscle cells. Muscle cells use phosphotransfer networks, consisting of multiple near-equilibrium enzyme reactions, to convey energy-rich phosphoryl groups between cellular compartments in a kinetically and thermodynamically efficient manner [34,136,137]. Most phosphoryl groups are transferred between sites of ATP production and consumption via multiple creatine kinase catalyzed phosphoryl exchanges.

CK is present in variable amounts in heart and skeletal muscles and catalyses the reversible transfer of a phosphate moiety between ATP and creatine. Four different isoforms have been described and are expressed in a tissue-specific and developmentally regulated manner. Cytosolic CK exists as dimers composed of two subunits, M and B, giving three isoenzymes, MM, BB, and MB. A fourth isoenzyme specifically found in the mitochondria (mi-CK), can form both octameric and dimeric structures [138] and represents 20 to 40% of all CK activity in cardiac cells. CK isoenzymes are not evenly distributed and the CK system constitutes an example of a compartmentalized metabolic pathway. Myofibrillar MM-CK is a structural protein of the myofilaments and is functionally coupled to the myosin ATPase, thus providing enough energy to sustain maximal force and normal kinetics of contraction [139,140]. MM-CK is also strongly bound to the sarcoplasmic reticulum (SR) membranes where it is functionally coupled to the Ca^{2+}-ATPase (SERCA), and ensures efficient energy provision for calcium uptake [95,141,142]. Another local functional coupling takes place in the intermembrane space of mitochondria, where mi-CK is found on the outer surface of the inner mitochondrial membrane, in the vicinity of the ANT. During active oxidative phosphorylation, ATP generated in the matrix is exported by ANT in the intermembrane space where it is trans-phosphorylated by mi-CK to PCr and ADP in the presence of creatine. ADP is then immediately available for oxidative phosphorylation and further stimulates respiration (for reviews and further references see [34,37,136,138]. Cardiac mitochondrial respiration is mainly controlled by creatine due to the tight coupling between mitochondrial creatine kinase and ANT in the intermembrane space and to the low sensitivity of respiration for bulk ADP. Addition of creatine thus lowers the apparent Km for ADP (for a recent review see [37]). This allows the fine coupling between energy utilization by cytosolic ATPases and mitochondrial respiration. The same is true for mitochondrial myokinase also present in the inner membrane space of mitochondria [143].

These localized functional couplings between ATP generating or consuming sites and CK, efficiently control local ATP/ADP ratios that thermodynamically and kinetically favor energy production in mitochondria (low ATP/ADP ratio) and energy consumption in cytosolic compartments (high ATP/ADP ratios). These sites are connected through the near-equilibrium CK reactions that take place in the cytosol, and result in almost instantaneous transfer of phosphoryl groups to ATPases and of metabolic signal to mitochondria. Quantification of ^{31}P NMR unidirectional fluxes of localized CKs [144] and mathematical modeling [145–147] provided strong evidence for the existence of localized adenine nucleotide pools interrelated through intracellular energy transfer by CK. Indeed, creatine kinase fluxes are compartmentalized in intact cells, and the distribution of ADP has to be heterogeneous for the system to work, thus emphasizing the importance of subcellular organization and compartmentation in energy transfer [146,148,149]. Among phosphotransfer kinases, CK system appears the most important, but others phosphotransfer systems such as myokinase are also present and compartmentalized within the cell [136]. Control of energy production transfer and utilization by phosphotransfer kinases allows servoing of mitochondria to excitation–contraction coupling.

6.2. Energy phosphotransfer in heart failure

The group of J. Ingwall in Boston has been pioneer in demonstrating alterations in the creatine kinase system in hypertrophy and heart failure [150]. Total creatine kinase decreases as much as 50% in heart failure and positively correlates with ejection fraction [151]. Energy reserve via the CK reaction was estimated by the product of total CK activity and the content of total creatine in the heart, and decreased energy reserve contributes to impaired contractile reserve in the failing myocardium [1,128]. Indeed, it has been consistently observed that both the cytosolic (MM-CK) and the mitochondrial (mi-CK) isoforms of creatine kinase are decreased in experimental [2,4,15,125,152] and human heart failure [2,4,15,125,152] (see [128] for review). The decrease in mi-CK activity exceeds the decrease in mitochondrial enzymes and is due to decreased protein content [15]. It has been shown that the abnormal myocardial high-energy phosphate metabolism is related to the decreased in mi-CK, which in turn is related to the severity of the hypertrophy [119]. Drop of mi-CK pre-exists in severe hypertrophy and has been considered as a hallmark of the transition to failure.

^{31}P NMR spectroscopy also allows performing enzymology of CK by using magnetization transfer of the phosphate moiety as a tracer of energetic fluxes. Alterations of the averaged CK flux have been early demonstrated in cardiac pathologies (for recent reviews see [4,128]). In severe hypertrophy, CK fluxes are decreased by 30 to 50% [118,119,153]. In parallel, myokinase system, which normally contributes to a lower extent to ATP supply, is significantly increased as revealed by ^{18}O experiments as a compensatory mechanism [143]. The decrease in CK flux is even more pronounced in heart failure as described both in animal models [154] and recently in patients [116,119,124,125,127,154,155]. The transition between severe hypertrophy and heart failure actually results in a strong CK flux decrease, with no additional change in metabolite level, most probably reflecting the decrease in CK activity [124]. Thus, the decrease of CK flux, rather than the level of hypertrophy, is an indicator of heart failure.

It should be kept in mind however, that global approaches of cellular fluxes in NMR do not allow to discriminate fluxes of the different CK isoforms nor it takes into account the compartmentation of energy fluxes [148,149,156]. Although quantification of ^{31}P NMR unidirectional fluxes of localized CKs [144,146] have not been performed for the failing heart, it can be hypothesized that the deficit in mi-CK will compromise the coupling between energy production and utilization by the CK shuttle and that most of the energy transfer will be insured directly by ATP.

7. Energy metabolism and cytoarchitecture

7.1. Mitochondria and direct energy transfer in normal heart

Energetic homeostasis of highly differentiated cells depends on cellular architecture. Organization of the cytoskeleton may play a major role in the regulation of energy exchange, since it is required for positioning mitochondria and anchoring myofibrils [157,158]. Cytoskeletal organization varies according to muscle type, and undergoes remodeling in response to changing workload, environmental constraints and in pathology [157,159,160]. Indeed, mitochondrial regulation by cytosolic ADP differs depending on muscle type [161], probably due to the interaction between cytoskeleton and mitochondria in oxidative tissues [37,162]. Changes in cell or organelle volume, associated with physiological or pathological situations may also affect the cytoarchitecture, energy exchange and contractile function [163,164]. In addition, perturbation of cellular energetics can actually lead to ultrastructural remodeling, for example due to CK gene ablation [161,165], pharmacological depletion of creatine [166], or hypoxia. Conversely, architectural perturbation can lead to energetic alteration [167–169]. This suggests that cytoarchitecture may have a significant influence on energetic signaling.

Energetic microdomains, consisting on distinct ATP/ADP ratio, exist between bound-CKs and ATPases but also at the interface of organelles and are involved in energy regulation. Direct energy cross talks between mitochondria and energy-consuming sites [165,170] are driven by restriction diffusion for adenine nucleotides at the interface of the organelles (Fig. 4) and are facilitated by the close apposition of sites that produce and consume energy. Muscle mitochondria, for example, appear to be clustered at sites of high ATP demand, because they are organized into highly ordered, elongated bundles that wrap around the myofibrils and skirt the SR. This suggests that direct coupling of organelles may also be possible, involving energy and signal channeling. Recent studies have shown that indeed, ATP produced locally by mitochondria could be directly channeled to ATPases and support calcium uptake and myofibrillar contraction almost as effectively as ATP supplied by CK/PCr, and more effectively than cytosolic ATP, suggesting a direct energetic crosstalk between these organelles through compartmentation of adenine nucleotides [165]. Direct energy channeling and CK-supported energy supply seem to work on a competitive basis. Assuming a one-to-one ATP production per creatine and an ADP/O ratio of <3, it was estimated that more than 64% of the ATP consumed by ATPases is directly channeled by the CK reaction and that direct channeling with mitochondria accounts for less that 36%, showing the greater efficiency of compartmentalized creatine kinase in basal conditions [165]. Moreover, the two systems can compensate for each other, indicating partial redundancy in the local ATP/ADP-controlling systems of cardiac muscle. This is evident in mice lacking creatine kinase were cardiac function can be rescued by direct energy channeling [165], and direct support for the SR ATPase by glycolysis in heart muscle [171] accompanied by intense cellular remodeling. However, it might be anticipated that although these systems may appear redundant at rest or during moderate workload in the heart, it is highly probable that at a higher energy demand, they would have to be additively recruited and their relative contribution may be modulated. In addition to controlling the local adenine nucleotide pool, the CK system, as opposed to direct energy cross-talk, can rapidly spread the information and harmoniously equilibrate the energetic state throughout the cell because of the presence of soluble CKs.

Further evidence for direct channeling of adenine nucleotides was provided by V. Saks and his collaborators [20,172], who showed that diffusion of ADP produced by cellular ATPases was restricted, and that it was preferentially channeled to mitochondria instead of being

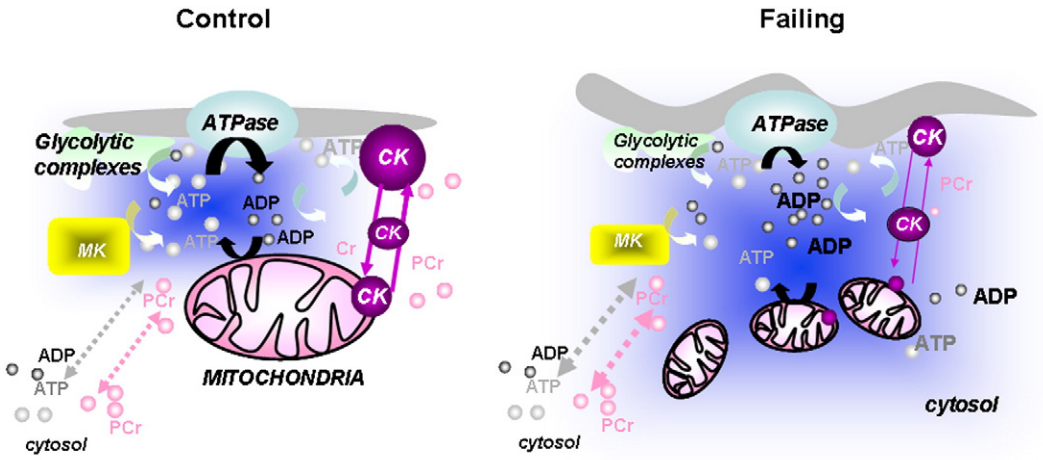

Fig. 4. Local bioenergetic alterations in heart failure. In normal heart, the ATP/ADP ratio at the vicinity of ATPases is finely controlled by bound phosphotransfer kinases (myokinase, MK and creatine kinase, CK), glycolytic complexes, and mitochondria in close contact with other organelles. In the failing heart, mitochondrial content is decreased as well as the amount of MK and CK. Moreover, disruption of the cell architecture weakens the direct nucleotide channeling between mitochondria and other organelles. This results in decreased ATP/ADP ratio, loss of microdomains, and kinetic and thermodynamic decrease in ATPase efficiency.

released into the bulk medium. Compartmentation and channeling of ADP increases the efficiency of interaction between mitochondria, myofibrils, the SR and probably other energy-consuming systems. This organization into intracellular energetic units is probably determined by the cytoskeleton, which governs the distribution of mitochondria within muscle cells. Indeed, perturbation of the cardiac cytoskeleton by desmin gene ablation affects mitochondrial localization and regulation [157,170].

All these data show that maintaining metabolic homeostasis despite fluctuating energy demand is an important prerequisite for contractile efficiency. This emphasizes the fact that cell architecture and metabolic networks are interrelated to build integrated phosphotransfer systems that improve cellular economy to tightly match cellular functions, and that alterations in this fine regulation can compromise cardiac function.

This may be especially important in the pathogenesis of muscle disease such as heart failure, in which energy handling is impaired concomitant with remodeling of mitochondrial morphology and the cytoskeleton.

7.2. Mitochondria and direct energy transfer in heart failure

HF is characterized by impairment in intracellular organization [173,174]. Alterations of microtubules or intermediate filament protein expression may contribute to the functional defect [64,175–177]. Cytoskeletal organization plays a role in energy transfer [162,169], as it is required for positioning mitochondria and anchoring myofibrils [157] and disruption of the cytoskeleton induces specific alteration of mitochondria–SR interaction and calcium homeostasis [170] as well as local loss of mitochondria [178]. However, it is important to know if locally, in the vicinity of ATPases, this decrease and these alterations have functional repercussions. For example, a decrease in calcium storage capacity of the SR directly linked to a local decrease in ATP/ADP ratio could be observed [82]. This was not due to a failure of calcium pump, because maximal activation of glycolysis was sufficient to restore a normal SR loading. This confirms that energy supply is a limiting factor for SR function in HF, and that glycolysis plays a more important role in HF in supporting SR function, to compensate for the impairment of CK and mitochondria. A similar alteration of energy transfer could be observed in myofilaments. Getting energy specifically to where it is required is thus an additional energetic problem in heart failure [179].

In the healthy heart, the two main energy-supplying systems (CK and direct mitochondrial energy channeling) can partially compensate each other, which is essential for having energetic reserve when energy demand of workload is increased. However, in HF, this is not anymore the case [82]. The decrease in mitochondrial content, in mi- and MM-CK activities, and the disorganization of the cytoarchitecture,

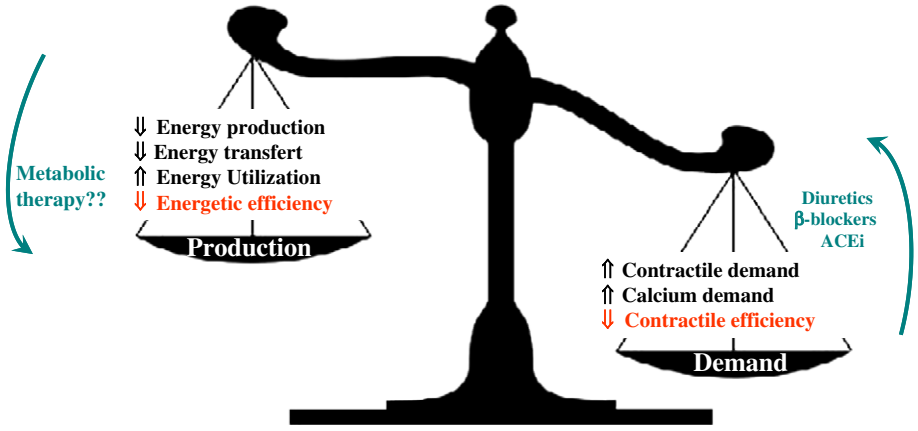

Fig. 5. Energetic unbalance in heart failure. Heart failure is characterized by an increase in energy demand and a decrease in energy production and transfer. Current treatments of heart failure tend to decrease energy demand. Future therapies of heart failure may tend to improve energy metabolism to re-equilibrate the energetic balance.

will all concur to decrease energy production, energy distribution and energy utilization participating in the failure of the cardiac pump.

Finally, HF is associated with morphologic abnormalities of cardiac mitochondria including increased number, reduced organelle size and compromised structural integrity, suggesting fragmentation of the mitochondrial network [65,99,173]. Mitochondrial injury identified as matrix depletion, membrane disruption and scrolling, positively correlates with indexes of heart failure severity like plasma norepinephrine, left ventricle (LV) end-diastolic pressure and ejection fraction [173]. An emerging hypothesis is that the mechanisms which control mitochondrial shape, and in particular mitochondrial dynamics, could play a role in heart disease [80,180]. In HF, a decrease in OPA1, a dynamin involved in the fusion of inner mitochondrial membrane, has been implicated in the regulation of energy fluxes and size and shape of mitochondria all factors that can be critical for optimum energy transfer [80]. However, it is not clear so far whether decreases in expression of proteins involved in fusion and fission processes are *per se* responsible for energetic disorders, or if there are just a consequence of mitochondrial mass decrease. Further experiments are needed to demonstrate the link between mitochondrial dynamics and energetic, especially in adult cardiomyocytes where only a few studies have been performed.

8. Towards a metabolic therapy of heart failure

Heart failure is still associated with an annual mortality rate of 10%, urging to develop new therapeutic strategies. Because heart failure becomes more common with increasing age, the number of affected individuals is rising with the rapidly ageing population. New treatments that target disease mechanisms at the cellular and whole-organ level are needed to halt and reverse the devastating consequences of this disease. Although the exact mechanisms are not completely understood, alterations in energy metabolism point at a more important role for energy metabolism in the pathophysiology of heart failure than previously thought. Physiological and biochemical studies, non invasive NMR spectroscopy of energy-rich phosphates, large scale studies in humans and more recently proteomic and transcriptomic studies have reactivated the concept of energy starvation of the failing myocardium as a major component of the pathophysiology of HF. It leads to an energetic unbalance between the work the heart has to perform and the production, transfer and utilization of energy (Fig. 5) that argue in favor of a metabolic therapy of heart failure [7,67,181–183].

Interestingly, part of the beneficial effects of the current treatments of heart failure can be explained by energy sparing effects. By decreasing circulating blood volume, diuretics decrease volume overload and thus energy demand. By decreasing peripheral resistance and RAAS activation, ACE inhibitors decrease the load against which the heart has to perform, thus also reducing energy demand and hormonal overdrive. A beneficial effect of ACEi therapies on oxidative capacity has been observed and proved to be effective in skeletal muscle but incomplete in cardiac muscle [57,62,63]. Beta-blockers that reduce adrenergic stimulation of the heart and cardiac frequency also result in energy sparing effects. Finally, cardiac resynchronization therapy (CRT) improves morbidity and mortality of CHF patients with ventricular dyssynchrony and potently affects both mitochondrial protein and function in association with improved cardiac function and efficiency [184–186]. Nevertheless, despite significant progresses in the last twenty years, heart failure is still associated with high morbi-mortality rate. The search for additional treatments is a burning issue. Metabolic therapy of heart failure is thus an original concept that has recently being proposed as a new field of research. From this perspective therapies aimed at preserving mitochondrial function and optimizing substrate metabolism appear to be worthwhile pursuits in the effort to stop the progression of heart failure [181]. Interventions aimed at counteracting the substrate switch has received recent attention but the success of such hypothesis depends on whether the shift from fatty acid towards glucose utilization should be considered beneficial or detrimental, a question that is still incompletely solved [8] and will strictly depend on the mitochondrial capacity to metabolize these substrates [187].

Because PGC-1α is the master regulator of energy metabolism, improvement of the cardiac energetic status by restoring PGC-1α transcriptional activity has promises as a new approach in the treatment of heart failure. Improving mitochondrial biogenesis by up-regulating PGC-1α is a strategy largely at work in metabolic diseases like metabolic syndrome, obesity and diabetes. Indeed, PGC-1α being upstream of all the regulation of energy metabolism, targeting it represents an original approach allowing a harmonious improvement of energy metabolism [67,188]. Normalizing PGC-1α content in the failing heart may improve substrate utilization, oxidative capacity, antioxidant defenses and potentially mitochondrial dynamic and energy transfer by increasing mi-CK expression. The combination of energy metabolism remodeling and load improvement, could synergistically rescue the failing heart. However, PGC-1α seems to be regulated in a cardiac specific manner [67] and more work is needed to understand its role and regulation in the normal and failing heart. Because HF is also a metabolic disease, such a strategy could be beneficial in this pathology.

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