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 ☆

Renée Ventura-Clapier *, Anne Garnier, Vladimir Veksler, Frédéric Joubert

*INSERM, U-769, F-92296 Châtenay-Malabry, France*
*Univ Paris-Sud, IFR141, F-92296 Châtenay-Malabry, France*

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.

* Corresponding author. U-769 INSERM, Faculté de Pharmacie, Université Paris-Sud, 5 rue J-B Clément, 92296 Châtenay-Malabry, France. Tel.: +33 1 46 83 57 62; fax: +33 1 46 83 54 75.
*E-mail address:* renee.ventura@u-psud.fr (R. Ventura-Clapier).

0167-4889/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2010.09.006

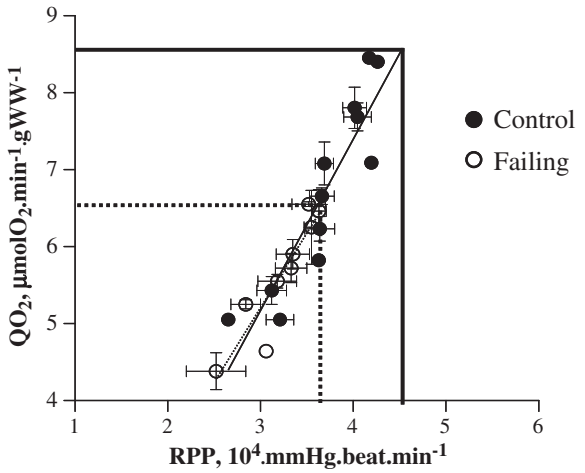


**Fig. 1.** Relationship between cardiac work and oxygen consumption in normal and failing rat hearts. RPP, rate pressure product, $QO_2$, oxygen consumption (drawn from De Sousa et al. [15]).

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