Mitochondria in the human heart

H. Lemieux · C. L. Hoppel

Abstract The heart relies mainly on mitochondrial metabolism to provide the energy needed for pumping blood to oxygenate the organs of the body. The study of mitochondrial function in the human heart faces many obstacles and elucidation of the role of mitochondria in cardiac diseases has relied mainly on studies with animal models. Cardiac diseases are the leading cause of mortality worldwide. With the emergence of new therapies to treat and prevent heart disease, some aiming at metabolic modulation, a need for acquiring a better understanding of mitochondrial function in the human heart becomes apparent. Our review is aimed at specific evaluation of the human heart in terms of (1) methods to understand mitochondrial function, with particular emphasis on integrated function, (2) data on the role of mitochondrial dysfunction in cardiovascular disease, and (3) possible applications of this knowledge in the treatment of patients with cardiac disease.

Keywords Oxidative phosphorylation · Electron transport complexes · Heart failure · Mitochondrial defect · Permeabilized fibers

Introduction

The rhythmic contraction of the heart ensures oxygenation of the organs of the body. Most of the energy needed for this arduous task is provided by mitochondrial metabolism, which produces a high-energy molecule, adenosine triphosphate (ATP). The process of energy production by mitochondria is called oxidative phosphorylation (OXPHOS), because it involves the coupling of oxygen to phosphorylation of ADP into ATP. The human heart daily synthesizes approximatively 30 kg of ATP (Ferrari et al. 2006).

In the failing heart, a decrease in energy reserves has been measured by phosphorus-31 NMR spectroscopy. This technique facilitates *in vivo* exploration of intracellular metabolism. A low phosphocreatine-to-ATP ratio (PCr/ATP), indicating a cardiac energy deficit, has been shown in the failing human heart (Beer et al. 2002; Conway et al. 1991; Hardy et al. 1991; Neubauer et al. 1997; Neubauer et al. 1992). This ratio is correlated with clinical symptoms (Conway et al. 1998) and predicts mortality better than the left ventricular ejection fraction (Neubauer et al. 1997). As the main energy source, mitochondria are suspected to be at least in part responsible for the low energy reserve in the failing heart (Mettauer et al. 2006). The NMR approach, however, does not reveal intrinsic mitochondrial content or function, even if it often has been interpreted as such.

Little information is available on mitochondrial function in the human heart. Most of the studies on the role of mitochondria in cardiac diseases have relied on animal models, which may not be representative of the human. However, tissue samples of the human heart are routinely removed in standard surgery (atrium cannulation, heart transplantation, cardiac biopsies), providing a resource that is underutilized for research on mitochondrial physiology and pathophysiology. The development of new methods to study mitochondrial function provides an opportunity to use the small amount of tissue available from routine surgeries to understand mitochondrial function. Our review

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is aimed at evaluating (1) the different methods available to understand mitochondrial function in the human, (2) the state of knowledge of the role of mitochondrial dysfunction in heart diseases, and (3) the possibility of applying this knowledge in the treatment of patients with cardiac diseases.

Methods to study human heart mitochondria

OXPHOS involves several interacting pathways. As a first step, most substrates for mitochondrial metabolism enter by transporters and are metabolized to produce reducing equivalents, usually through the action of dehydrogenases. For example, pyruvate is transported by the monocarboxylate transporter and dehydrogenated by the pyruvate dehydrogenase complex in the matrix, generating NADH and acetyl CoA. Fatty acids are transported by a complex carnitine transporter system and then go through beta-oxidation to generate NADH, $FADH_2$, and acetyl CoA (Kerner and Hoppel 2000). The TCA cycle, which produces NADH and $FADH_2$, funnels electrons into the electron transport complexes (ETC). The electron transport system is composed of four ETC: Complexes I (CI, NADH-ubiquinone oxidoreductase), II (CII, succinate ubiquinone oxidoreductase), III (CIII, ubiquionol-cytochrome *c* oxidoreductase), and IV (CIV, cytochrome *c* oxidase), and two main electron carriers (ubiquinone and cytochrome *c*). The transfer of electrons through three complexes coupled to the pumping of protons into the space between the inner and outer mitochondrial membranes creates a proton gradient, which drives the ATP synthetase in the inner membrane to produce ATP. The other substrates for the ATP synthetase are transported through the mitochondrial inner membrane by the adenine nucleotide translocase (ANT) and the phosphate carrier. The resulting matrix ATP is transported into the intermembrane space by ANT where mitochondrial creatine kinase (CK) catalyzes the transfer of the high-energy phosphate to creatine, which is stored in the form of cytosolic PCr for later use by the cardiac fibers for contraction.

Impaired mitochondrial function may be related to any steps involved in this complex process, either in term of the quantity, the concentration, or the functionality of the different components, or their interaction. Even in the face of the pivotal importance of mitochondrial energy production in the human heart, mitochondrial function unfortunately has not been studied in any depth. This part of the mini-review is aimed at providing a summary of the different methods available to enhance our knowledge of mitochondrial pathophysiology. Particular emphasis will be placed on methods allowing the measurement of integrated mitochondrial functions.

Activities of mitochondrial enzymes

In attempts to identify possible causes for a decline in mitochondrial function in diseased hearts, most studies have focused on the measurement of enzyme activities (EA, Table 1). The spectrophotometric assays for enzyme activities can be performed on isolated mitochondria, but the majority of the studies used homogenates of tissue, especially when the amount of tissue available was too small for isolation of mitochondria. Tissues or mitochondria can be used fresh or frozen for analysis, but some enzymes lose activity if frozen (Rustin et al. 1994). The measurement of mitochondrial enzyme activities yields valuable information about the capacity of some steps involved in mitochondrial metabolism, but has an important limitation when the objective is to evaluate the capacity of energy production by the whole system. The measurements are performed in mitochondria with permeabilized inner membrane, removing the transport barriers. Furthermore, the complex regulation of OXPHOS *in vivo* is not taken into account. For example, CIII and CIV are known to be present in amounts larger than needed to support the maximal electron flow in the ETC in human skeletal muscle (Kunz et al. 2000) and in human cells (Villani and Attardi 1997; Villani et al. 1998). The functional impairment in the pathway appears only when the capacity of the enzyme is reduced below the threshold activity (Rossignol et al. 2003). The excess capacity is highly variable in different tissues and species (Rossignol et al. 2000) and is unknown in the human heart. Thus, an apparent reduction in the activity of single step may have no effect on the whole process.

Integrated mitochondrial function-OXPHOS

To understand the effect of mitochondrial dysfunction in the pathophysiology of the human heart, a more integrative approach is to look at the process of OXPHOS by polarographic measurement of oxygen consumption in mitochondria in the presence of specific substrates that feed electrons into different sites of the ETC (Puchowicz et al. 2004). For example, in the presence of pyruvate + malate or succinate (+rotenone), the electrons fed into CI or CII, are transferred to ubiquinone, CIII, and CIV, where oxygen plus hydrogen are converted into water. Substrates derived from carbohydrate, amino acids, or fatty acids oxidation can be used to evaluate mitochondrial function. Oxygen consumption in the presence of ADP is coupled to the production of ATP by the phosphorylation system. The measurement of oxygen consumption in the absence of ADP (or after its complete consumption) is used as an estimation of the proton leak, i.e., the protons not used to phosphorylate the ADP. Uncouplers also can be added to

dissociate the proton gradient in the intermembrane space and to look at the limitation of the electron transport by the phosphorylation system. The measurement of OXPHOS assesses multiple components of mitochondrial metabolism and can uncover defects and differences in mitochondrial function not apparent by other techniques.

Isolated mitochondria

The conventional measurement of OXPHOS is performed after isolation of mitochondria from fresh tissue. The entire population of heart mitochondria can be isolated as a whole or, if the amount of tissue is sufficient, the subsarcolemmal and interfibrillar mitochondrial populations can be harvested separately (Palmer et al. 1977). The two populations have been shown to be differentially affected in an animal model of cardiomyopathy (Hoppel et al. 1982). The subpopulations of mitochondria were separated in cardiac tissue from patients undergoing a mitral valve replacement (Weinstein et al. 1986), but no information is available at present on the involvment of those populations per se on human cardiac pathophysiology.

The differential isolation of mitochondrial subpopulations requires a substantial amount of tissue available from the explanted heart of patients undergoing transplantation, but the roadblock is the difficulty in obtaining tissue from control healthy human heart. In enzymatic or genetic studies, autopsy samples often are used as controls (Table 1, groups CA), but they are, in some cases, taken several hours after death and cannot be used for OXPHOS measurements. A control group for OXPHOS measured in isolated mitochondria depends mostly on the availability of scarce donor hearts for transplantation that for some reason end up not being used.

Permeabilized fibers

The permeabilized fiber method (Veksler et al. 1987) allows the analysis of mitochondrial function in only a few milligrams of muscle tissues. Based on the selective permeabilization of the sarcolemma by mechanical separation with forceps and by exposure to a low concentration of saponin, the mitochondria can be studied in their cellular environment, depleted of cytosol, but with a functionally and morphologically intact architecture (Kunz et al. 1993; Kuznetsov et al. 2008; Saks et al. 1998). As for isolated mitochondria, different substrates, inhibitors, and uncouplers can be used to assess the OXPHOS pathway. With permeabilized myocardial bundles, both subsarcolemmal and interfibrillar mitochondrial populations are evaluated (Veksler et al. 1987).

This technique offers several advantages for the study of the human heart because it is possible to make measurements on very small amounts of tissue taken 1) during cardiac biopsy, e.g., for the follow up of rejection criteria in patients after a heart transplantation, 2) during routine surgery, e.g., removal of the atrial appendage (or part of it) before cannulation of the atrium and 3) from the donor heart when implanted into the recipient, overcoming the major problem of lack of control group in many studies. This technique is particularly attractive in combination with high-resolution respirometry (Oroboros, Innsbruck, Austria), making it possible to detect small differences in respiratory function. A possible limitation of this method is that sensitivity of respiration in response to the addition of substrates or inhibitors can be altered by inadvertent inclusion of non-mitochondrial structures such as myofibrillae and cells of non-myocyte origin, but the bias exists for normal and sick patients alike. Furthermore, the heterogeneity of structures in the tissues may lead to more variability between replicate measurements on different pieces of myocardial tissue from the same patient.

Anatomical sites in the heart

Another important problem in the study of the human heart is the different myocardial anatomical sites that are used as sources during diverse surgeries, with different chambers available from the explanted heart during transplantation (left and right atrium and ventricles), from surgeries requiring cardiopulmonary bypass (right atrial appendage), from biopsies (interventricular septum), and from the donor heart (left atrium). In end-stage heart failure (HF) patients undergoing transplantation, the rate of respiration in fibers per mg protein (Sharov et al. 2000) or in isolated mitochondria per mg mitochondrial protein (Lee et al. 1998) was similar in both ventricles. In fibers from atrial appendages, the respiration rate with all substrates is lower compared to ventricles, showing the decrease in mitochondrial content, but when OXPHOS was corrected for the amount of mitochondria (using the maximum uncoupled respiration) the respiration was similar in the three chambers (Lemieux et al. 2008).

The importance of studies focused on the mitochondrial function in the human heart

Animal models are of great utility for the study of cardiomyopathies and HF, but such studies may not explain the mitochondrial defect occurring in the failing human heart. The first reason is the major differences in history of the disease and degree of decompensation between animals and humans (Scheubel et al. 2002). A second could be the special features of human heart mitochondria (vida infra). Compared to human skeletal muscle, the activity of citrate synthase (CS) is three-fold higher in the human heart (18.6 and 58.6 umol/min/g tissue for skeletal muscle and heart,

Table 1 Mitochondrial respiration (OXPHOS, OX) and mitochondrial enzyme activities (EA) related to different pathologies in the human heart

References	Groups	OXPHOS and EA (tissues)	Related findings
(Chidsey et al. 1966)	HF-VD, TOF	OX (LV, RV, LVOT)[1,4]: PM, S(Rot), ATPase	No difference between the groups[b]
(Unverferth et al. 1988)	C, CMP-HF	EA (EMB): ATPase	↓ ATPase correlate with the loss of myocardial function
(Sylvén et al. 1988; Sylvén et al. 1989)	VD, IHD	EA (EMB, LV): CK, CS	↓ glycolytic capacity with a ↓ in ventricular function
(Buchwald et al. 1990)	CD, ES-DCM	EA[3]: CII, CIII, CIV, ATPase	↓ CIII and CIV in ES-DCM group compared to CD group; ↓ cytochrome content and in cytochrome-dependent enzyme
(Ingwall et al. 1990)	CB, CMP	EA (EMB: RV)[1,3]: CK	↓ CK[d] in CMP compared to CB, which correlates with the ejection fraction
(Saks et al. 1991)	HF classes I, II, and III	OX (EMB)[2,5]: GM, ADP kinetics, Cr effect; EA: CK	↓ OX[a] in Class III compared to Classes I and II; ↓ CK and Cr-stimulated OX in Class III compared to Classes I, II
(Maurer and Zierz 1992)	VD	EA (LV)[1,3]: CI + III, CII + III, CIV, CII, CS	↑ CI + III and coenzyme Q10 with increasing aortic valve pressure gradient
(Maurer and Zierz 1993)	VAS, ES-IDC, ES-CAD	EA (LV)[1,3]: CI + III, CII + III, CIV, CS	↑ CI + III, CII + III[d] in ES-IDC compared to ES-CAD or VASCIV and CS[d] similar in all groups
(Maurer and Zierz 1994)	CA (n=1), TOF, ES-CAD (age)	EA (RV, LV)[1,3]: CI + III, CII + III, CIV, CII, CS	↓ CI + III, CII + III, CII, CIV[d] in ES-CAD and TOF compared to CA; ↓ CI + III[d] in TOF compared to ES-CAD
Marin-Garcia 1995	ES-IDC	EA (LV): CI, CIII, CIV	Total 27 patients: 5 with a CIII defect, 1 with a CI defect, 9 with multiple defects (mostly CIII and CIV; 5)
(Pitkänen et al. 1996)	CA, CCLA	EA[1,4]: CS, CI, CI + III, CII, CII + III, CIV	↓ CI, CI + III, CII + III and CIV in CCLA compared to CA[b]
(Nascimben et al. 1996)	CA, CD, ES-DCM	EA (LV)[1,3] CK , CS	↓ CS and CK[d] in ES-DCM compared to controls
(Marin-Garcia et al. 1998)	CA, age	EA (LV)[1,3]: CS, CI, CII, CIII, CIV, ATPase	↑ CS[d] with age
(Bornstein et al. 1998)	CB, VH, ES-IDC, ES-CAD	EA (EMB)[1,3]: CI + III, CII + III, CII, CIV, CS	↑ CI + III, CII + III, CII, CIV[c] compared to CB, more pronounced in ES-IDC followed by ES-CAD and VH
(Arbustini et al. 1998)	CD, ES-DCM	EA (RV)[1,3]: CI, CII, CIV	↓ CIV and CI in ES-DCM presenting mtDNA mutations compared to CD or ES-DCM without mutation
(Lee et al. 1998)	ES-DCM (-LVAD), ES-DCM (+LVAD)	OX (LV, RV): KG, PM, G, S(Rot)	Improvement of mitochondrial OX[b] after long-term therapy with LVAD
(Gvozdjáková et al. 1999)	Rejection index after transplant	OX (EMB)[2,5]: G, S(Rot)	OX (G) and coenzyme Q10 content correlates with the rejection index
(Kalsi et al. 1999)	CD, ES-DCM, ES-HCM	EA (LV)[1,3]: CS	↓ CS[a] in both ES groups compared to CD group
(Quigley et al. 2000)	CA; CA-LVD, ES-IDC, ES-DCM	EA (LV)[1,3,4]: CIV, CII + III, CS	↓ CS[a, c] in both ES groups compared to CA and CA-LVD groups
(Sharov et al. 2000)	CD, ES ICM, ES-IDC	OX (LV, IS, RV)[2,5]: GM	↓ OX[d] in both ES groups compared to CD group
(Jarreta et al. 2000)	CD	EA (VTB)[1,3]: CI, CII, CIII, CI + III, CIV, CS	↓ CIII and CI + III CIII[c,d] in both ES groups compared to CD group

Reference	Groups	Assays	Results
(Mital et al. 2000; Mital et al. 2004)	ES-IC, ES-IDC; ES CHD, ES-CMP	LV[2,6]: Not permeabilized tissue respiration	↓ muscle oxygen consumption in ES-CMP reversed by improvement of nitric oxide availability
(Scheubel et al. 2002)	CD; ES-DCM, ES-CAD	EA (LV)[1,c]: CI, CII + III, CIII, CIV, CS	↓ CI[c] in both ES groups compared to CD; β-blockers therapy protects partly from defects, e.g., CIII
(Seppet et al. 2005)	SR; AF, RA	OX[5]: GM, S(Rot), COX, ATPase, CK	AF group is associated with increased OX[a] with S(Rot) relative to OX with GM
(Shinde et al. 2007)	CA; TOF	OX (RVOT)[2,4]: G or S(Rot); EA: CI + III, CII + III, CIV, SDH, CS, ATPase	↓ CI + III, CIV, ATPase in TOF compared to CA[b]; ↓ OX[b] in TOF compared to CA
(Mio et al. 2008)	CAD or VD; Mid-aged or old,	OX (RAA)[2,4]: PM	Anesthetic preconditioning preserve mitochondrial OX[b] better in the mild-aged group compared to the old subjects

Groups: control donors (CD), control biopsies (CB), control from autopsy (CA), ventricular hypertrophy due to aortic stenosis (VH), valvular aortic stenosis (VAS), valve disease (VD), left ventricular disease not fatal (LVD), cardiac surgery with or without atrial fibrillation (SR and AF, respectively), congenital heart disease (CHD), coronary artery disease (CAD), heart failure (HF), end-stage heart failure requiring transplantation (ES), dilated cardiomyopathy (DCM), ischemic dilated cardiomyopathy (IDC), hypertrophic cardiomyopathy (HCM), cardiomyopathy with cataracts and lactic acidosis (CCLA), tetralogy of fallot (TOF)

Tissues: left ventricle (LV), right ventricle (RV), right atrial appendage (RAA), right ventricular outflow tract (RVOT), endomyocardial biopsies (EMB), interventricular septum (IS), ventricular transmural biopsies (VTB)

Active mitochondrial respiration, coupled with ADP (OX) in the presence of the following substrates: glutamate (G), glutamate + malate (GM), pyruvate + malate (PM), succinate + rotenone [S (Rot)], α-ketoglutarate (KG)

Enzyme activity (EA) for Complexes I (CI), I + III (CI + III), II (CII), II + III (CII + III), III (CIII), or IV (CIV)

Assays performed in: [1]Frozen tissue, [2]Fresh tissue, [3]Homogenate, [4]Isolated mitochondria, [5]Permeabilized fibers, [6]Muscle not permeabilized

Assays expressed per: [a]Muscle tissue mass, [b]Mitochondrial proteins mass [c]Units CS activity,[d]Protein mass

respectively, unpublished data), in accordance with a three-fold increase in activity of CI, CII, CIII (unpublished data). The respiration rate of the human left ventricle is similar to human skeletal muscle (reviewed by (N'Guessan et al. 2004), and lower in the cardiac atrial appendage (Gellerich et al. 1994). With more mitochondria and more ETC activity in the human heart compared to skeletal muscle, why is the OXPHOS capacity not higher? Part of the explanation comes from the impressive limitation of OXPHOS capacity by the phosphorylation system in human heart mitochondria. The respiration coupled to the production of ATP was about 40% of the maximal capacity of the electron transport (measured after uncoupling) in the human heart (Lemieux et al. 2008) compared to 80% in the human skeletal muscle (Boushel et al. 2007). In mice and rats, however, OXPHOS capacity is much higher in heart compared to skeletal muscle, and the phosphorylation system in both tissues exerts almost no limitation on maximal OXPHOS capacity (Aragonés et al. 2008; Lemieux et al. 2006). Calcium accumulation by human heart mitochondria also was shown to be lower than in the hearts of a variety of animals (Lindenmayer et al. 1971). These examples showed the particularities of the human heart mitochondria that can be seen only by studying OXPHOS. It reinforces the importance of achieving a better understanding of the regulation of mitochondrial metabolism specifically in the human heart.

Mitochondrial dysfunctions in human heart: current knowledge

Table 1 presents an overview of knowledge of mitochondrial dysfunctions, enzyme activities, and OXPHOS in diseases of the human heart. Most of these studies concern HF, a complex, multifactorial syndrome resulting in the chronic and progressive loss of ventricular function leading to both cardiac and systemic perturbations. A number of underlying causes can lead to HF, including ischemic heart disease (coronary heart disease, myocardial infarction, and hypertension), cardiomyopathy (dilated, hypertrophic), valvular disease, and alcohol/drug-induced heart disease. In general, HF is preceded by an initial insult, e.g., cardiomyocyte loss or persistently increased workload, which activates compensatory mechanisms such as hypertrophy. In the short term, the compensation apparently restores cardiovascular function but the sustained activation of compensatory mechanisms can lead to secondary heart damage, i.e., deleterious alterations in ventricular mass, chamber size, and shape, leading to incapacity of the heart to meet the needs of the body (Latronico et al. 2008).

Most of the previous studies on mitochondrial function in human HF compared donor hearts with hearts from patients at end-stage HF at the time of transplantation (Table 1, ES groups, most of them in class III or IV of the New York Heart Association). End-stage HF was associated with multiple mitochondrial functional injuries, e.g., a decrease of ETC activities per muscle mass, most notably CI (Scheubel et al. 2002), CIII (Buchwald et al. 1990; Jarreta et al. 2000; Marin-Garcia et al. 1995), and CIV (Arbustini et al. 1998; Quigley et al. 2000), and a decrease in OXPHOS capacity in the presence of substrates directing electrons into CI in permeabilized fibers (Saks et al. 1991; Sharov et al. 2000). Part of the loss of mitochondrial ETC activity or OXPHOS per g of muscle is explainable by a decrease in mitochondrial content occurring also in end-stage HF (Kalsi et al. 1999; Nascimben et al. 1996; Quigley et al. 2000). The similarity in CS activity between end-stage HF and control groups (Maurer and Zierz 1994) may be explained by the age differences between groups, because the CS activity increases with age (Marin-Garcia et al. 1998). The decrease in mitochondrial content is not the only defect occurring in severe HF as the activity of CI (Scheubel et al. 2002) and CIII (Jarreta et al. 2000) expressed over the CS activity also significantly decreased.

It previously has been suggested that mitochondrial uncoupling occurs in HF patients. This uncoupling may offer a cardioprotective effect, reducing ROS production (Chen et al. 2007), but also would result in a further loss of cardiac efficiency by allowing protons to re-enter the matrix without ATP synthesis (Murray et al. 2007). The proposed uncoupling in heart disease is supported by increased cardiac levels of uncoupling protein 3 in patients undergoing coronary artery bypass surgery (Murray et al. 2004). While the decrease in respiratory control in end-stage HF has been used in support of uncoupling (Murray et al. 2007), the decrease in respiratory control is explained by the decrease in State 3 respiration rather than by an increase in leakage (Sharov et al. 2000); this is not uncoupling. Other evidence also shows that coupling is preserved in HF mitochondria (Chidsey et al. 1966) even at a late stage of the disease (Lemieux et al. 2008).

A disturbance of the phophorylation system also occurs in severe HF. In dilated cardiomyopathy, an upregulation (Sylven et al. 1993) and an increase in concentration (Schultheiss 1992) of the ANT carrier has been shown. This carrier upregulation, however, was associated with a decrease in function (Dörner et al. 2006; Dörner et al. 1997; Schultheiss 1992), explained by a change in the expression pattern of the ANT isoforms, i.e., increase in ANT1 and decrease in ANT2 (Dörner et al. 2006; Dörner and Schultheiss 2000; Dörner et al. 1997). ATPase activity also has been shown to be decreased in the failing human heart, but at least part of the decrease is explained by the decrease in mitochondrial content (Unverferth et al. 1988). The energy buffering and transfer capacity into the cells is

compromised in end-stage HF, partly due to a decrease in CK activity (Khuchua et al. 1992; Saks et al. 1991) and a diminution of creatine concentration (Kalsi et al. 1999; Nascimben et al. 1996). These observations agree with P NMR studies suggesting that a low PCr/ATP ratio is a consequence of the creatine pool depletion.

Interestingly, despite different clinical manifestations, end-stage HF from different etiology (dilated, hypertrophic, or ischemic cardiomyopathies) seems to end up with the same key changes in mitochondrial metabolism (Jarreta et al. 2000; Kalsi et al. 1999; Scheubel et al. 2002; Sharov et al. 2000), with the exception of the modification in the ANT isoforms, which is specific to dilated cardiomyopathy (Dörner and Schultheiss 2000).

The data on mitochondrial dysfunction acquired in patients during the end-stage HF do not help in understanding the involvement of mitochondria in the development of the disease. To determine whether alterations of mitochondrial function plays a primary or a secondary role in HF, we need to study patients at an early stage of HF or with pathologies that lead to HF, but when compensatory mechanisms still can maintain the cardiac output. Unfortunately, such data are rare, mostly limited to very specific enzymatic analysis and/or lack of an appropriate control group (see Table 1). The varying methods used in different laboratories make it difficult to compare the data between studies. Whether the impairment of mitochondrial function is primary or secondary in the development of HF remains to be elucidated, as is the localization of the defect in mitochondria.

Mitochondrial function in the prevention and treatment cardiac diseases

A few studies have shown that some treatments for severe HF improved mitochondrial function and structure, e.g., long-term implantation of left ventricular assist devices improved OXPHOS capacity (Lee et al. 1998), beta-blocker therapy reversed part of the defect in ETC activity (Scheubel et al. 2002), and administering a beta-adrenoceptor agonist increases cristae-to-matrix ratio and mitochondrial size (Unverferth et al. 1980). An evolving trend in the treatment of cardiac disease is the use of metabolic modulators, including therapeutic targets aimed at improving mitochondrial energy production (reviewed by Murray et al. 2007) to prevent or reverse the low energy status of the failing heart. The application of those therapies requires a better understanding of cardiac mitochondrial function. Severe HF is associated with a reversion of cardiac metabolism from a use principally of free fatty acid metabolism in the healthy heart to enhanced glucose oxidation in the failing heart (Tuunanen et al. 2008). Glucose oxidation is favored during hypoxia or ischemia, as a more oxygen-efficient substrate (Abozguia et al. 2006). The administration of metabolic regulators increasing carbohydrate oxidation, e.g., propionyl L-carnitine, has been shown to improve ATP production in the human heart (Bartels et al. 1992). There is, however, no information on fatty acid oxidation by mitochondria in the human heart, with the exception of measurements performed on patients with coronary artery diseases, without controls (Gellerich et al. 1994). One of the challenges for the future management of cardiac disease will be to understand the involvement of mitochondrial fatty acid oxidation in heart failure. Also, targeting early events in mitochondrial dysfunction may help to design therapies to prevent the development of the disease before reaching an end-stage, where multiple injuries make it very difficult to find an ameliorative treatment.

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