Cardiac and skeletal muscle energy metabolism in heart failure: beneficial effects of voluntary activity

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Abstract

**Objective:** Mitochondrial function and metabolic profile of slow and fast skeletal muscles and cardiac muscle are altered in chronic heart failure (CHF), suggesting a generalized metabolic myopathy in this disease. The aim of this study was to investigate the potential beneficial effects of voluntary activity on cardiac and skeletal muscle energetics in heart failure. **Methods:** Heart failure was induced in rats by aortic stenosis. Four months after surgery, part of sham and CHF animals were randomly assigned to activity cages equipped with running wheels for 8 weeks or kept sedentary. Mitochondrial capacity and regulation were measured using saponin skinned fibers in left ventricle, slow and fast skeletal muscles, and metabolic and myosin profiles were established. **Results:** Despite four times lower performances of CHF rats, alterations in metabolic and myosin parameters (oxidative capacity, mitochondrial enzymes, cytosolic and mitochondrial creatine kinase, myosin heavy chains) observed in all muscles of CHF animals were almost fully restored in soleus muscle though unchanged in heart and fast skeletal muscles. **Conclusions:** These results show the powerful beneficial effect of physical activity specifically on active slow oxidative skeletal muscle in CHF, without the worsening of cardiac muscle metabolism.

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1. Introduction

Limited exercise capacity, skeletal muscle fatigue and muscle weakness are main factors restricting the daily life of patients with chronic heart failure. Although, these patients have reduced cardiac output, decreased maximal oxygen uptake and increased peripheral resistance, these alterations are poorly correlated with decreased exercise capacity. The limitation is associated with early anaerobic metabolism and lactate production in the skeletal muscle. Numerous studies, in patients and animal models of heart failure, have described muscle abnormalities, that include muscle fiber atrophy, increased proportion of fast fibers at the expense of slow fatigue resistant fibers, trend to decreased oxidative metabolism, increased glycolytic metabolism and decreased resistance to fatigue (for a recent review see [18]). In a recent study, contractile abnormalities and increased fatigue were described in a short term model of heart failure that could not be explained by changes in intrinsic calcium sensitivity or SR protein expression [17] or tissue content of high-energy phosphates [19].

We recently showed that prolonged heart failure results in metabolic rather than contractile alterations in fast and slow skeletal muscles of rats [6]. In this study, mitochondrial capacity and regulation and cytosolic and mitochondrial isoenzymes of creatine kinase (CK), a key enzyme in energy transfer in muscle cells [33], were altered, thus compromising capacity and integration of energy production and utilization, as well as calcium homeostasis. Myocardium, fast and slow skeletal muscles as well as diaphragm muscles were all affected suggesting
the occurrence of a generalized metabolic myopathy in heart failure [5–7]. However, the reasons for these alterations are still unknown and several factors such as de-conditioning, decreased blood delivery, or altered hormonal status have been proposed.

It is becoming clear that moderate exercise training can prevent or even reverse alterations in haemodynamics, endothelium dependent coronary and peripheral resistance, as well as peak oxygen uptake in heart failure patients or animal models, and can attenuate adverse remodeling of myocardium and abnormal gene expression [9,11,13,16,25,34]. Exercise training can improve muscle blood flow, oxidative enzymes and restore fiber type profile [1,12,14,24]. However, no direct assessment of muscle oxidative capacity, energy transfer and mitochondrial function has been made so far. Moreover, it is not clear whether these effects depend on the level of activity, apply indifferently to slow and fast muscles and might also affect myocardial energetics.

Our aim was thus to investigate the effects of voluntary activity in CHF and sham rats on (1) the exercise capacity of animals, (2) the cardiac and skeletal muscle mitochondrial function and metabolic profile, (3) the respective metabolic responses of slow and fast skeletal muscles to increased physical activity.

The results show that although CHF rats exhibited a four times lower voluntary activity, the mitochondrial function and metabolic profile were greatly improved and almost normalized in slow but not fast skeletal muscles. This took place without an increase in mortality or worsening of anatomical parameters or cardiac mitochondrial function and metabolic profile. No effect of voluntary exercise was observed in sham animals. These results show the powerful beneficial effect of physical activity on slow skeletal muscle metabolism in CHF, without the worsening of cardiac muscle metabolism.

2. Methods

2.1. Rat model of CHF

Aortic stenosis was created in weaned male Wistar rats (60–70 g) by placing a stainless steel hemoclip on the ascending aorta via a thoracic incision as previously described [6,7]. Age-matched control animals underwent the same procedure without placement of the clip. All rats were fed a normal chow diet and water ad libitum with a 12 h–12 h photoperiod. This investigation conforms to the Guide for the Care and Use of Laboratory Animals published by US NIH.

Four months after surgery, part of sham (S group, n = 7) and CHF (CHF group, n = 8) were sacrificed. Another part of sham and CHF animals were randomly assigned to cages equipped with an activity wheel (active sham, SA, n = 9; active CHF, CHFA, n = 10) or to normal cages (sedentary sham, SS, n = 6; sedentary CHF; CHFS, n = 7) for 8 additional weeks.

At the end of the conditioning period, animals were anaesthetized with an intraperitoneal injection of urethane (0.2 g/100 g). Animals and organs were weighed. Soleus, superficial part of gastrocnemius, plantaris and left ventricle (LV) were isolated. A portion of the muscles was rapidly frozen for biochemical determinations.

2.2. Voluntary activity measurements

Activity cages consisted in Plexiglas cages equipped with running wheels connected to a DC generator allowing slight loading of the wheel (27.10^{-3} N m at mean maximal speed) and continuous recording of the output voltage of the DC generator on a PC computer. The daily work is derived from the power dissipated by the resistive load. Instantaneous speed is calculated from the voltage and the resistive load on the DC generator and allows calculating the daily distance. These daily values are averaged over each week for each animal. The total work performed over the 8 weeks for each animal was also calculated.

2.3. Mitochondrial respiration

Respiratory parameters of the total mitochondrial population were studied in situ in freshly saponin-skinned fibers [6,7]. Briefly, thin fiber bundles (100–250 μm in diameter) were excised from left ventricle, soleus, and gastrocnemius muscles and incubated for 30 min at 4°C in solution S (see later) containing 50 μg/ml saponin to permeabilize the sarcolemma. Respiratory rates were determined with a Clark electrode (Strathkelvin Instruments, UK) in an oxygraphic cell containing 3 ml respiration solution (solution R, see later) at 22°C with continuous stirring. Respiration rates were expressed as μmol O₂/min/g dry weight. Solutions S and R contained (in mM): ethylene glycol-bis(β-aminoethyl)tert-lether)N,N,N',N'-tetraacetic acid (EGTA)-CaEGTA buffer 10 (free Ca²⁺ concentration 100 nM), free Mg²⁺ 1, taurine 20, diithiothreitol (DTT) 0.5, and imidazole 20 (pH 7.1). Ionic strength was adjusted to 160 mM by addition of potassium methanesulfonate. Solution S also contained 5 mM MgATP and 15 mM PCr, whereas solution R contained 5 mM glutamate, 2 mM malate, 3 mM phosphate and 2 mg/ml fatty acid free BSA. The ADP-stimulated respiration (V_{ADP}) above basal oxygen consumption (V_o) was plotted as a function of [ADP] with or without creatine (20 mmol/l). The apparent Kₘ values for ADP and V_{ADP} were calculated with nonlinear fit of the Michaelis–Menten equation. The maximal respiration rate (V_{max}) was (V_{ADP} + V_o). The acceptor control ratio (ACR)
was $V_{\text{max}}/V_0$. From one to three determinations were made for each animal.

2.4. Biochemical determination

Frozen tissue samples were weighed and homogenized in ice-cold buffer (50 mg per ml) containing (in mM): HEPES 5 (pH 8.7), EGTA 1, DTT 1, MgCl$_2$ 5, and Triton X-100 (0.1%), and incubated for 60 min at 4°C to ensure complete enzyme extraction. Enzyme activities were determined as previously described [7]. The total activities of creatine kinase (CK), lactate dehydrogenase (LDH), and citrate synthase (CS) were assayed (30°C, pH 7.5) with coupled enzyme systems. CK and LDH isoenzymes were separated using agarose (1%) gel electrophoresis performed at 200 V for 90 min; individual isoenzymes were resolved either through incubation of the gels with a coupled enzyme system (CK), or commercial revelation system (Sigma LDH reagent kit). The five homo (H$_1$ and M$_4$) and hetero (H$_2$M, H$_3$M$_2$, and H$_4$M$_4$) tetramers of LDH were resolved. H-subunit of LDH was calculated as follows $H$-LDH$=H_1+3/4 H_2 M+1/2 H_3 M_2+1/4 H_4 M_4$. Native myosin was extracted as previously described [2]. Myosin heavy chain (MHC) isoforms were separated using polyacrylamide gel electrophoresis at a constant voltage of 90 V for 22 h, between 2 and 4°C [6]. Mi-CK protein was 298.6 ± 82 ml/min, $P < 0.05$) with a large scattering in sham animals (range 21–223 J/day). The averaged maximal speed of running was also lower in CHF (9.7 ± 0.8 ml/min, $P < 0.01$). None of the anatomical parameters were affected by activity either in sham or CHF rats, though that relative lung weight became insignificant between SHF and voluntary activity, and was followed by Newman–Keuls posthoc test when appropriate. Values of $P < 0.05$ were considered significant.

3. Results

3.1. Anatomical data and voluntary activity

Anatomical data are presented in Table 1. CHF animals exhibited decreased body weight ($P < 0.001$). Significantly increased absolute and relative weights of the heart, of both left and right ventricles and lung as well as decreased liver weight in the CHF group indicated severe heart failure already at 4 months. Anatomic evidence of cardiac decompensation (ascite, congestion, pleural effusion and edema), as well as our previous hemodynamic data (see [7] for details) confirmed the occurrence of severe CHF in this model. Both absolute and relative soleus and plantaris weights were significantly decreased showing muscle atrophy in CHF.

Fig. 1 represents the weekly averaged daily work (A) and running distance (B) as a function of time of sham and CHF rats in activity cages. After 8 weeks of running, the weekly averaged daily work and running distance were at least four times lower for CHF rats (11.2 ± 2.4 J/day and 70 ± 15 m/day) than for sham (66 ± 20 J/day, $P < 0.05$ and 298 ± 82 m/day, $P < 0.05$) with a large scattering in sham animals (range 21–223 J/day). The averaged maximal speed of running was also lower in CHF (9.7 ± 0.8 m/min) compared to sham (15.5 ± 1.1 m/min, $P < 0.01$).

None of the anatomical parameters were affected by activity either in sham or CHF rats, though that relative lung weight became insignificant between SAct and CHFAct. The mortality rate during the running period was not significantly different between sedentary and active CHF animals (83 and 79% survival, respectively, in CHFSed and CHFAct between 4 and 6 months).

Table 1

<table>
<thead>
<tr>
<th>Time after surgery</th>
<th>4 months</th>
<th>6 months</th>
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<tbody>
<tr>
<td></td>
<td>S</td>
<td>CHF</td>
</tr>
<tr>
<td>Body weight (BW) (g)</td>
<td>631 ± 18</td>
<td>396 ± 29*</td>
</tr>
<tr>
<td>Heart weight (HW) (g)</td>
<td>1.58 ± 0.07</td>
<td>2.5 ± 0.2*</td>
</tr>
<tr>
<td>Right ventricle (RV) (g)</td>
<td>0.29 ± 0.02</td>
<td>0.48 ± 0.02*</td>
</tr>
<tr>
<td>Left ventricle (LV) (g)</td>
<td>1.10 ± 0.05</td>
<td>1.5 ± 0.1*</td>
</tr>
<tr>
<td>Tibia length (TL) (cm)</td>
<td>4.55 ± 0.06</td>
<td>4.32 ± 0.08</td>
</tr>
<tr>
<td>HW/TL (mg/cm)</td>
<td>346 ± 14</td>
<td>580 ± 31*</td>
</tr>
<tr>
<td>RVW/TL (mg/cm)</td>
<td>63 ± 3</td>
<td>112 ± 7*</td>
</tr>
<tr>
<td>LVW/TL (mg/cm)</td>
<td>240 ± 9</td>
<td>353 ± 20*</td>
</tr>
<tr>
<td>LungW/TL (mg/cm)</td>
<td>378 ± 13</td>
<td>467 ± 45*</td>
</tr>
<tr>
<td>LiverW/TL (g/cm)</td>
<td>4.9 ± 0.3</td>
<td>3.5 ± 0.3*</td>
</tr>
<tr>
<td>SoleusW/TL (mg/cm)</td>
<td>57 ± 2</td>
<td>43 ± 3*</td>
</tr>
<tr>
<td>PlantarisW/TL (mg/cm)</td>
<td>124 ± 4</td>
<td>89 ± 5*</td>
</tr>
</tbody>
</table>

Values are means ± S.E.M. S, sham; CHF, heart failure, SSed, sham sedentary; CHFSed, CHF sedentary; SAct, active sham; CHFAct, active CHF. * $P < 0.05$, CHF versus sham.
None of these parameters was affected by activity either in sham or in CHF suggesting no alteration of myocardial energetics by activity. No correlation was found between $V_{\text{max}}$, mi-CK or CS and total work performed by the CHF animals over the 8-week period, while a positive correlation was found between mi-CK and total work in sham animals. As a whole, mi-CK ($P<0.0004$) and $V_{\text{max}}$ ($P=0.020$) but not CS correlated with total work when both groups were pooled (Fig. 2A).

3.3. Effects of heart failure and voluntary activity on soleus

The effects of 8 weeks voluntary activity on energy metabolism and MHC expression of soleus muscle are presented in Table 3. CHF significantly decreased the percentage of MHC-I ($P<0.001$) and proportionally increased the fast MHC-IIa content. It can be seen that voluntary activity could normalize the MHC-I and MHC-IIa contents in CHFAct animals.

In soleus muscle, heart failure induced an overall decrease in CS activity ($P$, 0.005), total CK, MM-CK ($P$, 0.001) and mi-CK activity and protein ($P$, 0.001). MB-and BB-CK were undetectable in soleus muscle. Oxidative capacity was also decreased as basal ($P$, 0.005) and maximal ($P$, 0.001) respiration rates were significantly lower, showing altered slow skeletal muscle energetics in heart failure.

Voluntary activity had no effects on soleus of sham animals except a significant increase in ACR. However, it induced a significant increase in total CK, mi-CK activity (but not protein) and MM-CK, as well as maximal respiration and ACR in soleus muscle of CHF animals, and it normalized CS activity showing a remarkable improvement of slow muscle energetics. Two-way ANOVA analysis showed a significant interaction between heart failure and activity on total CK ($P<0.005$), MM-CK ($P<0.01$), mi-CK ($P<0.05$), and CS ($P<0.03$) activity in this muscle. This evidences the effectiveness of physical activity on metabolic profile in CHF animals, but not in sham. Moreover, mi-CK correlated with total work in sham ($P=0.005$) and in all active animals ($P=0.0025$) but not in CHF alone.

3.4. Effects of heart failure and voluntary activity on gastrocnemius

The effects of 8 weeks voluntary activity on energy metabolism of the fast glycolytic gastrocnemius muscle are presented in Table 4. MB-and BB-CK were undetectable in gastrocnemius muscle. Heart failure induced an overall significant decrease in mi-CK ($P<0.04$), CS ($P<0.001$), as well as basal ($P<0.001$) and maximal ($P<0.001$) respiration rates in gastrocnemius muscle without affecting total CK activity (Table 4), showing the deleterious effects of heart failure on gastrocnemius energetics. However, in
contrary to what was observed in soleus muscle, voluntary activity did not improve mitochondrial parameters.

4. Discussion

Taken together, the results of the present study can be summarized as follows:

1. Heart failure induced decreased oxidative capacity and altered CK expression in cardiac, slow and fast skeletal muscles.
2. Voluntary activity of CHF rats estimated in cages equipped with running wheels was markedly reduced compared to sham.
3. These levels of activity had no effects on anatomical parameters of sham and CHF rats and on mortality rate.
4. Voluntary activity did not modify oxidative capacity or energy metabolism of LV, soleus or gastrocnemius muscles of sham animals except that coupling of oxidation to phosphorylation was slightly increased in the soleus. The work performed by sham animals correlated with both ventricle and soleus mi-CK.
5. However, the low level of activity of CHF rats was sufficient to significantly improve or even normalize metabolic alterations of slow oxidative, but not fast glycolytic muscle.
6. The level of activity strongly correlated with both soleus and ventricle mi-CK activity pointing out the importance of intracellular energy transfer for exercise performance.
7. These results show that even low voluntary exercise can counteract the deleterious effects of heart failure on slow muscle fibers, without further affecting the myocardium.
8. They further indicate that deconditioning is not the only mechanism responsible for the generalized metabolic myopathy in heart failure, suggesting that a circulating factor linked to the general neuro–humoral disorders of heart failure could be involved.

4.1. Effects of heart failure on cardiac and skeletal muscle energetics

Four months after surgery, intrinsic abnormalities including increase in fast MHC-IIa in soleus, decreased oxidative capacity of fibers, altered mitochondrial function and CK energy transfer system are already present, suggesting a generalized metabolic myopathy in heart failure [5–7].

4.2. Effects of activity on cardiac and skeletal muscle energetics

In this study we sought to investigate the real physical ability of the animals together with the effects of prolonged activity on cardiac and skeletal muscle energetics. For this, we chose the model of voluntary wheel running, which avoids stress that could be fatal for CHF rats. Moreover, this allows the animals to volunteer with respect to their day and night life, intensity and pattern of exercise and could reveal peripheral as well as central mechanisms. The counterpart being the large scattering of daily activity of sham animals, which was not observed for CHF, suggesting that heart failure was the limiting factor of physical activity of these animals. On average, sham
animals performed low voluntary activity and did not improve during the 8-week period, as could be expected for aged male rats [22].

CHF animals performed roughly four times less than sham animals, regardless of whether work, running distance, or speed is considered. This low degree of activity had no effects on anatomical parameters. Similarly there was no improvement of the physical capacity of the animals although this could have been masked by the progression of heart failure. More importantly activity did not aggravate or worsen any intrinsic metabolic properties of the myocardium, nor did it increase mortality in the failing animals.

We then studied the effects of voluntary exercise on the metabolic status of slow and fast skeletal muscle in rats. This low degree of activity had no effects on anatomical parameters. Most importantly it did not induce any sign of aggravation or increased mortality in the failing animals at least on parameters attainable in this study. Moreover, there was no worsening in intrinsic metabolic properties of

Fig. 2. Correlation between the level of activity and oxidative capacity (left panel) or mi-CK activity (right panel) in ventricle (A) and soleus (B) muscles of sham and CHF active rats. Continuous line is the linear fit to the data, $R$ is the correlation coefficient and $P$ is the statistical significance.
the myocardium, whether mean values or correlation with individual work of the animals were taken into account. This result is in line with studies showing even that exercise training does not have an unfavorable effect on anabolic/catabolic balance or neurohumoral activation in patients with congestive heart failure and can improve the adverse cardiac remodeling process [25].

The only effect of activity in sham animals was an increase in the coupling between oxidation and phosphorylation in soleus mitochondria. The low level of activity achieved by these old, heavy animals can explain the moderate effects of physical activity on muscle metabolic parameters in the sham animals. Interestingly, there was a strong correlation between mi-CK or respiration and the level of activity suggesting that mi-CK could be a limiting factor in the performance of the animals.

A major finding of this study was the normalized oxidative capacity, oxidative enzymes (CS and mi-CK) and myosin expression in the slow muscle of the CHF rats, despite their low level of voluntary activity. This result is in line with a recent report showing that functional limitation factor in the performance of the animals.

Table 3
Biochemical and respiratory parameters of Soleus muscle of CHF rats

<table>
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<th>Time after surgery</th>
<th>4 months</th>
<th>6 months</th>
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<tr>
<td></td>
<td>S</td>
<td>CH</td>
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<tr>
<td>Myosin isoforms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHC1,%</td>
<td>95.2±3.5</td>
<td>86.2±3.7</td>
</tr>
<tr>
<td>MHC2a,%</td>
<td>4.8±3.5</td>
<td>13.3±3.8</td>
</tr>
<tr>
<td>Biochemical data (I.U./gww)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>ND</td>
<td>0.55±0.55</td>
</tr>
<tr>
<td>CK</td>
<td>33.9±1.6</td>
<td>33.3±1.9</td>
</tr>
<tr>
<td>MM-CK</td>
<td>1418±114</td>
<td>1108±113</td>
</tr>
<tr>
<td>mi-CK</td>
<td>1366±114</td>
<td>1072±106</td>
</tr>
<tr>
<td>LDH</td>
<td>51.9±4.9</td>
<td>33.2±6.1</td>
</tr>
<tr>
<td>LDH H/M ratio</td>
<td>1.99±0.14</td>
<td>1.34±0.05*</td>
</tr>
<tr>
<td>mi-CK protein a.u.</td>
<td>Nd</td>
<td>Nd</td>
</tr>
</tbody>
</table>

*, Significantly different from sham, P<0.05.
†, Significantly different from Sed, P<0.05.
Nd, not determined; ND, not detectable.

Table 4
Biochemical and respiratory parameters of Gastrocnemius muscle of CHF rats

<table>
<thead>
<tr>
<th>Time after surgery</th>
<th>4 months</th>
<th>6 months</th>
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<tbody>
<tr>
<td></td>
<td>S</td>
<td>CH</td>
</tr>
<tr>
<td>Biochemical data (I.U./gww)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>12.9±1.1</td>
<td>6.6±0.5*</td>
</tr>
<tr>
<td>CK</td>
<td>4709±178</td>
<td>4885±285</td>
</tr>
<tr>
<td>MM-CK</td>
<td>6.9±3.3</td>
<td>4.4±3.0</td>
</tr>
<tr>
<td>LDH</td>
<td>4701±178</td>
<td>4877±288</td>
</tr>
<tr>
<td>mi-CK protein a.u.</td>
<td>874±80</td>
<td>945±69</td>
</tr>
<tr>
<td>Respiration parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V̇O₂,max (μmol O₂/min/gdw)</td>
<td>1.6±0.2</td>
<td>1.4±0.1</td>
</tr>
<tr>
<td>ACR</td>
<td>5.4±0.4</td>
<td>3.2±0.2*</td>
</tr>
<tr>
<td>K_mADP (μM)</td>
<td>3.7±0.3</td>
<td>2.6±0.2</td>
</tr>
<tr>
<td>K_mADP+ATP (μM)</td>
<td>9±2</td>
<td>9±2</td>
</tr>
</tbody>
</table>
|*, Significantly different from sham, P<0.05.
†, Significantly different from Sed, P<0.05.
4.3. Factors involved in the metabolic myopathy in heart failure and effects of exercise

An important issue concerns the factors involved in the metabolic myopathy and in the effects of exercise. Deconditioning has been frequently put forward to explain the skeletal muscle alterations in heart failure. However, in animal models, it can be considered that all animals are sedentary. Indeed, attempts to measure free locomotion of animals did not show differences between control and CHF groups [17,26]. Heart and diaphragm that are submitted to increased workload in CHF exhibit similar mitochondrial alterations as skeletal muscles [5,7]. Moreover, dramatic deconditioning induced in sedentary animals by hindlimb suspension failed to induce any modifications in mitochondrial capacity and regulation and induced an increase rather than a decrease in CK activity [2]. Thus deconditioning per se appears not sufficient to explain skeletal muscle metabolic alterations.

Impairment of the endothelial nitric oxide synthase (eNOS) expression in the vascular bed in heart failure may contribute to limitations in exercise capacity through inadequate coronary or peripheral blood delivery, and this could be improved by exercise [16]. Indeed, regular physical activity has been shown to correct endothelial dysfunction, and improves exercise capacity in patients [9,11]. However, the beneficial effects of exercise could, take place in our experimental model, despite the persistent reduced blood flow at the periphery induced by the aortic stenosis.

Recent data suggest that oxidative stress could be related to exercise intolerance in CHF patients [23]. Indeed, enhanced reactive oxygen species (ROS) generation and lipid peroxidation have been observed in limb muscle in a murine model of heart failure [31]. Various neurohormonal factors including catecholamines, angiotensin II and cytokines, all known to increase in heart failure, can activate the generation of ROS. High TNFα (a major cytokine in heart failure) levels are associated with exercise intolerance and neurohormonal activation in CHF patients [3]. As mitochondria and CK are also prone to deteriorate due to oxidative stress [8,15,28], the possibility that increased oxidative stress is responsible for the generalized metabolic alterations should also be envisaged. If this is the case, the restored energy metabolism in soleus muscle could be explained by reduced ROS damage by training. Indeed, it was shown in CHF patients that training induces a specific increase in antioxidative defences that accounts for improved vascular NO-mediated vasodilation [9], while such an effect was not observed in healthy subjects [30,32]. Further studies are needed to assess these different possibilities.

4.4. Relevance to humans

In a recent review, Coats examined history and results of the controlled clinical trials that showed a consistent increase in exercise capacity and physiological benefits following exercise training in CHF patients. Beneficial effects of training include improvements in hemodynamics, endothelial and skeletal muscle function, survival and significant reduction in hospital readmission for heart failure [4]. Our recent study in CHF patients at the time of transplantation showed the preservation of in situ mitochondrial function of vastus lateralis muscle compared to truly sedentary healthy individuals despite lower $V_{\text{O2,max}}$, pointing out the importance of activity (and/or effectiveness of treatment) in the preservation of mitochondrial capacity [20]. Training in patients improves phosphocreatine kinetics, type I fiber content, endothelial and skeletal muscle function. However, there are few reports concerning the improvement in mitochondrial ultrastructure and oxidative enzymes in exercising muscle [1,12,14,24]. Skeletal muscles of humans are composed of a mosaic of the different fiber types, and exercise training could positively affect all recruited fibers, increasing their cellular energy fluxes and oxidative capacity thus participating in increased performance and fatigue resistance of patients undergoing a rehabilitation program.

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References


