Aerobic interval training attenuates remodelling and mitochondrial dysfunction in the post-infarction failing rat heart

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Aims
Following a large myocardial infarction (MI), remaining viable muscle often undergoes pathological remodelling and progresses towards chronic heart failure. Mitochondria may also be affected by this process and, due to their functional importance, likely contribute to the progression of the disease. Aerobic interval training (AIT) has been shown effective in diminishing pathological myocardial transformation, but the effects of AIT on mitochondrial function in hearts undergoing remodelling are not known.

Methods and results
Adult female Sprague–Dawley rats were randomized to either 8 weeks of aerobic interval treadmill running (5 days/week), which started 4 weeks after left coronary artery ligation (MI-Trained), or a sedentary group (MI-Sedentary). Echocardiography was performed before and after the 8-week period, at which point the left ventricles (LVs) were also harvested. Twelve weeks after surgery, MI-Sedentary rats had significantly lower LV fractional shortening compared with MI-Trained rats. Complex I-dependent respiration assessed in isolated LV mitochondria was decreased by ≏37% in MI-Sedentary and 17% in MI-Trained animals (group differences \( P<0.05 \)), compared with sham-operated animals. This was paralleled with diminished ATP production and increased degree of protein oxidation in MI-Sedentary rats. The enzymatic activity of complex I was also decreased to a greater extent in MI-Sedentary than in MI-Trained animals, with no evidence of its reduced expression. When complex II substrate was used, no differences among the three groups were observed.

Conclusion
Exercise reduces LV contractile deterioration in post-infarction heart failure and alleviates the extent of mitochondrial dysfunction, which is paralleled with preserved complex I activity.

Keywords
Myocardial infarction • Heart failure • Aerobic interval training • Animal model • Mitochondria

1. Introduction

Chronic heart failure (CHF), an inability of the heart to pump sufficient blood to meet the metabolic demands of the body, is a complex clinical syndrome characterized by altered cardiovascular, skeletal muscle, and neurohormonal function. Following acute myocardial infarction (MI), adverse cardiac remodelling of the remaining surviving myocardium (remote myocardium) leading to CHF occurs in ≏20% of patients,¹ making acute MI one of the most significant causes of CHF in human population.

Intense research efforts have identified several key factors responsible for the post-MI pathological remodelling in the remote myocardium, including increased ROS production, altered Ca²⁺ regulation, and impaired energy metabolism.²–⁴ Specifically, energy depletion, evidenced by the loss of ATP, rise in ADP, and damaged energy transfer via creatine–phosphocreatine system, is implicated as a central factor in the development of cardiac contractile insufficiency.⁵ Mitochondria are at the centre of cardiac energy metabolism, since they satisfy ≏90% of heart's daily energy requirements through oxidative phosphorylation. Indeed, in the failing heart, mitochondria were shown to undergo pathological structural and functional remodelling. Specifically, changes in mitochondrial size and organization of cristae were described in both human and in animal models of CHF.⁶,⁷ Also, defective oxidative phosphorylation and altered supra-molecular
assembly of the electron transfer chain (ETC) respiratory complexes, as well as their decreased activities, have been described in CHF. However, findings of changes in activities of specific ETC complexes in CHF are very heterogeneous, with various studies pointing to different ETC components being primarily affected.

Beneficial effects of exercise in CHF are well established, with current treatment guidelines recommending exercise for patients with stable CHF in NYHA I–III groups. Exercise was shown to improve patients’ quality of life, decrease fatigue, and reduce the mortality. Exercise training is associated with neurohormonal changes, anti-inflammatory effects as well as cardiovascular, skeletal muscle, and pulmonary adaptations. Long-term aerobic interval training (AIT) was demonstrated to improve left ventricular ejection fraction, cardiac output, and end-diastolic and end-systolic volumes even in elderly CHF patients. At the level of cardiomyocytes, chronic exercise training was shown to ameliorate pathological changes in Ca2+ regulation and improve the contractility of the failing myocardial cells. However, experimental data on the mitochondrial effects of exercise in failing cardiac muscle are still lacking. Therefore, the goal of the current study was to investigate the effects of AIT on mitochondrial function in post-MI failing hearts.

2. Methods

This study was conducted according to the Directive 2010/63/EU of the European Parliament and was approved by the Croatian Animal Care Committee and Ethical Committee of the University of Split School of Medicine. More detailed description of the methods and materials used can be found in the Supplementary material online.

2.1 Chemicals

All chemicals used for this study, unless otherwise noted, were purchased from Sigma-Aldrich (St Louis, MO, USA).

2.2 Coronary artery ligation procedure

Adult female Sprague–Dawley rats (230–290 g) were anaesthetized with a mixture of ketamine (Ketaminol, 90 mg/kg, Intervet International, the Netherlands) and xylazine (Xylapan, 8 mg/kg, Vetoquinol, France) injected in the right hamstring muscle. In fully anaesthetized (confirmed by the absence of corneal reflex) and artificially ventilated animals, MI was induced by permanent ligation of the left coronary artery (LCA) via trans-abdominal, trans-diaphragmal approach. Age-matched control rats (sham animals) underwent the same surgical procedure without the ligation of LCA.

2.3 Echocardiographic measurements

Transrhotacic echocardiography was performed using a 12 MHz transducer connected to the Vivid 3 Expert ultrasound system (General Electric, Milwaukee, WI, USA) under isoflurane anaesthesia (1.5%) at 4 and 12 weeks after the surgery. Parasternal two-dimensional short-axis view at the level of papillary muscles was used to measure the following parameters: left ventricular diameter in diastole and systole (LVDD and LVDS, respectively), anterior wall thickness in diastole and systole, and posterior wall thickness in diastole and systole. Left ventricular fractional shortening (FS, %), was calculated according to the following formula:

\[ FS = \left( \frac{LVDD - LVDS}{LVDD} \right) \times 100. \]

Echocardiographic assessment at 4 weeks after surgery was used to evaluate the extent of MI (in MI-operated rats) and measure the cardiac contractile performance before commencement of further experimental procedures. The animals with high degree of myocardial damage and developed CHF, estimated at FS ≤ 35%, were included in the study. This selection criterion was based on the previous reports that correlated echocardiographic FS values with invasive measurements of left ventricle (LV) pressures for the assessment of heart failure in this animal model. Out of 63 MI-operated animals that survived a 4-week post-operative period, 31 rats met the inclusion criteria and were subsequently randomly assigned to either the MI-Sedentary or the MI-Trained group. During the course of the next 8 weeks, two of the trained animals were excluded from the study due to insufficient compliance for exercise. At 12 weeks after surgery, echocardiography was again performed followed by animal sacrifice within 3–6 days. All echocardiographic evaluations were performed blinded to rats’ group allocation. Finally, three groups of rats were assessed: MI-Trained (n = 14), MI-Sedentary (n = 15), and Sham sedentary (control) groups (n = 16).

2.4 Training protocol

Following echocardiographic evaluation at 4 weeks after surgery, MI-operated rats were randomly assigned to either the MI-Sedentary or the MI-Trained group. No statistical difference in any of the assessed echocardiographic parameters existed between the two groups at this time point. The MI-Trained group started an 8-week AIT protocol 2 days after the echocardiographic evaluation was performed. Animals were running on a treadmill specially designed for small animals (Model Exer-3R, Columbus Instruments, Columbus, OH, USA), 5 days a week for 70 min, including 10 min of warm-up at 40–50% of estimated maximal oxygen consumption (VO2max) and 60 min of interval running. Each interval consisted of 4 min of high-intensity running (estimated at ~85–90% of predicted VO2max) and 2 min of active recovery (estimated at ~50–60% of predicted VO2max). Running intensities for each week of training were based on the previous report studying the relationship between the running speed and VO2max in the same post-MI rat model exposed to AIT for 8 weeks. Specifically, the running speed was increased gradually for the first 6 weeks of training by 0.02 m/s per week, with last 2 weeks (seventh and eighth) having the same intensity level as in the sixth week. Treadmill inclination during training and testing was 25°.

2.5 Isolation of mitochondria

All animals were sacrificed for mitochondrial studies during the period of 3–6 days following the second (12 week) echocardiographic evaluation. Rats were anaesthetized using intramuscular injection of ketamine/xylazine (90 and 8 mg/kg, respectively), the hearts were excised, and mitochondria were isolated from the viable part of the LV by differential centrifugation as previously described.

2.6 Citrate synthase activity

Citrate synthase activity was determined spectrophotometrically (at 412 nm, 25°C) in isolated mitochondrial preparations using the kit from Sigma-Aldrich (CS0720).

2.7 Measurement of mitochondrial oxygen consumption

Mitochondrial oxygen consumption was measured at 30°C using an oxygen electrode (Oxygraph, Hansatech Instruments, Norfolk, UK). State 2 respiration was assessed in the presence of ETC complex I substrates pyruvate and malate (5 mmol/L each) or complex II substrate succinate (5 mmol/L) with complex I inhibitor rotenone (1 μmol/L). Respiration was then measured upon stimulation with ADP (250 μmol/ L, state 3), and after all ADP was consumed (state 4).
2.8 Measurement of mitochondrial ATP production rate

The rate of mitochondrial ATP production in the presence of different substrates was determined with a chemiluminescence-based method utilizing firefly luciferase and luciferin (Molecular Probes, Invitrogen, Eugene, OR, USA), as previously described. 18

2.9 Complex I (NADH: ubiquinone oxidoreductase) activity assay

Previously frozen mitochondria were thawed and solubilized on ice with 1% cholic acid in an MSM/EDTA buffer. Complex I enzymatic activity was determined by rotenone-sensitive reduction of NADH absorbance using decylubiquinone as an acceptor. The reaction mixture containing 20 μg/mL mitochondrial protein was warmed at 30°C, and transferred into a pre-warmed cuvette in a spectrophotometer (DU 800, Beckman Instruments, Fullerton, CA, USA). The reaction was initiated by adding decylubiquinone (0.075 mmol/L), and the change in NADH absorbance was measured at 30°C (regulated by a Peltier temperature controller) at 340 nm [extinction coefficient = 6.22 (mmol/L)⁻¹ cm⁻¹].

2.10 Western blotting

Following excision of atria and scar tissue, LVs were homogenized using Ultra-Turrax T25 in modified RIPA buffer supplemented with protease and phosphatase inhibitors. Cardiac homogenates were then separated by SDS–PAGE. After electrophoresis and transfer, the nitrocellulose sample and loading control) were analysed using the Image Lab 3.0 software and expressed relative to the Sham group. Differences in echocardiographic parameters at 4-week post-surgery between sham-operated and MI-operated animals were tested by the Kruskal–Wallis test followed by a posteriori Mann–Whitney comparisons. Differences in echocardiographic parameters at 4-week post-surgery between sham-operated and MI-operated animals were tested by the Kruskal–Wallis test followed by a posteriori Mann–Whitney comparisons.

2.11 Detection of protein oxidation

Protein carbonylation was assessed in LV homogenates, using the OxyBlot protein oxidation detection kit (S7150, Merck Millipore) according to the manufacturer’s instructions.

2.12 Statistical analysis

Data are presented as means ± standard deviation. Differences between MI-Trained, MI-Sedentary, and Sham sedentary rats were tested using the Kruskal–Wallis test followed by a posteriori Mann–Whitney comparisons. Differences in echocardiographic parameters at 4-week post-surgery between sham-operated and MI-operated animals were tested by the Kruskal–Wallis test followed by a posteriori Mann–Whitney comparisons.

<table>
<thead>
<tr>
<th>Table 1 Cardiac morphological and functional parameters after surgery and exercise training</th>
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<tr>
<td>Four-week post-surgery</td>
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<tr>
<td>FS (%)</td>
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<tr>
<td>LVDDd (mm)</td>
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<td>LVDDs (mm)</td>
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<td>AWTd (mm)</td>
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<td>PWTS (mm)</td>
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Values presented are mean ± SD. FS, left ventricular fractional shortening; LVDDd and LVDDs, left ventricular diameter in diastole and systole, respectively; AWTd and AWTS, anterior wall thickness in diastole and systole, respectively; PWTd and PWTS, posterior wall thickness in diastole and systole, respectively; W, body weight; W, heart weight.

*P < 0.05 vs. Sham.  
#P < 0.05 vs. Sham and MI-Sedentary.  
†P < 0.05 vs. 4-week value.
with the Mann–Whitney test for independent samples. Differences between 4- and 12-week post-operative echocardiographic values within the same group of rats were probed with the Wilcoxon test for paired samples. Statistical analysis was performed by employing commercially available software (MedCalc, Mariakerke, Belgium), and significance was accepted at $P < 0.05$.

3. Results

Echocardiography data are presented in Table 1. Four weeks after surgery, animals that underwent coronary artery ligation and exhibited LV FS $< 35\%$ were selected for the study (MI-operated group). As seen in the table, and also illustrated in Figure 1A, these animals had enlarged ventricular cavity and thinned myocardium comparing with the sham-operated animals. Twelve weeks after surgery, the contractile function of the LV deteriorated even further in the MI-Sedentary group (Figure 1B), while FS in the MI-Trained group remained at the 4-week level.

Twelve weeks after surgery, the expression of atrial natriuretic peptide in the LV, which is often found enhanced in pathological cardiac hypertrophy, was increased to a similar extent in MI-Trained and MI-Sedentary groups, when compared with the Sham (Figure 2) group. The expression of citrate synthase, a mitochondrial marker, was not changed in any experimental group (Figure 2), nor was its specific enzymatic activity different in isolated mitochondria ($1793 \pm 191$, $1925 \pm 205$, and $1853 \pm 212$ mU/mg protein for Sham, MI-Sedentary, and MI-Trained groups, respectively, (data not shown)). Furthermore, no difference was found in the LV expression of PGC-1$\alpha$, a marker of mitochondrial biogenesis (Figure 2).

Respiratory function of LV mitochondria was also analysed at 12 weeks after surgery. As displayed in Figure 3A, in the presence of complex I ETC substrates, ADP-supported respiration (state 3) was significantly reduced in mitochondria from MI rats, when compared with sham. However, it was better preserved in animals exposed to 8 weeks of exercise training ($211.5 \pm 38.1$ vs. $160.2 \pm 45.4$ nmol O$_2$/min/mg protein in MI-Sedentary rats and $254.1 \pm 38.8$ nmol O$_2$/min/mg protein in sham). The respiratory control ratio (RCR), calculated as the ratio of state 3 and state 4 respiration and used as an indicator of coupling of O$_2$ consumption and phosphorylation, was reduced only in MI-Sedentary rats, whereas in the trained animals, it remained at the same level as in Sham (Figure 3B).

When mitochondria were fuelled with substrates for complex II, no difference in ADP-supported respiration or the RCR between the Sham and any of the MI-operated animal groups was observed (Figure 4A and B). Measurements of mitochondrial ATP production were conducted in parallel with oxygen consumption experiments. In the presence of pyruvate and malate, the rate of ATP generation was significantly decreased only in mitochondria from MI-Sedentary

![Figure 1](https://academic.oup.com/cardiovascres/article-abstract/99/1/55/324269/19165524268) by guest on 27 March 2019

**Figure 1** Echocardiographic evaluation of operated animals. (A) Examples of M-mode of two-dimensional echocardiograms taken at 4 weeks after surgery in Sham-operated and animal with coronary artery ligation (MI-operated). In animal with induced MI, increased left ventricular cavity dimensions and reduced contractility and thickness of the ventricular muscle can be seen. (B) Left ventricular FS at 4 and 12 weeks after surgery. Sham, Sham-operated sedentary animals ($n = 16$); MI-Sed, sedentary animals with induced MI ($n = 15$); MI-Trained, animals with MI exposed to 8 weeks of exercise training ($n = 14$). *$P < 0.05$ vs. MI-Sed and MI-Trained, †$P < 0.05$ vs. MI-Sed, ‡$P < 0.05$ vs. 4-week value in the same group.
rats, when compared with Sham (Figure 5A). When succinate was used as an electron donor, no change in ATP production was observed in any of the tested groups.

Since data obtained from respiratory and ATP production measurements suggested ETC damage primarily at the level of complex I, we next measured the specific enzymatic activity of NADH: ubiquinone oxidoreductase in isolated mitochondria. Recording the rate of complex I enzymatic turnover revealed a similar pattern as detected in respirometry experiments. As can be inferred from Figure 5B, relatively high rate of NADH oxidation observed in Sham mitochondria (641.2 ± 68.3 nmol NADH/min/mg mitochondria) was substantially impaired in MI-Sedentary hearts (486.8 ± 35.3 nmol NADH/min/mg).

In mitochondria isolated from MI-Trained rats, although still depressed compared with Sham, the complex I activity was significantly better preserved than in the MI-Sedentary group (552.3 ± 39.4 nmol NADH/min/mg for MI-Trained). Probing the expression of the representative subunits for mitochondrial ETC respiratory complexes I, II, III, and V revealed no differences between the three experimental groups (Figure 6A and B). Whether a reduction in complex I activity is accompanied with altered degree of oxidative stress was also investigated. Protein carbonylation, an indicator of oxidative stress, was significantly increased in MI-Sedentary hearts with respect to Sham (Figure 6C and D), whereas MI-Trained rats showed no significant difference compared either with Sham or with MI-Sedentary rats.

Figure 2 Expression of atrial natriuretic peptide (ANP), citrate synthase and PGC-1α. (A) Image of representative western blots probed with anti-ANP, anti-citrate synthase, and anti-PGC-1α primary antibodies. (B) Average densities normalized to β-actin expressed relative to the Sham group. *P < 0.05 vs. MI-Sedentary (MI-Sed) and MI-Trained (MI-Tr), n = 6 animals per group. PC, PGC-1α positive control.
4. Discussion

The main finding of the present study is that AIT attenuates deterioration of mitochondrial function in post-infarction heart failure in rats. This is evidenced by better preservation of mitochondrial respiratory capacity and activity of the complex I of the ETC in animals that underwent 8 weeks of AIT, when compared with their sedentary counterparts.

In our study, we observed impaired mitochondrial function in the LV of the failing hearts, which is primarily attributable to the reduced activity of complex I of the ETC. This is evidenced by significantly decreased respiratory rates observed in mitochondria energized with specific complex I substrates. Moreover, measurement of complex I enzymatic activity revealed a diminished rate of NADH oxidation in mitochondria from infarcted hearts of sedentary animals, when compared with sham. Decreased complex I-dependent respiratory capacity was reported in saponin-permeabilized cardiac fibres in a similar animal model, but also in dog and human ischaemic dilated cardiomyopathy. Furthermore, a specific decrease in complex I enzymatic function, with preserved activity of other ETC complexes, was found in explanted failing human hearts, when compared with healthy donor hearts. Reduced complex I function may result from its diminished expression, as reported previously in a mouse model of post-infarction heart failure, where it was linked to LV mitochondrial DNA damage. In our model, this possibility is less likely, since the expression level of complex I representative subunit was not altered in MI-Sedentary rats. This is also in line with the study of Scheubel et al., where the mRNA levels of complex I subunits were not differentially expressed in human failing LV, despite the enzymatic activity of the entire complex being reduced. Alternatively, complex I activity may be depressed due to its specific inhibition. For example, a state of prolonged inflammation that persists in chronically failing heart was linked to enhanced activity of inducible nitric oxide synthase (NOS2). NO may act directly (S-nitrosylation) or via peroxynitrite formation (generated through interaction with reactive oxygen species) on complex I, selectively reducing its activity.

Reduced mitochondrial capacity for substrate metabolization, as observed here, may result in the decline of ATP production, which would cause substantial energy deficits in the muscle required to daily provide up to 30 kg of this energy-rich molecule. Indeed, in
cardiac mitochondria of post-MI sedentary animals, the rate of ATP production with complex I substrates was significantly reduced compared with that of sham-operated animals. This decreased ATP-producing potential, which may be coupled with the reported reduction in creatine kinase activity and creatine transporter function, is likely to contribute to cardiac contractile dysfunction, due to deficit in production and intracellular transfer of high-energy phosphates. Furthermore, deficiencies in complex I of the ETC were linked to excessive production of reactive oxygen species, inflicting damage to other cellular and mitochondrial elements. Indeed, we detected increased protein carbonylation in post-infarcted myocardium, indicating increased levels of oxidative stress. Therefore, owing to mitochondrial involvement in a number of cellular processes and a central role in myocardial energy production, their dysfunction likely causes further damage to the cardiac muscle and elicits progression of the disease.

In our animal model, echocardiographic evaluation also revealed progressive deterioration of LV contractile function in post-MI sedentary animals from 4 to 12 weeks after surgery, indicating further aggravation of the disease. In contrast to the post-MI sedentary animals, rats with high degree of myocardial damage that underwent 8 weeks of exercise training exhibited better preservation of LV contractile function and reduced cavity dilatation. This is in agreement with data, both from patients and animal models, showing that physical activity attenuates or even reverses pathological ventricular remodelling in CHF of various aetiologies. Therefore, exercise training, which was previously considered a risk for patients with post-infarction chronic heart disease, has recently been attributed a strong therapeutic potential for this condition. Although the beneficial effects of physical activity in a diseased heart have been associated with exercise training of different mode, intensity, and duration, AIT, with alternating high- and low-intensity exercise periods, was reported superior to other types of exercise, such as strength, endurance, or moderate continuous training. Its protective potential has been demonstrated in animal and human studies, through the significant reduction of pathological left ventricular remodelling.

There are multiple mediators and pathways suggested to underlie the beneficial exercise-induced effects in pathologically remodelled hearts. Some of them include enhanced endothelium-dependent vasodilatation and improved coronary blood flow, which may improve oxygen and substrate supply to the myocardium. In cardiac myocytes, chronic exercise has been reported to restore Ca²⁺ sensitivity and handling, thus, improving their contractility. In the model of post-MI failing heart used here, the existence of energetic imbalance in the myocardium is very likely, owing to the additive effect of at least two factors: the observed reduction in mitochondrial function and greater energy demand in a dilated heart. Therefore, we sought to investigate whether exercise improves the function of pathologically remodelled mitochondria in the failing myocardium. We demonstrated that mitochondrial respiratory capacity, which was significantly compromised by post-MI remodelling in sedentary animals, was better preserved in rats subjected to the training protocol. Higher respiratory rates observed in the trained animals were likely due to better preservation of complex I function. Measurements of complex I enzymatic activity further support this observation, as the NADH oxidation was maintained at the higher level in cardiac mitochondria of post-MI trained than in MI-Sedentary rats. The extent of protein carbonylation and oxidative stress in MI-Trained animals was found to be somewhere between the Sham and the MI-Sedentary group, with no statistically significant difference with either of them. Exercise-induced reduction in myocardial remodelling and mitochondrial protection was also documented recently in the swine model of pressure-overload heart failure; although the specific contribution of complex I was not investigated, cardiac mitochondria from trained animals exhibited lesser increase in sensitivity to the permeability transition.

The mechanism of the protective effect of exercise on complex I activity and on the overall mitochondrial function in the failing heart is still unknown. High levels of proinflammatory cytokines associated with this disease can elicit a number of cellular events (such as increased expression of NO₂⁻), thus, potentially contributing to the progression of ventricular remodelling and mitochondrial

Figure 5 Analysis of ATP production rate and the activity of complex I of the ETC. (A) The rate of ATP generation was assessed in isolated mitochondria in the presence of respiratory chain substrates, pyruvate and malate (complex I), or succinate (complex II), n = 8 animals for MI-Sedentary (MI-Sed) and MI-Trained and 7 animals for the Sham group. (B) The enzymatic turnover of NADH:ubiquinone oxidoreductase (complex I) was assessed in solubilized mitochondria by recording the change of NADH absorbance in a reaction stimulated with decylubiquinone. *P < 0.05 vs. Sham, *P < 0.05 vs. MI-Sed and Sham, n = 8 animals for each group.
Figure 6  Expression of the ETC respiratory complexes and protein carbonylation. (A) The image of the representative western blot showing bands corresponding to mitochondrial respiratory complexes I, II, III, and V. (B) Average densities normalized to β-actin expressed relative to the Sham group. CI corresponds to complex I; CII, complex II; CIII, complex III; and CV is complex V, n = 6 animals for each group. (C) The image of representative western blot showing carbonylated proteins after derivatization with dinitrophenyl hydrazine. (D) Average protein carbonylation normalized to Ponceau staining and expressed relative to the Sham group. *P < 0.05 vs. Sham, n = 6 animals per group.
Exercise protects mitochondria in the failing heart

dysfunction. Exercise training was reported to oppose the inflammatory cytokine effects in experimental models of chronic heart disease, which might counterbalance their detrimental actions, including those affecting mitochondria. Increased myocardial expression of antioxidant enzymes, also related to exercise training, may also confer mitochondrial protection against the proposed ETC inhibition by reactive oxygen and nitrogen species. Furthermore, exercise was shown to reduce the excessive sympathetic activity that is usually by nitric oxide: crucial role of S-nitrosylation of mitochondrial complex I and protection conferred by exercise has a significant potential to repress this vicious cycle and alleviate the progression of contractile dysfunction in post-infarction failing heart.

Supplementary material

Supplementary material is available at Cardiovascular Research online.

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References

5. Neubauer S, Horn M, Cramer M, Harre K, Newell JB, Peters W et al. Myocardial mitochondrial metabolic function and biogenesis. However, the PGC-1α down-regulation is not uniformly present in the failing myocardium, and, in our model, we did not observe altered PGC-1α levels in any post-MI animal group.

In conclusion, we demonstrated that AIT in rat post-infarction CHF model mitigated contractile deterioration of the LV. This was parallel with better preservation of mitochondrial functional parameters, as evidenced by the preserved activity of complex I of the ETC. Since damaged mitochondria contribute to the myocardial functional decline through multiple pathways, their protection conferred by exercise has a significant potential to repress this vicious cycle and alleviate the progression of contractile dysfunction in post-infarction failing heart.

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