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Original Article

Combined aerobic exercise reduces myocardial injury by protecting mitochondria import machinery in rats with acute myocardial infarction

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Abstract: Background and Aim: Myocardial infarction (MI) is accompanied by increased reactive oxygen species (ROS) which causes DNA damage and mitochondria dysfunction, resulting in cell necrosis. Mitochondrial function includes respiration and calcium handling and integrity, requiring import of proteins from cytosol via the translocase of the outer and inner membrane (TOM and TIM complexes). In the present study, we investigated the effects of MI on import machinery and the possible mechanism of combined aerobic exercise (CAE) protecting against heart injury using a rat model of myocardial infarction. Methods: MI rats were established by ligation of the coronary artery left anterior descending artery. This CAE program contained 3 weeks of continued exercise before surgery and 8 weeks of intermittent exercise beginning the second week after surgery. We assessed the effects of combined long term aerobic exercise on expression of cardiac OGG1 and resulting effects on Tom40, Tom20, and Tim23 in MI model of rats. Our combined long term aerobic exercise program took 3 weeks of exercise before myocardial infarction and 8 weeks of intermittent aerobic exercise after myocardial infarction. Expression of parts of the mitochondria import machinery were detected from the infarction adjacent region located in the left ventricle. Conventional morphological staining and ultrastructure observation were used to evaluate myocardial tissue structure change, collagen deposition, and ultra-structure change. ECG, heart coefficient, and hemodynamics assay were used to evaluate cardiac function. Results and Conclusions: CAE significantly reduced the infarction area, attenuated myocardial fibrosis and ultrastructure injury, and improved cardiac function in rats with MI. Combined pre-MI and post-MI exercise was more effectively protective than only one intervention. Results of Western blot indicated that CAE enhanced expression of mitochondrial DNA repair enzymes in MI rats. In addition, CAE improved mitochondrial function by upregulating expression of mitochondria import machinery.

Keywords: Myocardial infarction, aerobic exercise, mitochondria import machinery

Introduction

Cardiovascular diseases are major diseases that endanger human health. Coronary artery disease is the most prevalent exhibition. Coronary artery diseases, including myocardial infarction (MI), have a high mortality worldwide. Open coronary artery by-pass grafting (CABG) surgery is a main clinical treatment for coronary artery disease but it is not widely accepted due to morbidity and mortality caused by adverse postoperative syndrome. Therefore, it is urgent that we find a safer and more effective method to protect the heart from myocardial ischemia. A large number of epidemiological studies have shown that regular aerobic exercise is associated with low morbidity and mortality in healthy individuals [1]. Exercise can improve cardiac function and myocardial remodeling after MI [2] and plays an important role in treatment of coronary artery diseases [3]. The mechanism of exercise on protecting injured hearts, however, remains relatively unknown.

Several studies have proposed that reactive oxygen species (ROS) plays an essential role in the pathogenesis of MI [4]. ROS such as superoxide anions ($.O_2^-$) and hydroxy radicals (.OH) damage membrane phospholipids, proteins, and DNA [5]. During early stages of injury, ROS

can be prevented by superoxide dismutase (SOD), glutathione peroxidase (GSHPx), and catalase as well as by other non-enzymatic antioxidants. However, continued ROS production makes the antioxidant system unbalanced and excessive ROS can cause tissue structure and function damage. The main source of ROS is mitochondria, including mitochondrial electron transport. ROS inhibits mitochondrial import, affecting mitochondrial structural elements and metabolic pathways and further affecting function of mitochondria [6]. Prevention of damage of the mitochondrial biogenesis has been suggested as a potential mechanism to provide cardioprotection against MI-originated cell death [7]. It has been demonstrated that moderate aerobic exercise improves cardiac dysfunction of diabetic cardiomyopathy by restoring mitochondrial membrane potential and preventing excessive mitochondrial fission [8]. In addition, aerobic exercise training has been suggested to attenuate endoplasmic reticulum (ER) stress, oxidative stress, and calcium imbalances in heart failure animal models [9]. In the present study, our aim was to investigate whether combined pre-MI and post-MI exercise could protect heart injuries after MI by inhibiting mitochondrial DNA damage and downregulation of expression of mitochondrial transporter protein, providing a new approach for prevention of development of myocardial infarction through exercise.

Materials and methods

Experimental animals

Male Sprague-Dawley rats, 3-months old, were purchased from the Laboratory Animal Center of Xi'an, Jiaotong University. All rats were maintained in conventional facilities at Shaanxi Normal University with free access to chow food and water. Animal studies were in accordance with guidelines for animal experimentation and approved by the Review Committee for Use of Human or Animal Subjects of Shaanxi Normal University.

After all rats were adapted and fed for one week, they were assigned to one of the following four groups: 1) Sedentary plus MI plus Sedentary group (S-MI-S); 2) Three weeks of exercise plus MI plus Sedentary group (E-MI-E); 3) Three weeks of exercise plus MI plus eight weeks of exercise group (E-MI-E); 4) Sedentary plus MI plus eight weeks of exercise group (S-MI-E). After 3 weeks of being sedentary or with exercise training, MI operations were performed. The following eight weeks of exercise were carried out beginning the second week after MI.

Treadmill training

A motorized rodent treadmill (DSPT-202, Li Tai Technology, Hangzhou, China) was used in our training protocol. In our study, we used two modes of training programs. The three weeks of aerobic exercise program before MI was initiated for rats to adapt to training for five days. Exercise intensity was 15 m/min and 20 min/d. Speeds were up to 27-30 m/min, 25 min/d-30 min/d the second week, and 30 m/min, 60 min/d the third week. The later intermittent training program was performed, as described previously [10]. Post-MI exercise was performed one week after myocardial infarction. After surgery, rats began five days of adaptive training: 15 m/min and 30 min/d. The following exercise group ran five days per week for 60 minutes at speeds of 25 m/min for 7-min and 15 m/min for 3 min, a total of 8 weeks. All animals had a 5 minute warm-up and cool down with speeds of 15 m/min. At the end of the study, animals were sacrificed 48 hours after the last training.

Myocardial infarction procedure

After 3 weeks of aerobic exercise, rats were anesthetized by injecting 5% pentobarbital sodium (30 mg/kg) and ventilation. MI surgical procedure was performed using the previously described method [11]. In brief, the left coronary artery was ligated with a 6.0 suture silk. Elevation of ST-segment in electrocardiogram (ECG) was viewed as a marker of myocardial infarction.

Electrocardiogram and invasive hemodynamic measurements

ECG was recorded to monitor establishment of the MI model and to detect myocardial ischemia. Hemodynamics were measured to detect the cardiac function of rats. After an intraperitoneal injection of pentobarbital anesthesia (30 mg/kg), right carotid artery of rat was separated, a special catheter connected with pressure sensor was inserted into the left ventricle

Table 1. Effects of aerobic exercise on ECG parameters and HC in rats

	QRS interval (ms)	QT interval (ms)	T wave voltage (μV)	HC (mg/g)
S-MI-E	46.25±1.39▲▲	69.3±8.07▲▲	117.86±31.92▲	3.89±0.39▲
E-MI-S	47.69±4.35▲▲	67.38±6.75▲▲	90.10±10.81	3.80±0.32
S-MI-S	53.80±2.78	78.71±3.82	72.00±21.99	3.51±0.32
E-MI-E	45.43±1.27▲▲	61.25±2.19▲▲,★★,#	131.56±55.08▲▲,#	4.06±0.24▲▲

S-MI-E, aerobic exercise after the MI group, E-MI-S, aerobic exercise before the MI group; S-MI-S, MI group; E-MI-E, continuous aerobic exercise with the MI group; HC, heart coefficient; Data are expressed as mean ± SD (n>4). ▲p<0.05, ▲▲p<0.01 vs S-MI-S; ★★p<0.01 vs S-MI-E; #p<0.05 vs E-MI-S.

through right carotid artery. Left ventricular systolic blood pressure (LVSP), left ventricular end diastolic pressure (LVEDP), left ventricular pressure maximal rate of rise (+dp/dt max), and maximum rate of decline (-dp/dt max) indicators were measured by using RM6240 physiological signal acquisition system.

Morphological and ultrastructural observation [12]

Heart samples were harvested, fixed, sectioned, and stained with Masson's trichrome. For electron microscopy, heart tissues were fixed in a mixture of 2.5% glutaraldehyde and subsequently post-fixed in 2% cacodylate-buffered osmic acid and embedded in Epon 812. Ultrathin section thickness was 50-60 nm. After uranyl acetate and lead citrate double staining, images were acquired by transmission electron microscopy (Hitachi H-7650).

Western blot analysis

Total tissue lysates were prepared from the left ventricle by homogenization in RIPA buffer containing a mixture of protease inhibitors aprotinin, phenylmethyl-sulfonyl fluoride (PMSF), and sodium orthovanadate. Protein concentration was calculated according to the method of BCA. Equal amounts of total protein (20 μg) were resolved on a 10% sodium dodecyl sulfate (SDS)-polyacrylamide gel and transferred to a nitrocellulose membrane (Hybond TM-P; Amersham Biosciences, Piscataway, NJ, USA). After blocking for 30 minutes in 3% bovine serum albumin (BSA), membranes were incubated with primary antibodies OGG1 (1:500 dilution), Tom40 (1:500 dilution), Tom20 (1:500 dilution), and Tim23 (1:200 dilution) at 4°C overnight. The second day, after washing three times with TBST, membranes were incubated with an anti-rabbit secondary antibody linked to horseradish peroxida-se (HRP) (dilution 1:5000; Jackon, USA) for 2 hours at room temperature. After washing three times, chemiluminescence substrate ECL (Millipore) was utilized to detect immunoreactive proteins. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was invoked as a loading control.

Statistical analyses

Densitometry of Western blot images was performed using Image J software. All data were analyzed using one-way ANOVA with SPSS19.0 software. Data are expressed as mean ± SD. P<0.05 and P<0.01 were considered statistically significant.

Results

Combined aerobic exercise attenuates MI-induced cardiac remodeling and heart dysfunction

In order to evaluate the effects of exercise on cardiac remodeling and heart function in MI rats, we detected heart weight and morphological changes. Our results showed that, compared with S-MI-S group, the body weight of rats in S-MI-E and E-MI-S groups had a decreased tendency. Continual exercise before and after MI significantly reduced the body weight of rats (p<0.01). In addition, exercise had a significant effect on heart weight and heart weight/body weight in S-MI-E and E-MI-E (p<0.05) (**Table 1**). We further analyzed infarct size and ventricular wall thickness (VWT) by TTC (2, 3, 5-three triphenyltetrazolium chloride) staining. MI induced a significant increase in ischemia areas and chambers of the heart and a reduction in ventricular wall thickness. Exercise markedly reduced infarct size and prevented decline of ventricular wall thickness (VWT) (p<0.05, p<0.01) (**Figure 1**). The effects of combined pre-and post-exercise are better than single exercise intervention.

Before MI operation, the phenotype of ECG had no abnormalities in each group. After MI,

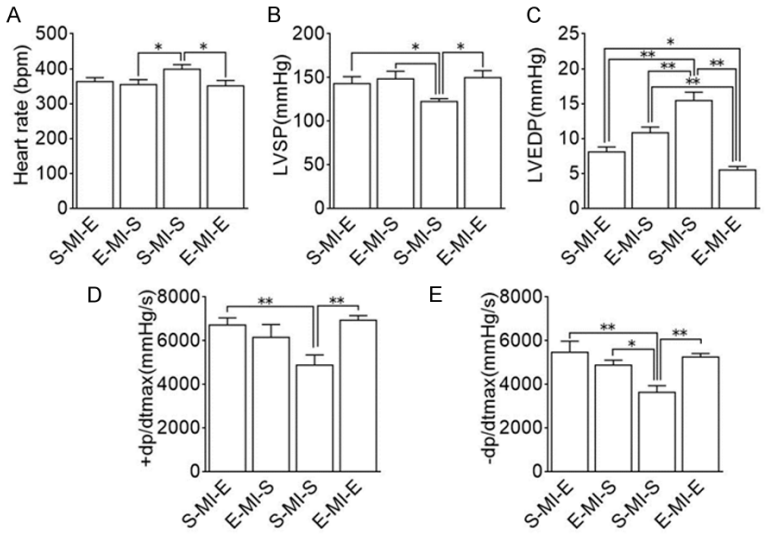

Figure 1. Effects of combined aerobic exercise on hemodynamic parameters in rats. (A) heart rate; (B) LVSP, left ventricular systolic pressure; (C) LVEDP, LV end-diastolic pressure; (D) + dp/dtmax, positive maximum values of the instantaneous first derivative of LV pressure and (E) -dp/dtmax, negative maximum values of the instantaneous first derivative of LV pressure were detected by physiological signal acquisition system in each group.

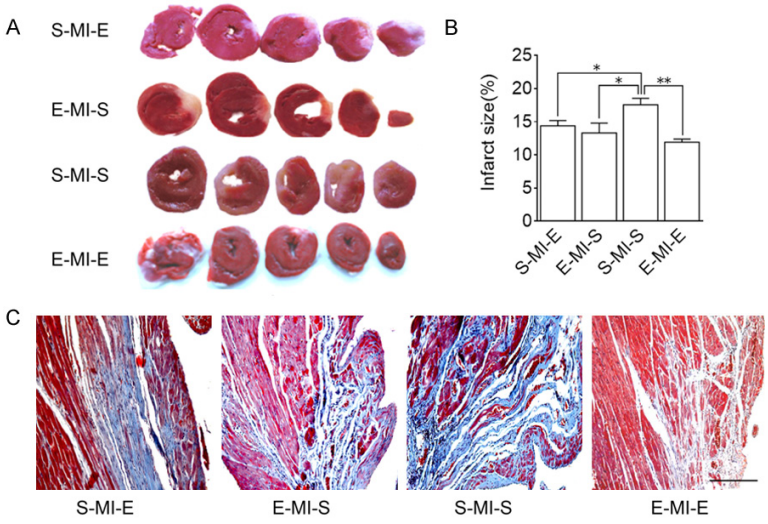

Figure 2. Effects of combined exercise on infarct size and myocardial fibrosis. (A and B) Infarct size and ventricular wall thickness (VWT) was analyzed by TTC. Exercise reduced infarct size after MI and prevented ventricular wall becoming thinner. Data are mean + SD (n = 3); *p<0.05; **p<0.01; (C) Heart fibrosis was evaluated by Masson's staining. Exercise reduces fibrosis of the heart tissue.

ST-segment elevation and T-wave changes suggested that myocardial infarction model was successfully performed (data not shown). Compared with S-MI-S, QRS interval and QT interval in S-MI-E and E-MI-S were significantly decreased (p<0.01) and T-wave voltage of S-MI-E and E-MI-E increased significantly (p<0.01, p<0.05). Combined pre-MI and post-MI exercise significantly reduced QT interval when compared with S-MI-E and E-MI-S groups (**Table 1**).

To analyze exercise effects on cardiac function in MI rats, invasive hemodynamic experiments were performed. Results showed that heart rate and LVEDP decreased slightly in S-MI-E group. LVSP and dp/dtmax significantly increased (p<0.05, p<0.01). Continual exercise, before and after MI, prevented the increase of heart rate and LVEDP and ameliorated LVSP and dp/dt max. Results of our present study indicate that combined exercise ameliorates heart dysfunction accompanied by MI (**Figure 2**).

Combined aerobic exercise attenuates MI-induced cardiac fibrosis deposition and ultrastructural damage

To assess long-term exercise effects on cardiac fibrosis caused by MI, we used Masson's trichrome staining. MI significantly increased interstitial fibrosis, collagen fibers extend to surrounding interstitial in the infarct border zone, and noninfarct area. However, both pre- and post- MI effectivly reduced myocardial infarct size and MI-induced interstitial fibrosis was significantly reduced in sustained exercise group (**Figure 2**).

In this experiment, we observed effects of exercise on myocardial ultrastructure of MI with an electron microscope. The ultrastructure of experimental results showed that MI induced sarcomeres to arrange disorderly and the structure of mitochondria was destroyed, presenting

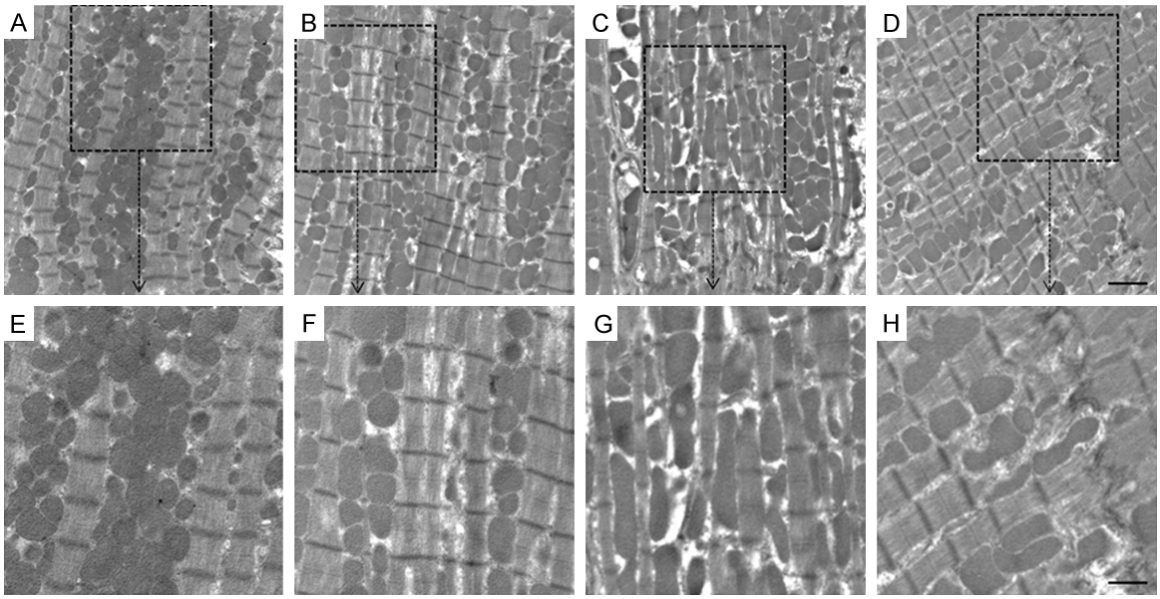

Figure 3. Effects of combined exercise on myocardial ultrastructure of MI with electron microscope. (A) S-MI-E, aerobic exercise after the MI group, (B) E-MI-S, aerobic exercise before MI group; (C) S-MI-S, MI group; (D) E-MI-E, continuous aerobic exercise with the MI group; Scale bar: 2 μm; (E-H) The image is an amplification of the upper black box with scale bar is 1 μm.

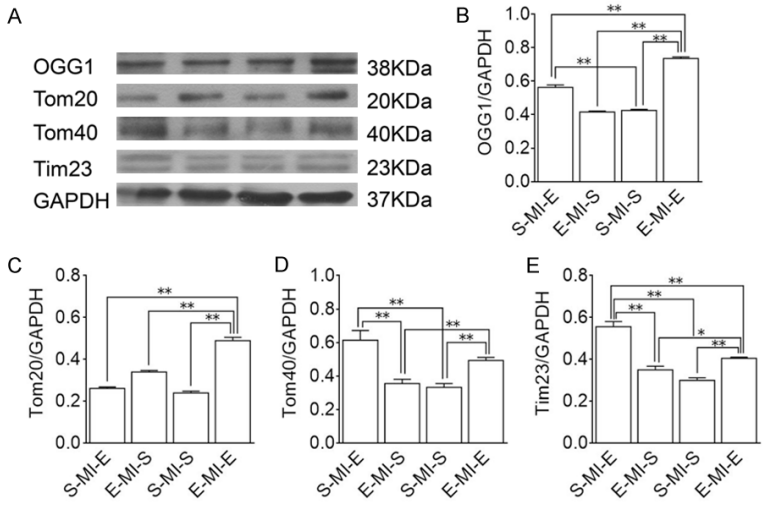

Figure 4. Effects of combined exercise on cardiac OGG1, Tom20, Tom40, and Tim23 expression with MI. Data are expressed as mean ± SD (n = 3). Expression of cardiac OGG1, Tom20, Tom40, and Tim23 was detected using Western blot. The results show that myocardial infarction decreased expression of OGG1, Tom20, Tom40, and Tim23 significantly, which was significantly increased by aerobic exercise. Effect of combined pre-MI and post-MI exercise increased more than a single intervention; *p<0.05, * *p<0.01.

the cristae disappeared and vacuoles increased. Exercise increased the number of mitochondria and ameliorated cell damage in MI rats. Sarcomere and intercalated disc arrangement was more regular in E-MI-E group than the single intervention group (**Figure 3**).

Combined aerobic exercise protects mitochondrial function by preventing injury of mitochondria import machinery

Expression of the OGG1 protein in S-MI-E, E-MI-S, and E-MI-E groups was significantly higher than that in S-MI-S group ($p<0.01$). Combined exercise significantly increased OGG1 expression ($p<0.01$). When compared with the S-MI-S group, expression of Tom40, Tom20, and Tim23 had no significant differences between S-MI-E and E-MI-S group, whereas it was significantly increased in E-MI-E group ($p<0.01$). These results suggest that constant exercise may prevent protein transport mechanism from impairing myocardial infarction (**Figure 4**).

Discussion

This study investigated the protective role of combination of aerobic exercise, before and after MI, on protecting mitochondrial protein transport function in rats with MI. The main findings were as follows: 1) 3 weeks of exercise preconditioning and combination of aerobic exercise, before and after MI, ameliorated LV dysfunction and interstitial fibrosis. 2) Combining aerobic exercise, before and after MI, improved myocardial ultrastructure. 3) Combination of aerobic exercise, before and after MI, protected myocardial mitochondrial function through preventing decrease of channel proteins. These findings highlight the importance of continuous aerobic exercise as a non-pharmacological therapy for cardiac diseases.

The results of ECG and TTC staining showed that the MI model was accomplished. In agreement with previous reports [13], MI resulted in LV remodeling and LV pump dysfunction. We observed that exercise of rats, via 3 weeks of treadmill training, blunted LV dysfunction induced post-MI. It has been reported that exercise after MI decreases LV pump dysfunction in mice [14]. Clinical studies, as well, have suggested that moderate exercise improves the structure and function of left ventricle with 40% infarction area [15, 16]. In contrast, the effect of exercise within 1 week or without 1 week after MI is two-sided. Movement starting 3 weeks after MI had no good effect on healing of myocardial infarction and even enlarged the chambers of heart and induced myocardial hypertrophy [17]. High-intensity intermittent aerobic exercise protocols, 1 week after MI, was referenced by Wisløff et al. [18] No deaths were reported in the whole training process.

MI leads to pathological remodeling of the left ventricle and impaired left ventricular function. Left ventricular remodeling is an independent risk factor for development of heart failure [19]. After 8 weeks of MI, malignant left ventricular remodeling occurred including myocardial interstitial collagen deposition, myocardial hypertrophy, and reduction of the number of capillaries. Moreover, MI severely damaged heart function containing the decrease of maximum contraction and relaxation rate [14]. In our study, the combination of pre-MI or post-MI exercise decreased myocardial infarction size and collagen deposition in remote non-infarcted myocardium. It attenuated left ventricular dysfunction characterized by increased heart coefficient, LVSP, and dp/dt max. These observations are in agreement with a previous study which reported that moderate exercise can attenuate adverse collagen deposition and LV dysfunction [20]. Myocardial ischemia reperfusion injuries have severe hyperplasia of collagen fiber, with collagen content increasing in the infarct area after 3 days and remaining at high levels after 42 days [21]. Long-term aerobic exercise can lead to adaptive changes in the structure of the heart. Post-MI exercise reduces myocardial cell apoptosis, alleviates left ventricular dilatation, and improves heart function [22]. Aerobic exercise changes the components of myocardial interstitial, which can effectively reduce infarct size and collagen deposition [23].

An interesting observation in the present study was that combined pre-MI and/or post-MI exercise increased the number of mitochondria and decreased dilation of intercalated disc in the remote MI area, enhancing mitochondrial function and protecting heart function. Mitochondria are major organelles of energy metabolism and have many important cellular processes. Oxygen free radicals are thought to be the main cause of cardiac injury in pathological remodeling and heart failure [24]. However, generation of oxygen free radicals in the body can lead to a disastrous cycle of DNA damage in mitochondria. Most of the damage is to 8-OHG, which is highly mutated and further damaged mitochondria. In order to fix DNA damage, the cell itself has a set of mechanisms which include mitochondrial DNA repair enzymes. The main mitochondrial DNA repair enzyme (OGG1) is of great importance to maintenance of mitochondrial function and mitochondrial DNA repair function. During development of antioxidant damage, high levels of OGG1 expression improve mitochondrial DNA damage repair function. Results of the present study indicate that OGG1 plays an important role in ameliorating MI induced oxidative damage by exercise. Combined pre-MI or/and post-MI exercise more effectively promotes expression of OGG1 in myocardium after MI. The results indicate that combined exercise is more effectively protective of the heart. In addition, mitochondrial biosynthesis includes protein transport function which relies on the ordered process of transport proteins in outer and inner membrane of

mitochondrial. Oxidative stress has been reported to inhibit mitochondrial import [6]. Myocardial infarction seriously impairs myocardial mitochondrial transporter and expression of mitochondrial transporter is decreased and preserved by exercise. Pre-MI and/or post-MI exercise prevents the reduction of mitochondrial transporters which indicates that exercise offers a protective effect on the heart through protecting mitochondrial transport function. The expression change of mitochondrial transport protein, after MI, through intervention of exercise revealed a mitochondrial protection mechanism of exercise. However, the effects of exercise on precise regulation of mitochondrial transport proteins and function is still yet to be studied. Our experiments focused on protective effects of combined aerobic exercise on cardiac structure and function of myocardial infarction rats and its possible mitochondrial protection mechanisms. Our study has several limitations. First, we did not directly isolate mitochondria to detect expression of its transporter protein. Moreover, we did not directly detect the effect of exercise on mitochondrial function.

Conclusion

In conclusion, we have clearly demonstrated that combined long term aerobic exercise can effectively protect structure and function of rats, after MI, by preventing decrease of mitochondrial import and enhancing expression of OGG1. Preservation of the import machinery of mitochondria may contribute to the protective effects of exercise after MI. In addition, combined pre-MI and post-MI exercise has more effectively protective effects than only one intervention. These observations provide an experimental basis involved in improving ability against ischemia and hypoxia in healthy people and choice of exercise protocol for clinical patients suffering acute MI.

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Disclosure of conflict of interest

None.

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