Effects of Exercise Training on Myocardial Fatty Acid Metabolism in Rats With Depressed Cardiac Function Induced by Transient Ischemia

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The effects of exercise training on metabolic and functional recovery after myocardial transient ischemia were investigated in a rat model. Male Wistar Kyoto rats were subjected either to a 30-min left coronary artery occlusion followed by reperfusion or to a sham operation. At 4 weeks after operation, the rats were randomly assigned either to sedentary conditions or to exercise training for 6 weeks. In the ischemic rats, pinhole SPECT (single photon emission computed tomography) imaging with thallium-201 (201Tl) and 123I-(L-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) showed a reduction of both myocardial perfusion and fatty acid metabolism in the risk zone of the left ventricle (LV). The LV was dilated and the ejection fraction was decreased after ischemic injury. The severity score showed a significant decrease on both 201Tl and BMIPP (201Tl, from 19.9±2.7 to 17.0±2.2, p<0.05; BMIPP, from 21.5±2.4 to 18.6±1.9, p<0.05) after exercise training in the ischemic trained rats, but did not change significantly in their sedentary counterparts. Plasma levels of free fatty acids normalized in the ischemic trained rats, but elevated in the ischemic sedentary rats (0.53±0.05 vs 0.73±0.06 mmol/L, p<0.05). Furthermore, the trained rats had a significant increase in LV stroke volume (0.25±0.02 vs 0.21±0.01 ml/beat, p<0.05) and adaptive cardiac hypertrophy. These findings demonstrate that adaptive improvements in myocardial perfusion, fatty-acid metabolism and LV function were induced by exercise training after transient ischemia. (Jpn Circ J 2001; 65: 550–555)

Key Words: Exercise training; Free fatty acids; 123I-(L-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP); Ischemia

Restoration of blood flow in the large coronary arteries of patients with acute myocardial infarction has become an established therapeutic intervention. If blood flow is restored before irreversible ischemic injury occurs, regional function recovers slowly. This loss of contractile function is biochemically related to reduced levels of high-energy phosphates, which are produced primarily in mitochondria through oxidative metabolism of various substrates by way of the citric acid cycle and the electron transport chain. Free fatty acids (FFA) are the major energy source of the normal working heart and when the heart is deprived of oxygen by ischemia, β-oxidation of FFA is inhibited early during ischemia, leading to depressed energy production. In addition, peripheral lipolysis secondary to the release of stress hormones contributes to the elevated plasma levels of FFA in patients with myocardial ischemia. These non-esterified fatty acids in excess have detrimental effects on the heart during ischemia.

Exercise training is now an accepted treatment modality in patients with depressed left ventricular (LV) function after myocardial ischemia and has been shown both clinically and experimentally to increase maximal oxygen uptake (VO2max) by improving exercise capacity, increase maximal cardiac output, and improve measures of quality of life. In addition, exercise training results in a reduced concentration of circulating plasma FFA. However, whether training can reverse some or all of metabolic and functional changes brought about by myocardial ischemia remains to be determined.

With the development of single photon emission computed tomography (SPECT), the noninvasive assessment of cardiac regional metabolism has become possible. 123I-(L-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) is a FFA analogue that is trapped in the myocardium, thus allowing evaluation of the metabolic state of the post-ischemic myocardium and prediction of metabolic and functional recovery using SPECT. The present study evaluated the effects of chronic dynamic exercise on metabolic and functional recovery after transient myocardial ischemia in a rat model.

Methods

Animal Model

This study followed the Guidelines for Animal Experiments of Kyoto University established in 1988. Male Wistar Kyoto rats (8 weeks old, ~250 g, n=32) were anesthetized with sodium pentobarbital (40 mg/kg body weight, ip), intubated via tracheotomy and connected...
to a respirator for artificial ventilation with room air. Left-sided thoracotomy was performed through the fourth to fifth intercostal space, exposing the heart. In the ischemia–reperfusion group (n=20), myocardial ischemia was produced by occlusion of the left coronary artery (LCA) near its origin with a 6-0 silk suture for 30 min, but this was not carried out in the sham operation group (n=12). The chest was then closed. Each animal was allowed a minimum of 4 weeks of recovery after the operation on standard chow and water ad libitum.

**Exercise Training Protocol**

After the 4-week recovery period, the surviving rats were randomly assigned to either a sedentary or an exercise-training group, which resulted in 4 final groups: ischemic sedentary (n=7), ischemic trained (n=8), sham sedentary (n=5) and sham trained (n=6).

The exercise-training groups ran at 10 m/min for 60 min/day, 5 days per week for 6 weeks on a wheel-running apparatus (1.57 m in circumference).

**Echocardiography**

Before (initial study) and after (final study) the exercise training program, transthoracic echocardiography was performed to assess LV function and geometry using an echo/Doppler system (Model SSA-380A, Toshiba Co, Japan) with a 7.5-MHz transducer. Rats were lightly anesthetized with sodium pentobarbital (20 mg/kg BW, ip) and placed in a partial left lateral decubitus position. Using the 2-dimensional parasternal short-axis imaging plane as a guide to the level of the papillary muscles, an M-mode tracing of the LV was obtained. The LV anterior and posterior wall thickness at end diastole, LV end-diastolic internal diameter, end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and ejection fraction (EF) were measured according to standard procedures. All measurements were averaged on at least 3 consecutive cardiac cycles. The LV dimension/wall thickness ratio was calculated. In addition, heart rate (HR) was measured and cardiac output (CO) were calculated as: CO=SV×HR.

**Myocardial SPECT Imaging**

Myocardial perfusion and fatty acid metabolism were assessed with thallium-201 (201Tl) and 123I-BMIPP in a pinhole SPECT system for small animals before and after the exercise training program. After 18 h of fasting, rats were re-anesthetized, 74 MBq of 201Tl and 111 MBq of 123I-BMIPP were administered simultaneously via the femoral vein. Approximately 7 min later, dual-SPECT imaging was performed with a high-resolution pinhole SPECT-2000H scanner (Hitachi Medical Co, Japan). Projection data were acquired from 64 views over 360° using a 64×64 matrix and a 20% energy window (centered on the 159-KeV X-ray photopeak for 123I-BMIPP and 75-KeV for 201Tl). Short-axis and vertical and horizontal long-axis slices were reconstructed using a computer (HARP-II, Hitachi Medical Co). The same stress procedure was used for the initial and final studies.

The reconstructed tomographic sections were displayed on a computer monitor and slices were selected for the evaluation of both 201Tl and BMIPP images. Each rat heart was divided into 20 segments, as previously described. A 10×10 pixel region of interest (ROI) in each segment was measured for luminous intensity as the relative value of 201Tl or BMIPP uptake. The 201Tl and BMIPP severity scores were obtained by summation of all the respective segmental scores and a quantitative 4-point scoring system was used: 0 = normal tracer uptake, 1 = slightly (<25%) reduced uptake, 2 = moderately (<50%) reduced uptake, 3 = severely (>50%) reduced uptake. The 201Tl and BMIPP severity scores were obtained from 64 views over 360° using a 64×64 matrix and a 20% energy window (centered on the 159-KeV X-ray photopeak for 123I-BMIPP and 75-KeV for 201Tl). Short-axis and vertical and horizontal long-axis slices were reconstructed using a computer (HARP-II, Hitachi Medical Co). The same stress procedure was used for the initial and final studies.

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**Measurement of Plasma FFA Concentration**

A 1-ml blood sample from the abdominal aorta was taken at the end of experiment, and the plasma was separated and stored at −80°C for later analysis. Then the animal was killed and the heart was rapidly removed and weighed. Plasma FFA was assayed colorimetrically as described by Mizuno et al.

**Statistical Analysis**

All values are expressed as mean±SEM. A 2-way ANOVA was used to examine the effects of reperfusion (ischemia vs sham) and exercise training (trained vs sedentary) on variables related to parameters of echocardiography and body and heart weights. Comparisons in discrete variables were made using Bonferroni tests. Mann-Whitney U-test was used on myocardial SPECT score for ischemic rats (trained and sedentary). Differences between the baseline and final studies on myocardial SPECT score were examined by using Wilcoxon 1 Sample test. A probability value of less than 0.05 was considered significant.

**Results**

Although 5 rats in the ischemic group and 1 rat in the sham group died from acute heart failure (3 rats) after operation or respiratory failure (3 rats) related to anesthesia...
during echocardiography or myocardial SPECT, there were no deaths during the exercise training program. Twenty-six rats completed the experimental protocol and were analyzed.

### Table 2  Left Ventricular Morphology and Function in the Experimental Groups

<table>
<thead>
<tr>
<th></th>
<th>Sham rats (n=5)</th>
<th>Trained (n=6)</th>
<th>Ischemic rats (n=7)</th>
<th>Trained (n=8)</th>
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</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
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<tr>
<td>Pre</td>
<td>434±20</td>
<td>436±11</td>
<td>421±16</td>
<td>420±15</td>
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<tr>
<td>Post</td>
<td>458±11</td>
<td>449±26</td>
<td>420±21</td>
<td>428±15</td>
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<tr>
<td><strong>LV dimension (mm)</strong></td>
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<tr>
<td>Pre</td>
<td>5.7±0.3</td>
<td>5.8±0.1</td>
<td>7.0±0.3*</td>
<td>7.1±0.4††</td>
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<tr>
<td>Post</td>
<td>6.1±0.1</td>
<td>6.5±0.1</td>
<td>7.4±0.3**</td>
<td>7.6±0.3††</td>
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<tr>
<td><strong>Anterior wall thickness (mm)</strong></td>
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<tr>
<td>Pre</td>
<td>1.51±0.05</td>
<td>1.52±0.05</td>
<td>1.36±0.11</td>
<td>1.35±0.07</td>
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<tr>
<td>Post</td>
<td>1.66±0.05</td>
<td>1.62±0.06</td>
<td>1.40±0.10</td>
<td>1.65±0.11</td>
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<td><strong>Posterior wall thickness (mm)</strong></td>
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<tr>
<td>Pre</td>
<td>1.78±0.16</td>
<td>1.80±0.08</td>
<td>1.73±0.07</td>
<td>1.78±0.10</td>
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<tr>
<td>Post</td>
<td>1.83±0.07</td>
<td>1.83±0.09</td>
<td>1.74±0.08</td>
<td>1.83±0.09</td>
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<tr>
<td><strong>LVd/AWT</strong></td>
<td></td>
<td></td>
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<tr>
<td>Pre</td>
<td>3.78±0.12</td>
<td>3.85±0.15</td>
<td>5.37±0.59*</td>
<td>5.41±0.54‡</td>
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<tr>
<td>Post</td>
<td>3.70±0.07</td>
<td>4.03±0.18</td>
<td>5.53±0.57**</td>
<td>4.80±0.41</td>
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<tr>
<td><strong>LVd/PWT</strong></td>
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<tr>
<td>Pre</td>
<td>3.29±0.30</td>
<td>3.37±0.14</td>
<td>3.94±0.28</td>
<td>4.07±0.31</td>
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<td>Post</td>
<td>3.38±0.16</td>
<td>3.60±0.23</td>
<td>4.30±0.22</td>
<td>4.26±0.40</td>
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<td><strong>End-diastolic volume (ml)</strong></td>
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<tr>
<td>Pre</td>
<td>0.20±0.02</td>
<td>0.22±0.02</td>
<td>0.39±0.05*</td>
<td>0.42±0.07‡</td>
</tr>
<tr>
<td>Post</td>
<td>0.23±0.02</td>
<td>0.28±0.02</td>
<td>0.42±0.06**</td>
<td>0.46±0.03††</td>
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<tr>
<td><strong>End-systolic volume (ml)</strong></td>
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<tr>
<td>Pre</td>
<td>0.03±0.004</td>
<td>0.03±0.004</td>
<td>0.19±0.03*</td>
<td>0.21±0.06‡</td>
</tr>
<tr>
<td>Post</td>
<td>0.03±0.003</td>
<td>0.03±0.002</td>
<td>0.20±0.04**</td>
<td>0.20±0.04‡</td>
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<tr>
<td><strong>LV ejection fraction (%)</strong></td>
<td></td>
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<tr>
<td>Pre</td>
<td>86±1</td>
<td>87±1</td>
<td>54±3***</td>
<td>56±6†††</td>
</tr>
<tr>
<td>Post</td>
<td>86±1</td>
<td>88±1</td>
<td>55±4***</td>
<td>59±6†††</td>
</tr>
<tr>
<td><strong>Stroke volume (ml/beat)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre</td>
<td>0.17±0.01</td>
<td>0.19±0.02</td>
<td>0.20±0.02</td>
<td>0.21±0.01</td>
</tr>
<tr>
<td>Post</td>
<td>0.19±0.02</td>
<td>0.25±0.02‡</td>
<td>0.21±0.01</td>
<td>0.25±0.02‡</td>
</tr>
<tr>
<td><strong>Cardiac output (ml/min)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>73.21±3.01</td>
<td>83.82±6.00</td>
<td>84.20±6.31</td>
<td>86.30±3.53</td>
</tr>
<tr>
<td>Post</td>
<td>88.31±7.45</td>
<td>112.44±7.70†</td>
<td>85.69±5.86</td>
<td>104.89±6.86†</td>
</tr>
</tbody>
</table>

Pre, initial study; Post, final study (after 6 weeks); LV, left ventricular; LVd, left ventricular dimension; AWT, anterior wall thickness; PWT, posterior wall thickness. All values are mean±SEM. *p<0.05; **p<0.01; ***p<0.001 in ischemic sedentary vs sham sedentary group. ¶p<0.05; ¶¶p<0.01; ¶¶¶p<0.001 in ischemic trained vs sham trained group. †p<0.05, trained vs sedentary in ischemic rats. ‡p<0.01, trained vs sedentary in sham animals.

1. Representative M-mode tracing of LV obtained with 2-D guidance from short-axis view from a sham rat (A) and an ischemic rat 3 weeks post-ischemia (B). Note the thinning and hypokinesis of the anterior wall, and the increase in the LV internal diameter in the ischemic rat. AW, anterior wall; PW, posterior wall; LV, left ventricle.

2. **201Tl and 123I-BMIPP SPECT images in an ischemic trained rat show decreased uptake in the antero-lateral wall before exercise training, and the improvement of uptake after exercise training. Pre, initial study; Post, final study.**

**Body and Heart Weight Response (Table 1)**

There were no significant differences in BW among the groups in either the initial or final study. However, the
heart weight (HW) and the HW to BW ratio increased in the ischemic trained rats by 12.8% (p<0.01) and 15.9% (p<0.001), respectively, compared with the ischemic sedentary rats. The HW to BW ratio increased in sham trained rats by 16.5% (p<0.01) compared with sham sedentary rats.

**Effects of Exercise on LV Remodeling and Function (Table 2)**

In the initial study, there were significant increases in the LV diastolic dimension, EDV and ESV and a decrease in LVEF induced by myocardial transient ischemia (Fig 1). Although the thinning of the LV ischemic anterior wall showed no statistical difference, the LV dimension/anterior wall thickness ratio was significantly elevated compared with sham rats. In addition, there was a trend for ischemic rats to have an increased LV dimension/posterior wall thickness ratio (p=0.13, sham trained vs ischemic trained). After the 6-week exercise-training or sedentary period, SV and CO increased in both sham and ischemic trained rats compared with their sedentary counterparts. In addition, ischemic trained rats showed an increase in the thickness of the ischemic anterior wall (1.65±0.11 vs 1.40±0.10mm, p=0.06) when compared with ischemic sedentary animals. The LV dimension/anterior wall thickness ratio was significantly elevated in ischemic sedentary rats only. There was no significant difference in HR during the echocardiographic study under anesthesia among the groups.

**Myocardial Perfusion and Fatty Acid Metabolism**

Pinhole dual-SPECT (201Tl and BMIPP) images of myocardium were obtained in all rats before and after the 6-week exercise-training period. All sham rats showed normal myocardial perfusion and fatty acid metabolism in the 201Tl and BMIPP images. In the ischemic rats, the 30-min occlusion of the LCA followed by reperfusion resulted in decreased uptake in the antero-lateral wall on both 201Tl and BMIPP SPECT images in the initial study, and exercise training resulted in an improvement of 201Tl and BMIPP uptake at the final study (Fig 2). The 201Tl severity score after exercise training was significantly decreased, to 17.0±2.2, compared with before exercise training (19.9±2.7) (p<0.05). Similarly, the BMIPP severity score after exercise training was significantly decreased (from 21.5±2.4 to 18.6±1.9, p<0.05). However, the ischemic sedentary group did not change significantly (201Tl, from 16.3±2.4 to 17.6±0.9, p=NS; BMIPP, from 19.0±2.4 to 18.7±1.8, p=NS) (Fig 3). Nevertheless, no significant difference in the severity scores between the 2 ischemic groups was found at the initial or final study. In addition, 201Tl/BMIPP mismatch did not show a significant difference between the ischemic sedentary and ischemic trained groups at initial study (3/7 rats: 42.9%; 3/8 rats: 37.5%, respectively, p=NS) or at final study (1/7 rats: 14.3%; 2/8 rats: 25.0%, respectively, p=NS).

The plasma concentration of FFA was elevated in the ischemic sedentary rats, but normalized in the ischemic trained rats (0.73±0.06 vs 0.53±0.05 mmol/L, p<0.05) (Fig 4).

### Discussion

There are 2 major findings in the present study. First, rats subjected to chronic treadmill exercise for 6 weeks exhibited significant increases in CO and SV at rest compared with their sedentary controls, indicating that exercise training enhances cardiac function. Second, there were significant improvements in myocardial perfusion and fatty acid metabolism and concomitant normalization of plasma FFA in ischemic trained rats, but not in ischemic sedentary rats. In the present study, a low-intensity training was chosen to minimize the possibility of fatalities that could possibly occur in rats with LV dysfunction. No negative reactions occurred during this exercise training program.

### Ischemia and Fatty Acid Metabolism

Long-chain FFA are the preferred metabolic substrate of the myocardium under aerobic conditions. Fatty acid metabolism is very sensitive to ischemia, which has been shown by 123I-BMIPP. The metabolism of BMIPP is closely associated with the severity of myocardial ischemia. In the present study, comparison with the 201Tl images showed that the uptake of BMIPP correlated closely with flow. When the heart is deprived of oxygen, as with ischemia, β-oxidation of fatty acids is inhibited, leading to an accumulation of metabolic intermediates. High concentrations of FFA are common in patients suffering from acute myocardial ischemia, and in the present study, plasma concentrations of FFA were elevated in...
ischemic sedentary rats 10 weeks after reperfusion, which indicates that the myocardium was still exposed to high concentrations of FFA during the recovery period after reperfusion. Nohara et al found that an excess fat concentration causes a decrease in BMIPP metabolism and uptake\(^{14}\) and experimental studies in animal hearts have been shown that high concentrations of fatty acid are detrimental to recovery of mechanical function\(^{27-31}\).

**Functional and Metabolic Changes After Reperfusion**

In the present study, despite restoration of myocardial perfusion by the release of the coronary occlusion, BMIPP uptake and cardiac function were impaired in salvaged myocardium during the 10-week period of the study. This failure of immediate functional recovery of reversibly injured tissue has been reported previously and referred to as ‘stunned myocardium\(^{32-34}\).’ The time course and magnitude of posts ischemic functional recovery mainly depend on the severity of original ischemia—reperfusion-induced myocardial injury. The size of the myocardial infarct induced by ischemia would further affect cardiac function and metabolism. Oh et al\(^{35}\) found that 45 min of left coronary ischemia followed by reperfusion induced approximately 13% infarction in female Sprague-Dawley rats, therefore the 30-min coronary occlusion followed by reperfusion in male Wistar Kyoto rats in the present study would induce minor infarct. Our data showed that cardiac function and fatty acid metabolism decreased after ischemic injury and that slow functional recovery of reversibly injured myocardium occurs in parallel with slow metabolic recovery. In addition to impaired energy production and utilization, there are several possible mechanisms underlying posts ischemic dysfunction or myocardial stunning: calcium overload, insensitivity of myofilaments to calcium, excitation-contraction uncoupling, oxyradical generation, and so forth.\(^{36}\)

**Training Effects on Cardiac Function and Metabolism After Reperfusion**

The present study demonstrated significant increases in SV and CO at rest in sham rats after exercise training, which is consistent with a recent study by Jin et al\(^{37}\) that found that exercise training significantly augments the resting cardiac index and SV index in healthy rats. The improvement in cardiac function by exercise training might relate to a reduction in systemic vascular resistance (a decrease in afterload) and an increase in myocardial contractility. Furthermore, Jin et al found that treadmill-trained rats displayed improved cardiac function in association with altered cardiac gene expression (induction of \(\text{\`-myosin heavy chain} \) as distinct from pathological cardiac adaptation\(^{38}\)). \(\text{\`-myosin} \) heavy chain is associated with high ATPase activity and increased contractility, which might contribute, in part, to the enhanced cardiac function observed in the exercise-trained rats\(^{37}\).

In the present study, the ischemic rats undergoing exercise training also exhibited a significant enhancement in CO and SV at rest compared with their sedentary controls. In addition, the LV dimension/wall thickness ratio, which reflects relative changes of diastolic wall stress, was elevated in the ischemic wall of the ischemic sedentary rats, but not in the ischemic trained rats compared with their sham counterparts. The decrease in ventricular wall tension in the ischemic trained rats may contribute to the enhanced cardiac function. Another mechanism of the training-induced improvement in ventricular performance be a favorable adaptation in the coronary circulation\(^{11}\). In addition, recent studies have demonstrated that the ventricular expression of some genes coding for the fetal phenotype (including \(\text{\`-myosin heavy chain} \) increased during ventricular remodeling after myocardial infarction in rats\(^{37-39}\)). A further study is needed to determine the effect of exercise training on abnormal gene expression, which may play a significant role in cardiac adaptations to exercise training.

In the present study, resting HR did not change after exercise training, which is consistent with previous reports\(^{37,40-42}\) that demonstrated little or no change in resting HR in conscious and anesthetized normal rats after exercise training. With an unchanged HR, the increased SV would elevate CO in exercise-trained rats.

At the end of this experiment, we did not find a significant improvement in LVEF after 6 weeks of exercise training. Our data suggest that functional recovery in stunned myocardium is slow, but that exercise training might play an important role in the improvement of cardiac function.

It is known that exercise training is associated with an increase in nitric oxide formation, which may be involved in the regulation of vascular tone in skeletal muscle and in the coronary circulation by promoting/enhancing metabolic vasodilation\(^{33,44}\). In the present study, ischemic trained rats exhibited an increase in CO and an improvement in myocardial perfusion, which might provide increased oxygen delivery to support aerobic energy production.

Chronic exercise reduces myocardial triglyceride stores and produces an apparent increase in fatty acid flux through the myocardial triglyceride pool\(^{35-47}\). In the present study, ischemic trained rats exhibited significant improvement in myocardial fatty acid metabolism and concomitant normalization of plasma FFA after 6 weeks of exercise training, but these changes were not observed in ischemic sedentary rats. However, the severity scores for \(^{201}\)TI and BMIPP did not show a significant difference between the 2 groups in the final study, which might result, in part, from the fact that ischemic trained rats had insignificantly higher severity scores than ischemic sedentary rats for \(^{201}\)TI and BMIPP in the initial study. Our findings that myocardial perfusion and fatty acid metabolism improved, and the plasma concentration of FFA returned to normal after exercise training, support the hypothesis that exercise training can positively influence myocardial lipid oxidation. The improvement in myocardial perfusion and oxidative metabolism may have facilitated functional recovery of dysfunctional but still viable myocardium.

Our data indicate that in rats with LV dysfunction, chronic dynamic exercise may improve myocardial perfusion, fatty acid metabolism and LV function. The findings suggest that exercise training is an advisable and effective treatment for patients with ischemic heart disease. Further studies are necessary to elucidate the cellular and molecular mechanisms underlying training-induced adaptations on cardiac function and energy metabolism after myocardial ischemia.

**Acknowledgments**

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**References**

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