Expression of MHC-β and MCT1 in cardiac muscle after exercise training in myocardial-infarcted rats

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1Department of Environmental Physiology, Graduate School of Human and Environmental Studies, and 2Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8501; and 3Division of Cardiology, Department of Medicine, Kitano Hospital, Osaka 530-8480, Japan

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Hashimoto, Takeshi, Naoshige Kambara, Ryuji Nohara, Masayuki Yazawa, and Sadayoshi Taguchi. Expression of MHC-β and MCT1 in cardiac muscle after exercise training in myocardial-infarcted rats. J Appl Physiol 97: 843–851, 2004. First published May 7, 2004; 10.1152/japplphysiol.01193.2003.—To evaluate the hypothesis that increasing the potential for glycolytic metabolism would benefit the functioning of infarcted myocardium, we investigated whether mild exercise training would increase the activities of oxidative enzymes, expression of carbohydrate-related transport proteins (monocarboxylate transporter MCT1 and glucose transporter GLUT4), and myosin heavy chain (MHC) isoforms. Myocardial infarction (MI) was produced by occluding the proximal left coronary artery in rats for 30 min. After the rats performed 6 wk of run training on a treadmill, the wall of the left ventricle was dissected and divided into the anterior wall (AW; infarcted region) and posterior wall (PW; noninfarcted region). MI impaired citrate synthase and 3-hydroxyacyl-CoA dehydrogenase activities in the AW (P < 0.01) but not in the noninfarcted PW. No differences in the expression of MCT1 were found in either tissues of AW and PW after MI, whereas exercise training significantly increased the MCT1 expression in all conditions, except AW in the MI rats. Exercise training resulted in an increased expression of GLUT4 protein in the AW in the sham rats and in the PW in the MI rats. The relative amount of MHC-β was significantly increased in the AW and PW in MI rats compared with sham rats. However, exercise training resulted in a significant increase of MHC-α expression in both AW and PW in both sham and MI rats (P < 0.01). These findings suggest that mild exercise training enhanced the potential for glycolytic metabolism and ATPase activity of the myocardium, even in the MI rats, ensuring a beneficial role in the remodeling of the heart.

IN FAILING HEARTS, CARDIAC metabolism becomes more dependent on glucose and lactate as respiratory substrates, whereas fatty acids are the major energy source in healthy and well-perfused cardiac muscle (1, 31, 52). In failing tissues, glucose and lactate are readily transported into the cell to be oxidized. Several studies have reported that lactate and pyruvate were carried across the cell membrane by monocarboxylate transporters (MCTs) (5, 9, 18, 32). MCT1 is abundant in mitochondrial and cell membrane fractions of cardiac muscle high in oxidative capacity (6, 10). Lactate uptake was significantly increased in the moderately trained rat hearts in which MCT1 expression was increased (3). Furthermore, Brooks et al. (11) reported the presence of lactate dehydrogenase 5 in mitochondria of the left ventricle (LV), suggesting lactate oxidation in mitochondria. Although it is controversial whether lactate is oxidized to pyruvate mainly in the cytosol or in the mitochondria, it was considered that MCT1 expression is associated with an increased oxidation of lactate, which may be beneficial to the failing heart. In fact, a previous study showed an increased expression of MCT1 in surviving myocardium after myocardial infarction (MI) in rat (31).

In another biochemical adaptation after MI, pressure overload on the surviving myocardium is known to increase the expression of myosin heavy chain (MHC-β) isoform during the process of left ventricular (LV) remodeling, whereas MHC-α isoform was predominantly expressed in the control rat hearts (38, 46, 63). This shift of MHC isoform improved myocardial work efficiency but impaired cardiac contractile system ATPase activity (2, 27, 30). Our laboratory previously suggested that the increase in the expression of MHC-β in hypoxia-induced hypertrophied ventricles was an adaptive compensation necessary to sustain cardiac contractile efficiency in response to an impairment in oxidative metabolism of the ventricles in rats (24). In contrast, contractile systems that possess higher myosin ATPase activities are capable of greater power outputs, but they consume more ATP to maintain the same level of force (39, 57). Thus an adequate expression of MHC-α based on the steady state of energy metabolism would benefit the functioning of the cardiac contractile system.

Exercise training is thought to be the only known biological stressor that produces uniformly positive central and peripheral cardiovascular adaptations (39). As a potential for glycolytic metabolism, it was considered that exercise training increased MCT1 in the cardiac muscle at a lower training intensity than in skeletal muscle (3, 5). Thus even mild exercise training may lead to biochemical benefits in MCT1 expression, which would increase lactate uptake in animal myocardium with LV dysfunction. However, the effect of exercise training on the expression of MCT1 remains unclear in the failing heart. We hypothesized that mild-intensity exercise training would increase the activities of oxidative enzymes and expressions of carbohydrate-related transport proteins (MCT1 and glucose transporter GLUT4) in myocardium of the MI rats. Exercise training may, therefore, ensure an increased expression of MHC-α necessary to improve cardiac contractile function.

Our laboratory has previously demonstrated that oxidative enzyme activities of the infarcted myocardium were signifi-
cantly less than those of the noninfarcted myocardium in the same LV (26). Rosenblatt-Velin et al. (50) have shown regional differences in the regulatory proteins of metabolism in postinfarcted heart. In addition, the adenylyl cyclase activity was decreased in the infarcted LV and increased in the right ventricle (RV), suggesting a compensatory role of the RV in failing heart in MI rats (55). In contrast, little is known about the regional biochemical responses of the LV to exercise training after MI. We hypothesized that the noninfarcted myocardium would compensate for the infarcted myocardium in terms of the contractile role of the LV in response to exercise training. The purpose of this study was to investigate the effects of mild-intensity exercise training on the expression of cardiac MCT1 and GLUT4 and MHC isoforms in both infarcted and noninfarcted regions of the LV after surgically induced anterior myocardial ischemia in rats.

METHODS

Animals, care, and experimental groups. Male Wistar-Kyoto rats (8 wk of age, 250 ± 10 g) were randomly assigned to four groups: 1) sedentary sham (SS; n = 5), 2) sedentary MI (SMI; n = 7), 3) exercise sham (ES; n = 6), and 4) exercise MI (EMI; n = 8). All rats were housed in a temperature-controlled environment (22 °C) with a 12:12-h light-dark cycle and fed ad libitum. These experiments confirmed with the Guiding Principle for the Care and Use of Animals approved by the Council of the Physiological Society of Japan.

Operation to create MI. In MI-operated groups, myocardial ischemia was surgically induced in accordance with a previous study by occluding the left coronary artery near its origin with a 6-0 silk suture for 30 min while the rats were anesthetized with pentobarbital sodium (40 mg/kg), and then they were reperfused (25). In the sham-operation groups, only a left thoracotomy was performed without left coronary artery occlusion. Each animal was allowed 4 wk of recovery from the operation before the training regimen commenced. Animals were maintained on standard chow and water ad libitum.

Exercise training protocol. After a 4-wk recovery period, the exercise training program began. Rats ran at 10 m/min for 60 min/day, 5 days per week, for 6 wk on a motor-driven wheel treadmill (1.57 m in circumference). Before and after the exercise training program, transthoratic echo-Doppler system (model SSA-380A, Toshiba, Tochigi-Ken, Japan) with a 7.5-MHz transducer. In addition, heart rate was measured, and cardiac output was calculated as cardiac output = stroke volume × heart rate. The details of this measurement are described in a previous study (26).

Tissue sampling. After the echocardiographic measurement following 6 wk of the exercise training program, all animals were anesthetized with pentobarbital sodium (50 mg/kg). With the rats under ventilation with a rodent respirator, their whole hearts were isolated, and immediately tissue wet weights were obtained. Tissue samples were applied to 12% SDS-polyacrylamide gels. In SDS-PAGE, the composition of the gels was developed according to the method of Bass et al. (4). Briefly, homogenate was added to 70 mM Tris buffer, 0.1 mM DTNB, 0.3 mM acetyl-CoA, and 0.5 mM oxaloacetate and read for 5 min at 412 nm. 3-Hydroxyacyl-CoA dehydrogenase (HAD) was determined using the reaction mixture of 88.3 mM Tris buffer with 4.4 mM EDTA, 75 µM NADH, and 0.1 mM acetoacetyl-CoA and read for 5 min at 340 nm. Enzymatic activities were expressed as micromoles of substrate per minute per gram measured muscle weight.

Western blotting of MCT1 and GLUT4. MCT1 antibody was a donation from Dr. H. Hatta (Dept. of Life Science, University of Tokyo, Tokyo, Japan). GLUT4 antibodies (rabbit anti-GLUT4) were obtained from Chemicon (Temecula, CA). Sample preparation for Western blotting was done according to McCullagh et al. (37). The samples were applied to 12% SDS-polyacrylamide gels. In SDS-PAGE, the composition of the gels was developed according to

![Fig. 1. Thorium-201 (TI) and iodine-123-labeled 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) single-photon-emission computed tomography (SPECT) image in myocardial-infarcted (MI) rat after transient ischemia. Base means representative of basal ventricular region. Arrows show decreased uptake of BMIPP in the anterolateral wall, whereas ²⁰¹TI uptake reperfused enough.](image-url)
Exercise effect on MHC and MCT after MI

Table 1. Body weight, heart weight, and left ventricular morphology and function

<table>
<thead>
<tr>
<th></th>
<th>Sham MI</th>
<th>Exercise</th>
<th>MI</th>
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<tbody>
<tr>
<td>Body weight, g</td>
<td>373 ± 9</td>
<td>355 ± 10</td>
<td>368 ± 8</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>0.80 ± 0.03</td>
<td>0.96 ± 0.02</td>
<td>0.99 ± 0.03†</td>
</tr>
<tr>
<td>LV dimension, mm</td>
<td>6.13 ± 0.12</td>
<td>6.48 ± 0.14</td>
<td>7.40 ± 0.32‡</td>
</tr>
<tr>
<td>AW thickness, mm</td>
<td>1.66 ± 0.05</td>
<td>1.62 ± 0.06</td>
<td>1.40 ± 0.10</td>
</tr>
<tr>
<td>PW thickness, mm</td>
<td>1.83 ± 0.07</td>
<td>1.83 ± 0.09</td>
<td>1.74 ± 0.08</td>
</tr>
<tr>
<td>AW-to-PW thickness ratio</td>
<td>0.92 ± 0.05</td>
<td>0.90 ± 0.05</td>
<td>0.81 ± 0.08</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>458 ± 11</td>
<td>449 ± 6</td>
<td>420 ± 21</td>
</tr>
<tr>
<td>Stroke volume, ml/beat</td>
<td>0.19 ± 0.02</td>
<td>0.25 ± 0.02‡</td>
<td>0.21 ± 0.01</td>
</tr>
<tr>
<td>Cardiac output, ml/min</td>
<td>88.31 ± 7.45</td>
<td>112.44 ± 7.01</td>
<td>85.69 ± 5.86</td>
</tr>
</tbody>
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Values are means ± SE. MI, myocardial infarction; LV, left ventricle; AW, anterior wall; PW, posterior wall. *P < 0.05, †P < 0.01 vs. corresponding sham-operated group. ‡P < 0.01 vs. corresponding sedentary group.

Talmadge and Roy (60) with modifications: 1) the acrylamide content of the separating gel was increased to 12% and 2) the glycerol content of separating and stacking gels were reduced to 10%. Gels were run at a constant voltage of 200 V for 2 h (Bio-Rad Mini Protein III Cell electrophoretic system utilizing a Bio-Rad PowerPac 1000 power supply) in a chamber controlled at 4°C. Western blotting of MCT1 and GLUT4 was done according to previous studies (34, 37). Proteins were transferred from the gel to the membrane (15 V, 25 min) (Bio-Rad Trans Blot SD Cell blotting system utilizing a Bio-Rad PowerPac 200 power supply). Membranes were blocked by 20 mM Tris-HCl, 137 mM NaCl, 0.1% Tween 20, and 10% nonfat dry milk, pH 7.5, solution for 24 h. Membranes were then incubated with antibody solution (either MCT1 or GLUT4) for 1 h. After being washed in 20 mM Tris-HCl, 137 mM NaCl, and 0.1% Tween 20, pH 7.5, membranes were incubated with donkey anti-rabbit IgG horse-radish peroxidase-conjugated secondary antibody (1:7,500; Amersham Biosciences). Band imaging was scanned using laser densitometer equipped with an integrator (Multi-Analyst, Bio-Rad).

Statistical analysis. Data are expressed as means ± SE. The statistical significance was determined by a two-way analysis of variance (sedentary/exercise vs. sham/MI), and a Bonferroni test was used to determine the significance of difference between means. Comparisons were made between the AW and the PW of each group by using a paired t-test. Statistical significance was considered to be P < 0.05.

RESULTS

LV morphology and function. Table 1 shows the body weights, heart weights, and LV morphology and function in all groups. There were no significant differences in body weights among the groups. Heart weight was significantly increased in MI groups compared with corresponding sham-operated groups. Furthermore, the heart weight in the EMI group was higher than that in the SMI group (P < 0.01). The LV dimensions of MI rats were significantly enlarged compared with sham rats. There were no significant differences in wall thickness among the groups in either AW or PW. In addition, AW-to-PW thickness ratio was unchanged in each group. There were no significant differences in heart rate among the groups. Exercise enhanced the LV function in terms of increased stroke volume and cardiac output in both Sham and MI groups.

Oxidative enzyme activities. MI impaired CS and HAD activities in the AW (A) (P < 0.01), but the PW (B) remained unchanged in both activities (Figs. 2 and 3). In MI rats, CS and HAD activities in the PW were significantly higher than those in the AW. No exercise training effect was observed in oxidative enzyme activities in all conditions studied (Figs. 2 and 3).

MCT1 and GLUT4 expression. MCT1 and GLUT4 protein expressions were determined by Western blot techniques; representative blots are shown in Fig. 4. Figure 5 summarizes the MCT1 protein contents in both AW (A) and PW (B). No significant associations between changes in the expression of MCT1 and acute MI were observed in both walls (8% increase in SMI compared with SS in the PW; P > 0.05). Compared with the SS group, the ES group significantly enhanced the expression of MCT1 by 38% in the AW and by 65% in the PW (P < 0.05). The expression of MCT1 in the EMI group was also significantly higher by 34% than the SMI group (P < 0.01 vs. corresponding sham-operated group. †P < 0.05, ‡P < 0.01 vs. corresponding sedentary group.

Fig. 2. Citrate synthase (CS) activities in anterior (AW; A) and posterior walls (PW; B) of the left ventricle. Values are means ± SE. **P < 0.01 vs. corresponding sham-operated group. #P < 0.01 vs. corresponding sedentary group.
However, in the MI group in AW, exercise did not increase the MCT1 content. In the EMI group, the expression of MCT1 in the PW was significantly higher than that in the AW (P < 0.05). Figure 6 summarizes the GLUT4 protein contents in both AW (A) and PW (B). Exercise training enhanced the expression of GLUT4. The GLUT4 expression was significantly higher in the AW for the ES group than that of the SS group and in the PW for the EMI group than that of the SMI group (P < 0.01 and P < 0.05, respectively). The GLUT4 expression was significantly lower in the AW for the EMI group than that of the ES group (P < 0.01). In the EMI group, the expression of GLUT4 in the PW was significantly higher than that in the AW (P < 0.05).

**MHC isoforms expression.** Representative separations of MHC-α and MHC-β are shown in Fig. 7. MI group showed a large percentage of shifts in MHC-β in both AW (A) and PW (B) compared with sham-operated groups (P < 0.01; Fig. 8). On the other hand, exercise training induced a significant reduction of MHC-β expression in both AW and PW, concomitantly indicating an increased MHC-α expression (P < 0.01; Fig. 8). In the SMI and EMI groups, the expression of MHC-α in the PW was significantly higher than that in the AW (P < 0.01 and P < 0.05, respectively).

Figure 9 shows the ratio of MHC-β expression in the AW vs. PW in both sedentary and exercise sham and MI groups. Both exercise training and MI decreased relative expression of MHC-β in the PW compared with the AW. In the EMI group, a large expression of MHC-β was observed in the AW compared with the PW.

**DISCUSSION**

Our present study used a mild-intensity exercise training program, because an intense exercise program might be potentially harmful in animals with LV dysfunction (17, 41). In connection to this, Orenstein et al. (46) suggested that one of the factors accounting for more favorable ventricular remodeling was a normalization of the wall tension due to a reduced cavity volume and an increased wall thickness after exercise training. However, there was no significant difference in morphological changes in dimensions and ventricular walls of both sham and MI rats, although stroke volume and cardiac output increased after exercise training (Table 1).

Our results revealed that surgically induced MI in the sedentary rats impaired CS and HAD activities in the AW but not in the PW. These findings were consistent with previous studies (26, 44). There was no change in oxidative enzyme activities (CS and HAD) in ventricular wall tissues after exercise training. In contrast to the skeletal muscle, it is likely that the low-intensity training does not change the metabolic state in myocardium of small mammals that sustain high oxidative metabolism (23, 39).

The expressions of GLUT4 and MCT1 were not affected by the induction of ischemia and transient MI in both AW and PW of the LV. This unchanged observation of GLUT4 is similar to a previous result in failing rat hearts, although GLUT1 protein levels were increased in the myocardium (31, 50). Thus it is possible that the increased GLUT1 protein may enhance glucose utilization in the failing heart. Muscle glucose transport activity has been shown to be primarily related to the number of facilitative glucose transporters present in the sarcolemmal membrane (36). Furthermore, the translocation of GLUT4 and GLUT1 to the sarcolemma can be activated by ischemia or increased work (62). In the present study, total GLUT4 protein...
contents of whole homogenated cardiac muscle were measured; however, the precise glucose transport activity in the sarcolemma membrane could not be substantiated.

The data from the present study showed no shift of relative protein expression in MCT1 in post-MI rats. This observation is in contrast to a previous study by Johannsson et al. (31), who reported a 259% increase. We expected that MCT1 would be upregulated in rat myocardium with MI because failing hearts have been shown to switch their metabolic preference from mainly fatty acids to carbohydrates (1, 31, 52). One possible explanation for the discrepancy in results is the difference in occlusion and recovery protocols between the studies. For example, our study reperfused the rats after 30 min of occlusion of the left coronary artery, and after 11 wk they were killed. On the other hand, Johannsson et al. (31) continued to ligate the left coronary artery throughout the experiment for 6 wk, which resulted in congestive heart failure (CHF) with larger cardiac hypertrophy. Therefore, the MCT1 expression of the survived myocardium in the previous study (31) may suggest that a greater amount of MCT1 protein would be expressed to uptake and deliver lactate, thereby compensating the ischemic region in the heart. Additionally, it might be plausible to suppose that cardiac MCT1 expression would be upregulated by chronic stimulation induced by exercise training and/or CHF. Baker et al. (3) demonstrated increased cardiac MCT1 with increased duration of moderate exercise. A recent study (16) has shown a 270% increase in MCT1 protein expression in CHF rats induced by 8 wk of volume overload compared with sham-operated rats. In addition, Cuff et al. (13) have demonstrated that expression of the butyrate transporter, MCT1, is subject to upregulation by butyrate in colonic epithelial cells and that increased expression of MCT1 mRNA and protein with butyrate treatment is both dose and time dependent. Moreover, butyrate also stabilized MCT1 mRNA in colonic epithelial cells (13). Therefore, we suspect that transient ischemia in the present study, resulting in less of an increase in heart weight compared with the previous studies (16, 31), did not induce continuous stimulation enough to cause a large amount of MCT1 expression. The precise mechanisms to upregulate the cardiac MCT1 transcription and protein expression are unclear, however, it has been demonstrated that the human MCT1 5′-flanking region contains potential binding sites for a variety of transcription factors, including activator protein-1 (AP-1) and nuclear factor-κB (NF-κB), which are well described cellular reaction to oxidative stress (14, 53). The transcriptional induction mediated by NF-κB is transient be-

Fig. 5. MCT1 protein expression in AW (A) and PW of the LV. Values are means ± SE. OD, optical density. †P < 0.05 vs. corresponding sedentary group. *P < 0.05, AW vs. PW.

Fig. 6. GLUT4 protein expression in AW (A) and PW (B) of the left ventricle. Values are means ± SE. **P < 0.01 vs. corresponding sham-operated group. †P < 0.05; ††P < 0.01 vs. corresponding sedentary group. *P < 0.05, AW vs. PW.

Fig. 7. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis for myosin heavy chain (MHC)-α and MHC-β of AW and PW in each group.
cause of a rapid downregulation of NF-κB DNA-binding activity by inhibitor (58). In rat pheochromocytoma cells, binding to AP-1 element remain elevated during prolonged exposure to hypoxia (24 h) (45). The time course of both MCT1 gene transcription level and stability of transcript remain to be elucidated.

In contrast to the workload on myocardium in post-MI rats in the present study, a considerable low-intensity chronic exercise increased relative expression of MCT1 protein in normal myocardium. In support of this, Bonen (5) suggested the possibility that moderate exercise training also increases MCT1 in the heart. Furthermore, for the first time, we have demonstrated that exercise training increased the MCT1 expression in the noninfarcted region of the myocardium in the rats with MI, although the details of MCT1 localization in cell domains were unknown. This finding suggests that mild-intensity exercise training, which might be less harmful in MI rats, enhances the potential capacity to uptake lactate and oxidize it as an energy substrate in cardiac muscle of MI rats. As mentioned above, AP-1 and NF-κB are activated by oxidative stress (53), which could be induced by exercise training (54). By these effects, chronic exercise training could therefore be thought to increase the amount of MCT1 in rat myocardium.

It is important to mention that exercise training did not enhance the MCT1 expression in the AW in MI rats in which impaired oxidative enzyme activities were observed. Previous studies have reported that MCT1 facilitates lactate uptake and oxidation in cells with high mitochondrial densities (10, 11, 15, 37). The AW with low mitochondrial density in MI rats did not have sufficient capacity to oxidize lactate and therefore did not support the benefit of an increased expression of MCT1 protein. In contrast, the expression of MCT1 in the PW maintained with normal mitochondrial density of rat myocardium was significantly higher than that in the AW in EMI group. Therefore, it is plausible that cardiac MCT1 responds to exercise training in part as CS and HAD to the extent that some of the change is mitochondrial and in part like GLUT4 because it is sarcolemmal. Cell domains of the MCT1 respond to exercise training in the myocardium should be elucidated by dissecting
the components of MCT1 localized in mitochondria and sarcolemma (10).

Although a recent series of studies has investigated the mechanisms in upregulation of GLUT4 gene expression in skeletal muscles by exercise (20, 36, 43), increase in the expression of GLUT4 protein has not been observed in cardiac muscle (22, 23). Hall et al. (22) have shown that exercise training significantly increased GLUT4 mRNA levels, but did not alter GLUT4 protein levels of myocardium in male Fischer 344 rats at 7 mo of age, suggesting either a decreased translational efficiency or an increase in the rate of protein degradation. In the present study, the GLUT4 gene translational efficiency and/or protein degradation rate remain questionable, although we provided the first evidence that shows an increased expression of cardiac GLUT4 protein after long-term exercise training. It is possible that, in the present study, the increased GLUT4 protein in trained muscle would be localized in plasma membranes, transverse tubules, and intercalated disks, which were enriched in our membrane preparation (47, 48), and acted to facilitate continuous glucose utilization to meet the substrate demand.

We have further demonstrated an increased shift in relative amount of MHC-β in both AW and PW after MI. Under a stress condition such as pressure overload, the rat hearts primarily expressed MHC-β isoform (24, 29, 38, 46). Myocardial fibers that contain relatively more MHC-β than MHC-α isoform produce efficiently normal tension at a lower oxygen cost (27, 30). It was likely that a shift to MHC-β isoform expression reflected a compensative adaptation of myocardial metabolism at a lower energy cost to a required oxygen demand in cardiac dysfunction.

We assessed whether mild-intensity exercise training would increase expressions of MCT1, GLUT4, and MHC-α in the myocardium of MI rats to improve the cardiac contractile function. Exercise training enhanced the relative expression of MHC-α isoform in the AW and PW of both sham and MI rats. A previous investigation also reported that swimming training enhanced the expression of MHC-α in both normotensive and spontaneously hypertensive rat hearts (51). In addition, several studies have demonstrated that both running exercise and swimming exercise attenuated the relative expression of MHC-β in the noninfarcted myocardium in rat with MI (42, 46, 63). Furthermore, previous studies have shown that several factors, such as sympathetic nervous activity, intracellular cAMP, and thyroid hormone, could induce an increased expression of MHC-α during and/or after exercise training, indicating an enhanced shortening velocity of muscle fibers (2, 19, 21, 29, 61). However, the mechanisms of the difference in the expression of MHC isoforms in the response to physiological (trained heart) and pathological (post-MI heart) stimuli remain to be unknown. A previous study demonstrated that β1-adrenergic receptor (β1-AR) mRNA concentration in the LV was increased in both trained rats and spontaneously hypertensive rats, but in the spontaneously hypertensive rats the β1-AR kinase mRNA concentration was also increased, suggesting an impairment in β1-AR signal transduction system (28). Activation of the β1-AR signal transduction system has been shown to increase intracellular cAMP concentration, which would result in an increased expression of MHC-α (18, 40). Therefore, it is possible that a difference in an activity of β1-adrenergic system is one of the causal factors for the difference in MHC-α expression between the trained and post-MI heart. As a physiological effect of exercise training, this increased contractile velocity would result in the reversal of the chronotropic incompetence previously observed in MI rats (2, 42).

Our results provide the first evidence that the low-intensity running exercise can enhance the expression of MHC-α in the surviving myocardium of both infarcted and noninfarcted regions in post-MI rats. However, the ratio of the MHC isoforms shift to MHC-α in the PW after exercise training was larger than that in the AW in MI rats (Figs. 8 and 9). Takashi and Ashraf (59) demonstrated that, after 30 min of left coronary artery occlusion and 120 min of reperfusion, in the rat LV 36.3% of the cells remained normal, 26.6% were necrotic, and 25.0% were reversibly injured. In the present study, a MHC-α-to-MHC-β isoform shift was imposed on the surviving myocardium to a greater extent in the AW of the LV where oxidative enzyme activities were impaired and simultaneously without changes in the expression of GLUT4 and MCT1. The observation of a greater shift in MHC-β in the surviving myocardium of the AW, which may result in an improvement of myocardial work efficiency, could be an adapted response to an augmented delivery of oxygen (24). This interpretation is at least partly supported by the fact that there was a greater expression of MHC-β in the AW than in the PW in MI rats (Fig. 9). Particularly in the EMI group, it is likely that the cardiac muscle in the PW compensates as a whole contractile machine for the dysfunction of the AW contraction in MI rats by expressing a greater amount of MHC-α isoform compared with the AW, which would be supported by the increased expressions of GLUT4 and MCT1. With the findings taken together, we concluded that mild-intensity chronic exercise training increased the expression of MHC-α isoform based on the increased expression of GLUT4 and MCT1 in the PW, improving the LV function.

It is plausible that the relationship between the exercise-induced MCT1 expression and MHC isoform shift in the cardiac muscle is somewhat different from that in the skeletal muscle. In skeletal muscle, increases in the MCT1 after endurance training or electrical stimulation were accompanied with a fiber-type shift to a more oxidative type, which has lower ATPase activity (7, 8, 15). On the other hand, our results have shown that the unaltered expression of MCT1 by exercise training or electrical stimulation were accompanied with a fiber-type shift to a more oxidative type, which has lower ATPase activity (7, 8, 15). On the other hand, our results have shown that the unaltered expression of MCT1 by exercise training in the AW in MI rats was not in parallel with the alteration of MHC isoform expression. This observation may be due to high oxidative capacity of the cardiac muscle whether or not it has relatively more of the faster ATPase MHC-α isoform. This view is supported by the fact that the exercise training enhanced the MHC-α expression but did not change the oxidative capacity in the sham-operated group. Further research is needed to define the mechanisms of the MCT expression and cell domains occupied by MCT1 and other transport proteins in both cardiac and skeletal muscles.

In summary, surgically induced MI impaired oxidative enzyme activities in the AW but not in the PW of the LV in rats. No differences in the expression of MCT1 were found in either tissues of AW and PW after MI, whereas exercise training significantly increased the MCT1 expression in all conditions, except AW in the MI rats. Similarly, exercise training resulted in an increased expression of glucose transporter GLUT4 protein in the AW in the Sham rats and in the PW in the MI.
rats. The relative amount of MHC-β was significantly increased in the AW and PW in MI rats compared with sham control. However, exercise training resulted in a significant increase of MHC-α expression in both AW and PW in both sham and MI rats (P < 0.01). The ratio of the MHC isoforms shift to MHC-α in the PW after exercise training was larger than that in the AW in MI rats. Stroke volume and cardiac output increased after exercise training. These findings suggest that mild-intensity chronic exercise training increased the expression of MHC-α isoform on the basis of the increased expression of GLUT4 and MCT1 in the PW, improving the LV function. Mild exercise training enhanced the potential for glycolytic metabolism and ATPase activity of myocardium even in the MI rats, ensuring a beneficial role in the remodeling process of a failing heart.

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