Impaired β-cell function attenuates training effects by reducing the increase in heart rate reserve in patients with myocardial infarction

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Abstract

Background: Insulin resistance (IR) is characterized as a metabolic disorder syndrome that is upstream of hypertension, dyslipidemia, and diabetes mellitus (DM). This study investigated exercise training effects on the exercise tolerance and heart rate dynamics in patients with IR or pancreatic β-cell dysfunction.

Methods: Seventy patients (mean age, 60.1 years) with myocardial infarction (MI) participating in a phase II cardiac rehabilitation program were studied. Patients diagnosed with DM were excluded. Homeostasis model-assessment indices were used to divide patients into three groups – A: IR; B: normal; and C: β-cell dysfunction.

A cardiopulmonary exercise test (CPX) was performed and peak oxygen uptake (\(\dot{V}O_2\)) was measured. After baseline testing, subjects participated in a supervised, combined aerobic and resistance exercise program.

Results: Peak \(\dot{V}O_2\) at baseline was comparable among the three groups, and it improved after training in all groups (\(p < 0.05\)). However, both the increase and percentage increase in peak \(V_O2\) were smaller in Group C than in Group A (\(p < 0.05\)). Heart rate (HR) reserve (peak HR – rest HR), and HR recovery immediately 1 min after exercise during CPX were calculated in 45 patients who were not taking negative chronotropic agents. Group C alone did not show any significant increase in HR reserve. HR reserve at both baseline and after training had significant positive correlations with peak \(V_O2\). HR recovery was 1.9 beats/min lower in group C than group A, but this was not significant. HR recovery in group C did not increase after cardiac rehabilitation.

Conclusion: Impaired HR reserve increase after training in patients with pancreatic β-cell dysfunction attenuates exercise training effects on functional capacity. Comprehensive treatment including vigorous exercise training will be needed in such prediabetic patients.

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Introduction

Recently, the number of patients diagnosed with diabetes mellitus (DM) has increased dramatically in both Western and Asian countries [1]. Over 20 million individuals have definitive or borderline DM in Japan, and approximately 40% of patients with acute myocardial infarction (MI) treated at our hospital have DM [2]. Similar to other studies [3,4], we had previously reported that maximum oxygen uptake (peak \(V_O2\)) was attenuated in patients with acute MI complicated with DM compared with patients with MI and without DM [2,5,6]. We also reported that exercise tolerance in DM patients remained low after 3 months of exercise training compared with non-DM patients, and we speculated that blunted heart rate (HR) response to sympathetic nerve stimulation may be the cause of reduced peak \(V_O2\) and blunted training effects [2,5,6].
Insulin resistance (IR) is characterized not only as a syndrome of metabolic disorder that exists upstream of hypertension, dyslipidemia, and DM, but also as an alternative risk factor for atherosclerosis and poor prognosis [7]. However, little is known about how exercise training effects are influenced by IR and pancreatic β-cell dysfunction. In this study, we investigated differences in exercise training effects in patients with IR or pancreatic β-cell dysfunction. We also investigated whether exercise training effects are influenced by HR response in prediabetic patients and DM patients.

Methods

Subjects

This study included 70 patients (58 men, 12 women, mean age 60.1 ± 10.8 years) with acute MI who were participating in phase 1 and phase II cardiac rehabilitation program at our hospital. All the patients successfully underwent revascularization therapy of diseased vessels in the acute phase, and no severe complications were present during hospitalization or after discharge. This study was approved by the Ethics Committee of our University (Certification No. 356), and all the participating patients provided written informed consent. The exclusion criteria were inability to perform exercise test, chronic obstructive pulmonary disease, orthopedic disorders, uncontrollable ventricular arrhythmia, uncontrolled heart failure, chronic atrial fibrillation, and a previous history of MI. Patients diagnosed with DM before, and patients who were taking any antidiabetic agents including thiazolidines or biguanides to improve insulin sensitivity were not included in this study. The diagnostic criteria of DM were a fasting blood sugar (FBS) equal to or greater than 126 mg, or a post-prandial glucose equal to or greater than 200 mg/dL, or a 120 min glucose level after the 75 g oral glucose tolerance test (OGTT) was equal to or greater than 200 mg/dL, combined with a hemoglobin A1c greater than 6.5% (National Glycohemoglobin Standardization Program). All the patients underwent a 75 g OGTT to screen for DM during hospitalization.

Methods

Serum FBS and immunoreactive insulin (IRI) were measured at rest in the early morning during hospitalization. The blood tests were performed after the patients were in stable condition, and IR and pancreatic β-cell function were evaluated using homeostasis model assessment (HOMA) [8]. HOMA indices were calculated as follows:

\[
\text{HOMA-IR} = \frac{\text{IRI} \times \text{FBS}}{\text{mg/dL} / 405}
\]

\[
\text{HOMA-}\beta = 360 / \text{IRI} \times 63 / \text{FBS}
\]

Serum high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were also measured at baseline and at 3 months after the rehabilitation period.

Cardiopulmonary exercise testing

Before exercise training, we performed cardiopulmonary exercise testing (CPX) approximately 1 month after the onset of MI. CPX was performed on a MAT-2500 treadmill (Fukuda Denshi Co., Tokyo, Japan) using an exercise protocol that we developed for the treadmill test [9], in which exercise load intensity increases gradually by approximately one metabolic equivalent every minute by increasing speed or slope. HR response, ST-T changes, and arrhythmias during the exercise test were monitored continuously with an ML-5000 stress-test system (Fukuda Denshi Co.). A standard 12-lead electrocardiogram was recorded and examined every minute. Blood pressure (BP) was also recorded with an STBP-780 automated sphygmomanometer (Colin Co., Aichi, Japan) every minute. The criteria for halting exercise testing in this study are outlined in the guidelines of the American College of Sports Medicine [10]. The exercise test was performed without a cool-down exercise phase and patients sat down in a chair immediately after finishing the exercise test, while in the recovery phase.

Expired gas analysis was performed throughout testing using a breath-by-breath method with an AE-300S cart (Minato Medical Science, Osaka, Japan). The parameters determined from the CPX were the anaerobic threshold (AT), peak VO₂, and slope of the ventilatory equivalent (VE) to carbon dioxide output (VCO₂; i.e. the VE vs. VCO₂ slope). Gas exchange ratio (GER) during exercise was obtained by VCO₂/VO₂. These parameters were calculated with the accessory software of the AE-300S.

Knee extension muscular strength measurement

A Biodex System 2 isokinetic dynamometer (Biodex Medical Systems, Inc., Shirley, NY, USA) was used for the knee extension muscular strength measurement. The machine was calibrated at the beginning of the study. The measurements were performed according to the method we previously described [11]. Isokinetic test results were analyzed with Biodex System 2 software. We measured the knee extension muscular strength peak torque (PT) per body weight value of both the right and left knees, and used the maximum obtained value as the index of knee extension muscular strength.

Exercise training

Exercise training was performed based on the results of CPX and the muscle strength test. After baseline testing, outpatients participated in a supervised combined aerobic and resistance exercise program twice a week for 1 h. Aerobic exercise intensity was maintained at HR at approximately the AT level during treadmill walking. For resistance training, four sets of a series of two upper-extremity exercises (shoulder flexion and abduction from anatomic position) were performed with an iron weight array at a resistance that allowed completion of five repetitions with a rating of perceived exertion (RPE) of 11–13 (according to the Borg 6–20 scale) [12]. Four sets of a series of knee extensions and calf raises were performed as lower-extremity exercises. Exercise intensity for calf raises was also maintained at a RPE of 11–13. Each session was preceded and followed by a series of upper- and lower-extremity and body stretches.

Evaluation of HOMA indices

We defined IR as a HOMA-IR > 2.0, and impaired β-cell function as a HOMA-β < 50 (%). Both definitions were obtained by using data from previous reports [13,14].

Patients in this study were divided into three groups: A, insulin resistance group with HOMA-IR > 2.0 and HOMA-β > 50%; B, normal group with HOMA-IR < 2.0 and HOMA-β > 50%; and C, impaired β-cell function group with HOMA-IR < 2.0 and HOMA-β < 50%. Comparisons were made between these three groups.

Statistics

All data are expressed as mean ± standard deviation. A paired Student’s t-test was used to evaluate the differences before and after exercise training. Chi-square tests were used to analyze patients’ background and analysis of variance (ANOVA) followed by multiple comparisons with Tukey’s test was used to analyze the differences
among groups. The univariate relationship between variables was assessed by using Pearson’s correlation coefficient. A p-value of <0.05 was considered significant. Data were evaluated by using the commercially available statistical software SPSS version 18 (IBM Co., Tokyo, Japan).

Results

Group A comprised 23 patients; Groups B and C comprised 23 and 24 patients, respectively. Patient characteristics in each group are listed in Table 1. None of the subjects terminated exercise testing for severe cardiac ischemia or ventricular arrhythmia. All the patients underwent exercise testing until near exhaustion with a peak GER greater than 1.10.

Baseline and changes in HOMA indices and lipid profile

Although body mass index in Group A at baseline was significantly higher than that in Group C (p < 0.05), no significant difference was seen after training (Table 2). At baseline, both IRI and FBS in Group A were higher than those in Group B (p < 0.01, respectively). In Group C, IRI at baseline was lower than that in Group A and Group B (p < 0.01, p < 0.05, respectively), and FBS was higher than Group B (p < 0.01).

A positive correlation between HOMA-IR and HOMA-β was obtained at entry (r = 0.55, p < 0.001). Both HOMA-IR and HOMA-β at baseline in Group A were significantly greater than those in Groups B and C (p < 0.01). After training, HOMA-IR improved in Group A only, in which patients had IR and maintained β-cell function (from 2.94 to 2.30, p < 0.05). HOMA-β changed only in Group B (71.7% to 54.4%, p < 0.05). HDL cholesterol increased significantly in all three groups, and LDL cholesterol decreased significantly in Groups B and C after the 3-month rehabilitation period (p < 0.05).

Changes in peak VO₂ and the VE vs. VCO₂ slope

The peak VO₂ at baseline was comparable among Groups A, B, and C (24.5, 26.1, and 25.7 mL/min/kg, respectively). After training, they improved to 29.4, 29.4, and 28.2 mL/min/kg, respectively (p < 0.01). However, both the increase and percentage increase in peak VO₂ were lower in Group C than Group A, (p < 0.05). VE vs. VCO₂ slope was comparable among the three groups (28.7, 28.8, and 28.6, respectively) and significantly decreased in all three groups, but no inter-group difference was obtained after training (Table 2, Fig. 1).

Table 1
Characteristics of study population in each group.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>LVEF (%)</th>
<th>HbA1c (%)</th>
<th>MI site</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>61.8 ± 6.9</td>
<td>18 (78.3)</td>
<td>55.3 ± 10.3</td>
<td>5.52 ± 0.41</td>
<td>13 (56.5)</td>
<td>14 (60.9)</td>
</tr>
<tr>
<td>57.3 ± 12.5</td>
<td>19 (82.6)</td>
<td>52.1 ± 9.8</td>
<td>5.48 ± 0.35</td>
<td>11 (47.8)</td>
<td>12 (52.2)</td>
</tr>
<tr>
<td>1.3 ± 0.8</td>
<td>21 (87.5)</td>
<td>49.9 ± 13.4</td>
<td>5.61 ± 0.38</td>
<td>12 (50.0)</td>
<td>12 (50.0)</td>
</tr>
<tr>
<td>61 ± 2.9</td>
<td>11 (41.7)</td>
<td>41 (14.8)</td>
<td>1 (4.2)</td>
<td>11 (45.8)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%); ns, not significant; LVEF, left ventricular ejection fraction; HbA1c, glycated hemoglobin A1c; MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2
Changes of clinical values pre- and post-rehabilitation.

<table>
<thead>
<tr>
<th>BMI</th>
<th>A: Insulin resistance</th>
<th>B: Normal</th>
<th>C: β-cell dysfunction</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>24.3 ± 2.3</td>
<td>23.3 ± 2.9</td>
<td>22.6 ± 2.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Post</td>
<td>24.0 ± 2.3</td>
<td>23.1 ± 2.4</td>
<td>22.6 ± 2.5</td>
<td>ns</td>
</tr>
<tr>
<td>IRI</td>
<td>Pre</td>
<td>11.2 ± 2.7</td>
<td>6.0 ± 1.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>9.1 ± 4.8</td>
<td>5.2 ± 2.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>Pre</td>
<td>104.8 ± 12.8</td>
<td>93.7 ± 6.6</td>
<td>107.1 ± 13.3</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>101.5 ± 7.9</td>
<td>99.7 ± 6.9</td>
<td>109.2 ± 12.7</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Pre</td>
<td>2.94 ± 0.98</td>
<td>1.40 ± 0.39</td>
<td>1.13 ± 0.39</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>2.30 ± 1.20</td>
<td>1.29 ± 0.68</td>
<td>1.23 ± 0.43</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>Pre</td>
<td>105.1 ± 41.3</td>
<td>71.7 ± 17.6</td>
<td>35.7 ± 10.5</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>74.0 ± 35.8</td>
<td>54.4 ± 27.2</td>
<td>36.9 ± 11.9</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>Pre</td>
<td>99.8 ± 27.3</td>
<td>107.5 ± 22.5</td>
<td>116.7 ± 22.2</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>95.8 ± 23.7</td>
<td>98.9 ± 31.4</td>
<td>107.5 ± 26.5</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>Pre</td>
<td>39.7 ± 12.8</td>
<td>40.7 ± 8.8</td>
<td>37.3 ± 8.8</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>50.8 ± 11.8</td>
<td>48.6 ± 9.1</td>
<td>52.7 ± 12.6</td>
</tr>
<tr>
<td>Peak VO₂ (mL/min/kg)</td>
<td>Pre</td>
<td>24.5 ± 4.3</td>
<td>26.1 ± 5.2</td>
<td>25.7 ± 5.4</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>29.4 ± 5.0</td>
<td>29.4 ± 6.4</td>
<td>28.2 ± 6.5</td>
</tr>
<tr>
<td>HA Peak VO₂ (mL/min/kg)</td>
<td>Pre</td>
<td>4.89 ± 4.06</td>
<td>3.32 ± 3.03</td>
<td>2.47 ± 2.14</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>3.32 ± 0.47</td>
<td>3.32 ± 0.47</td>
<td>2.47 ± 2.14</td>
</tr>
<tr>
<td>%Peak VO₂ (%)</td>
<td>Pre</td>
<td>21.6 ± 21.3</td>
<td>13.2 ± 11.9</td>
<td>9.4 ± 7.7</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>28.7 ± 3.8</td>
<td>28.8 ± 3.6</td>
<td>28.6 ± 3.9</td>
</tr>
<tr>
<td>VE vs. VCO₂ slope</td>
<td>Pre</td>
<td>27.6 ± 3.8</td>
<td>27.7 ± 3.1</td>
<td>27.3 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>1.79 ± 0.41</td>
<td>1.88 ± 0.52</td>
<td>1.87 ± 0.52</td>
</tr>
<tr>
<td>PT (Nm/kg)</td>
<td>Pre</td>
<td>1.90 ± 0.53</td>
<td>2.05 ± 0.53</td>
<td>2.07 ± 0.56</td>
</tr>
</tbody>
</table>

BMI, body mass index; IRI, immunoreactive insulin; FBS, fasting blood sugar; HOMA, homeostasis model assessment; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VO₂, oxygen uptake; Δ, increase; VE, minute ventilation; VCO₂, carbon dioxide output; PT, peak torque.  

p < 0.05 vs. pre.  
p < 0.01 vs. pre.

Fig. 1. Comparison of percentage increase in peak VO₂ among the three groups.  Percentage increase in peak VO₂ in the Group A was significantly higher than that of the Group C. ANOVA, analysis of variance; VO₂, oxygen uptake.
Knee extensor muscle strength peak torque

The maximum knee extensor power was comparable between the three groups both at baseline and after 3 months of training (Table 2). PT increased significantly in all groups and the percentage increase in PT had no significant inter-group difference.

Heart rate reserve and heart rate recovery in patients who do not use β-blockers or other negative chronotropic agents

In these subjects, HR dynamics were evaluated by using HR during CPX. This sub-analysis was performed in patients not taking β-blockers, digitalis, verapamil, or other negative chronotropic agents that influence HR dynamics. The number of subjects who were not taking such drugs was 45 (16, 14, and 15 patients in Groups A, B, and C, respectively). HR reserve was calculated as peak HR – rest HR, and was obtained during CPX. Chronotropic response (CR, %) was calculated as 100 × peak HR/220 – age (estimated peak HR). Additionally, HR recovery immediately after the exercise test was obtained as peak HR – HR 1 min after exercise. In this sub-study group, the same results of reduced peak VO₂ increase in Group C and comparable knee muscle strength were obtained.

HR reserve both at baseline and after training was comparable among the three groups. Although the HR recovery in Groups A and B significantly increased after training (baseline vs. after training: 73.4 vs. 85.5, 74.6 vs. 83.5, respectively, p < 0.01), it was unchanged in Group C (76.7 vs. 80.4) (Table 3).

HR reserve both at baseline and after training was significantly correlated with peak oxygen uptake (r = 0.57 and 0.55, respectively, p < 0.01), and the increase in HR reserve from baseline to after training was positively correlated with the increase in peak VO₂ (r = 0.32, p < 0.05).

Correlation between percentage increase in CR and increase in muscle strength

A rough, but significant positive correlation was obtained between percentage increase in CR and the increase in muscle strength (r = 0.24, p < 0.05).

Discussion

In general, IR occurs upstream of metabolic disorder. It is thought that the more severe IR, the more frequent progression to β-cell dysfunction and finally to DM. However, it was reported that populations of Asian descent, including that in Japan, had smaller β-cell number and volume compared with Westerners. This means that β-cell dysfunction in Japanese will manifest at an earlier stage of glucose intolerance and will easily progress to DM. Therefore, it is important to investigate the IR and β-cell function in patients with metabolic disorder or atherosclerosis if they have not yet been diagnosed with DM.

The HOMA-model used in this study is established as an index of both IR and pancreatic β-cell function [8]. The biggest advantage of this model over other methods is its simplicity; HOMA indices can be easily calculated both during hospitalization and at outpatient clinics by measuring only FBS and IRI. Many investigators have used this model for its convenience although the gold standard for evaluating IR is a steady-state plasma glucose or the glucose clamp method. Matthews et al. [8] reported that both IR and pancreatic β-cell function evaluated by using the HOMA model were well-correlated with those evaluated by using the glucose clamp method. IR evaluated by using the HOMA model was reported to be possibly inaccurate when the subjects’ FBS was greater than 140–150 mg/dL [16]. In the present study, baseline FBS was uniformly below 126 mg/dL, which is one of the defining components of DM. In the present study, HOMA-IR in the normal group significantly decreased and tended to decrease in the IR group after training. Insulin secretion may have decreased because of improved sensitivity after 3 months of training, whereas pancreatic β-cell function had not yet improved. HOMA-IR decreased on calculation. A longer training period or stronger training intensity may be necessary for improving HOMA-IR.

The most interesting and important result of the present study is the autonomic dysfunction that was already present in the prediabetic IR phase, along with pancreatic β-cell dysfunction. Impaired HR reserve in Group C might be influenced by autonomic dysfunction, because the HR recovery, an index of autonomic...
function, was also impaired in Group C, and HR recovery in group C did not increase after cardiac rehabilitation.

The HR reserve increase was attenuated after rehabilitation; the impairment in HR reserve increase directly influenced the improvement in exercise capacity. Impaired HR reserve increase after training was speculated to reflect low cardiac output increase after exercise training and may be caused by autonomic dysfunction or diastolic dysfunction as in patients with DM. In this study, exercise tolerance was positively correlated with HR reserve and its increase was limited in patients with attenuated pancreatic β-cell function. As in our previous studies on MI complicated with DM [2,5,6], HR reserve may already be attenuated during β-cell dysfunction (the prediabetic phase). The precise mechanism of reduced HR reserve in these patients remains unclear. However, we speculated that cardiac autonomic nervous dysfunction, as in the systemic nervous system, may already have begun in this prediabetic phase.

Yufu et al. [17] reported that autonomic dysfunction occurs in the advanced stage of diabetes, and can be a prognostic predictor for patients with DM. On the other hand, baroreflex sensitivity (BRS), an index of cardiac autonomic function, is reportedly impaired in the prediabetic hyperglycemic state as well as DM [18]. Moreover, BRS was reported to decrease in patients with IR and in the offspring of patients with type II DM, including those in whom DM had not manifested [19]. The mechanism of autonomic dysfunction in these patients involved an abnormal BP circadian rhythm, reduced BP, and a sympathetic vagal tone that decreased from day to night. Autonomic dysfunction preexists in patients with IR and may be a trigger for the development of hypertension or DM. Moreover, it was reported that autonomic function was impaired, characterized by sympathetic overactivity, in obese female adolescents (mean age, 12.7 years) who had IR but not impaired β-cell function [20]. In such cases of metabolic syndrome, autonomic dysfunction occurs in a younger population with a few other risk factors. Lifestyle modifications, including weight reduction and exercise training are needed to improve such sympathetic overactivity.

Slentz et al. [21] studied the effects of different intensities of an 8-month exercise training program on pancreatic β-cell function in middle to older aged sedentary, overweight, or mildly obese and moderately dyslipidemic subjects. They reported that both moderate and vigorous intensity exercise training improved β-cell function, whereas vigorous exercise intensity led to a compensatory decrease in insulin secretion, which was not shown in moderate intensity exercise. They regard vigorous training intensity as 65–80% of peak VO2, and moderate intensity as 40–55% of peak VO2. Vigorous intensity exercise is relatively risky for cardiac patients. However, it was reported that 7 consecutive days of supervised aerobic exercise training (1 h/day, 60–70% HR reserve) improved β-cell function and IR in older sedentary individuals [22]. Both the intensity and volume of exercise were lower than that in the report by Slentz et al. [21]. The intensity required to improve β-cell function may be at least 60–70% HR reserve during daily aerobic exercise.

Solomon et al. [23] showed that improved pancreatic β-cell function in patients with type II DM was obtained after lifestyle modification including 60–65% maximum HR intensity exercise following 80–85% exercise for 1 h/day and 5 days/week, and diet therapy for reducing 300 kcal/day total caloric intake. They also showed a mean weight decrease of 5.0 kg and improved insulin secretion from β-cells that was directly related to glucose-dependent insulinotropic polypeptide. Comprehensive interventions, including exercise and diet therapy, will be needed for prediabetic patients who do not have drug therapy indications. No correlation between the change in β-cell function and the changes in exercise tolerance and HR dynamics was obtained in the present study. The β-cell functions did not improve after 3 months’ training in all groups, because the duration and intensity of exercise training seemed to be relatively short and mild compared with the studies previously reported.

**Study limitations**

First, this study was designed retrospectively and was performed in a relatively small patient population. We carefully checked their medical histories from clinical charts, and fasting glucose and insulin measurements during MI hospitalization, because the inclusion of patients with DM among the present study subjects may confound the results. Additionally, the HR recovery in Group C tended to be lower, but not significantly. This might be caused by the small study population number. Further, it was suspected that their autonomic dysfunction was relatively mild. Patients with such prediabetic β-cell dysfunction may have relatively mild autonomic dysfunction compared with DM patients. Finally, a study with a larger study population and with different levels of severity is warranted.

We used the definition of IR as a HOMA-IR > 2.0, and impaired β-cell function as a HOMA-β < 50% in the present study, which were different from those frequently reported in the literature. Generally, a HOMA-IR > 2.5 and a HOMA-β < 40% have been used in reports by Western authors. However, it was reported that a HOMA-IR > 1.73 is useful as a standard for IR and concentration of coronary risk factors in the Japanese population [24]. Moreover, a HOMA-β < 50% was defined from the data of Japanese populations [14]. So, the definitions of IR and impaired β-cell function we used in the present study could fit appropriately to population in Japan.

Optimal medical therapy after MI has changed dramatically in this decade and several guidelines for cardiac patients recommend β-blocker administration after MI. In this study, the incidence of β-blocker administration was relatively low, approximately 38%. This may be because we included patients across a relatively long study period to evaluate the relationship between autonomic dysfunction and β-cell function. However, optimal medical treatment including coronary reperfusion therapy and rehabilitation were also performed equally.

**Conclusions**

Exercise training effects on functional capacity were attenuated even in patients with MI complicated by pancreatic β-cell dysfunction. It may be caused by attenuated HR reserve increase against exercise training. Comprehensive treatment including vigorous exercise training as well as drugs to improve β-cell function should be considered for such prediabetic patients.

**Conflicts of interest**

The authors have no conflicts of interest to declare.

**References**


