Journal of Cardiology 65 (2015) 128–133

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

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

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ARTICLE INFO

Article history:
Received 16 May 2013
Received in revised form 12 April 2014
Accepted 27 April 2014
Available online 19 June 2014

Keywords:
Insulin resistance
Pancreatic β-cell function
Cardiac rehabilitation
Heart rate reserve
Heart rate recovery

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 $\dot{V}O_2$ 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 $\dot{V}O_2$. 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.

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 $\dot{V}O_2$) 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 $\dot{V}O_2$ and blunted training effects [2,5,6].

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http://dx.doi.org/10.1016/j.jjcc.2014.04.012
0914-5087/

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 I 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:

$$\text{HOMA-IR} = \text{IRI}\,(\mu\text{U/mL}) \times \text{FBS}\,(\text{mg/dL})/405$$

$$\text{HOMA-}\beta = \text{IRI} \times 360/(\text{FBS-63})$$

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 $\dot{V}O_2$, and slope of the ventilatory equivalent ($\dot{V}E$) to carbon dioxide output ($\dot{V}CO_2$; i.e. the $\dot{V}E$ vs. $\dot{V}CO_2$ slope). Gas exchange ratio (GER) during exercise was obtained by $\dot{V}CO_2/\dot{V}O_2$. 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