Effects of cardiac rehabilitation in patients with metabolic syndrome after coronary artery bypass grafting

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KEYWORDS
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Summary
Background: Cardiac rehabilitation (CR) has numerous beneficial effects, including the modification of coronary risk factors and improvement of the prognosis, in patients with coronary artery disease (CAD). Limited data are available regarding the effects of CR on the physical status and risk factors in patients with metabolic syndrome (MetS) after coronary artery bypass grafting (CABG).

Methods and results: We enrolled 32 patients with MetS after CABG, who participated in a supervised CR program for 6 months. Metabolic parameters, blood chemistry, exercise tolerance, and muscle strength of the thigh were measured before and after CR. After CR: (1) the body mass index, waist circumference, and fat weight significantly decreased; (2) peak VO2 and anaerobic threshold were significantly increased; (3) isokinetic peak torques of knee extensor and flexor muscles significantly increased; (4) metabolic scoring defined by the number of the modified Adult Treatment Panel criteria of the US National Cholesterol Education Program.

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Metabolic syndrome (MetS), which is a clustering of cardiac risk factors caused by visceral fat accumulation, is closely linked with the initiation and progression of cardiovascular disease [1,2]. The accumulation of visceral fat is essential for the diagnosis of the MetS, which is considered to locate upstream of multiple risk factors [3]. The main concept of the MetS is to recognize the effective reduction of multiple coronary risk factors and subsequent cardiovascular diseases by the reduction of visceral fat [3]. Recently, much attention has focused on the relationship of inflammation in adipose tissue with the pathogenesis of MetS and atherosclerotic diseases [2—5]. It is clear that cardiac rehabilitation (CR) has numerous benefits involving not only modulating risk factors, but also preventing future cardiac events [6,7]. However, the impact of CR on metabolic parameters in patients with MetS after coronary artery bypass grafting (CABG) is still unclear. The purpose of the present study was to investigate the clinical usefulness of CR, including the improvement of metabolic risk factors and the inflammatory state, in patients with MetS after CABG.

Methods

Subjects

We enrolled 32 patients with MetS, defined by the modified Adult Treatment Panel criteria of the US National Cholesterol Education Program (waist size: male ≥85 cm and female ≥90 cm) after CABG at Juntendo University Hospital. All patients participated in CR after CABG (5—14 days). Patients with ongoing congestive heart failure, liver dysfunction, renal failure (creatinine ≥2.0 mg/dL), or systemic diseases, including malignancy and collagen disease, were excluded. All patients received anti-platelet therapy. The subjects took the following medications: calcium-channel blockers, n = 18; beta-blockers, n = 13; angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, n = 15; statins, n = 14; oral hypoglycemic agents, n = 8 and insulin, n = 5. No subjects underwent a change of medication throughout the study period except for three patients newly treated with statins. Subjects received full verbal and written explanations of the nature and purposes of the study, and each gave written informed consent. This study was approved by the Ethical Committee of Juntendo University.

Rehabilitation protocol

Supervised CR, which was composed of warm-up stretching, aerobic exercise, resistance training, and cool-down stretching, was performed once or twice a week for 6 months, as we described previously [8,9]. Aerobic exercise consisted of a cycle ergometer, treadmill, and walking on an in-room track. The total aerobic exercise time was approximately 60 min. The exercise intensity was prescribed individually at the anaerobic threshold (AT) level, as measured by an ergometer test using expiratory gas analysis or a rating of 11—13 (from fairly light to somewhat hard) on the standard Borg’s perceived exertion scale. Resistance training, which was gradually added to the exercise program at least 6 weeks after the beginning of participation, consisted of four types of training (sit-ups, back kicks and front raises, squats and push-ups) using the patients’ own weight. In addition, patients were encouraged to perform home-based aerobic exercise for more than 20 min at a rating of 11—13 of the perceived exertion on Borg’s scale twice a week. All subjects were instructed to follow the phase II diet of the American Heart Association after CABG at the beginning. An educational program was also provided for each subject by physicians, nurses, and dietitians regarding ischemic heart disease and risk factors at the baseline.

Measurements

We assessed body composition, exercise tolerance, and muscle strength before and after CR. Anthropometric parameters were assessed using the body mass index (BMI) and waist circumference. The percentages of body fat and lean body weight were measured by a BOD POD® (Life Measurement, Inc., Concord, CA, USA), as we described previously.
To measure peak oxygen consumption (peak VO₂) and the AT, patients underwent ergometer testing (Corival 400, Lode B.V. Groningen, Netherlands) using an expiratory gas analysis machine (Vmax-29S, SensorMedics Co., Yorba Linda, CA, USA). After a period of resting, warm-up was performed for a few minutes at 20 W, followed by ramp loading (15 W/min) until subjective exhaustion, progressive angina, ST-segment depression (≥2 mm), or sustained tachyarrhythmia. The point of AT was determined by the ‘V-slope’ method. The power of the thigh muscles was measured using the Cybex770 system (Cybex Division of Lumex, Ronkonkoma, NY, USA), as we reported previously [8,9]. The isokinetic peak torques of the knee extensor and flexor muscles were measured at 60°/s, and those were adjusted by body weight according to the following formula: strength (Nm) × 100/body weight (kg). Serum lipid profiles, including total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), and high-sensitivity C-reactive protein (hsCRP) were determined by an auto-analyzer after at least 12 h of fasting before performing CR. Concentrations of low-density lipoprotein cholesterol (LDL-C) were calculated with the Friedewald equation using the concentrations of TC, HDL-C, and TG.

**Definition of MetS score**

In the present study, the MetS score (from 0 to 5) was defined by the number of criteria of the modified Adult Treatment Panel criteria of the National Cholesterol Education Program. Each criterion, excluding waist size (male ≥85 cm and female ≥90 cm), was utilized following the original definition [10].

**Statistical analysis**

The results are expressed as the mean value ± standard deviation. Data at the baseline and after 6 months were compared in each patient by the paired t-test. A p-value of less than 0.05 was considered significant.

**Results**

**Baseline characteristics**

The baseline characteristics of the subjects are presented in Table 1. The prevalence of hypertension, diabetes, and dyslipidemia, was relatively high, because this study consisted of patients with MetS. Ninety-four percent of the subjects underwent an off-pump operation, and the mean number of times performing CR was 34.

### Parameters after CR for 6 months

**Physiological variables**

Physiological variables at the baseline and after CR are presented in Table 2. After CR, waist size (from 87.1 ± 8.5 to 84.0 ± 6.9 cm, p < 0.01), body weight (from 65.4 ± 9.5 to 63.5 ± 8.4 kg, p < 0.01), fat weight (from 18.5 ± 5.1 to 17.2 ± 4.7 kg, p < 0.05), and % fat (from 28.7 ± 5.5 to 26.8 ± 6.0%, p < 0.01) were significantly decreased and the lean body weight was increased (from 45.6 ± 6.9 to 46.5 ± 6.7 kg, p < 0.005).

**Exercise tolerance and strength of thigh muscles**

Exercise tolerance and the strength of the thigh muscles at the baseline and after CR are presented in Figs. 1 and 2, respectively. Peak VO₂ and AT significantly increased after CR (from 14.2 ± 3.7 to 19.2 ± 5.2 ml·kg⁻¹·min⁻¹, p < 0.001, and 8.8 ± 1.9 to 11.5 ± 3.1 ml·kg⁻¹·min⁻¹, p < 0.001, respectively). The isokinetic peak torques of the knee extensor and flexor muscles were significantly increased after CR (from 149 ± 41 to 169 ± 47 Nm·kg⁻¹ × 100, p < 0.001, and 85 ± 28 to 98 ± 30 Nm·kg⁻¹ × 100, p < 0.001, respectively).

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics.</th>
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<tr>
<td>N</td>
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<tr>
<td>Age (year)</td>
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<tr>
<td>Male (%)</td>
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<tr>
<td>Body mass index (kg·m⁻²)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
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<tr>
<td>Diabetes mellitus (%)</td>
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<tr>
<td>Dyslipidemia (%)</td>
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<tr>
<td>% fat</td>
</tr>
<tr>
<td>Off pump (%)</td>
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<tr>
<td>Number of bypass grafting (n)</td>
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<td>Exercise in hospital (times)</td>
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Data are presented as the mean value ± S.D.

<table>
<thead>
<tr>
<th>Table 2 Physiological variables.</th>
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<tr>
<td>Pre</td>
</tr>
<tr>
<td>Waist (cm)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Fat weight (kg)</td>
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<tr>
<td>Lean weight (kg)</td>
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<td>% fat</td>
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Figure 1 Left: change of peak VO$_2$ (oxygen uptake) between pre- and post-training. Right: AT (anaerobic threshold) between pre- and post-training.

Figure 2 Left: change of knee extension between pre- and post-training. Right: knee flexion between pre- and post-training.

Serum lipid profiles, glucose parameters, and blood pressure
Serum lipid profiles, glucose parameters, and blood pressure at the baseline and after CR are presented in Table 3. Serum concentrations of TC and LDL-C were significantly decreased after CR (from 199 ± 34 to 182 ± 28 mg/dL, p < 0.01 and from 122 ± 29 to 111 ± 22 mg/dL, p < 0.05, respectively). However, no significant changes were observed in other values.

Table 3 Clinical variables pre- and post-cardiac rehabilitation.

<table>
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<tr>
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<th>Pre</th>
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<tr>
<td>TC (mg/dL)</td>
<td>199 ± 34</td>
<td>182 ± 28</td>
<td>0.008</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>122 ± 29</td>
<td>111 ± 22</td>
<td>0.047</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>174 ± 74</td>
<td>139 ± 66</td>
<td>0.060</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>43 ± 13</td>
<td>44 ± 11</td>
<td>0.602</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>135 ± 45</td>
<td>131 ± 50</td>
<td>0.420</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.2 ± 1.3</td>
<td>6.2 ± 1.3</td>
<td>0.613</td>
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<tr>
<td>SBP (mmHg)</td>
<td>140 ± 16</td>
<td>134 ± 19</td>
<td>0.143</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 ± 11</td>
<td>76 ± 8</td>
<td>0.897</td>
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</table>

Data are presented as the mean value ± S.D. TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Serum levels of hsCRP
Serum levels of hsCRP were significantly decreased after CR (from 0.30 ± 0.21 to 0.25 ± 0.29 mg/dL, p < 0.001) (Fig. 3). A significant decrease was also observed after the exclusion of three patients who were newly prescribed statins after CABG (from 0.27 ± 0.19 to 0.19 ± 0.18 mg/dL, p < 0.005).

MetS score
The MetS score was significantly decreased after CR (from 3.6 ± 0.7 to 2.4 ± 1.0, p < 0.001) (Fig. 4).

Discussion
The present study showed that CR for 6 months ameliorated not only metabolic parameters, but
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also the exercise capacity, muscle strength, and inflammatory state in MetS patients after CABG.

The prevalence of MetS, closely linked to the initiation and progression of cardiovascular diseases, has markedly increased in not only developed countries, but also developing nations [11,12]. Indeed, we and other groups reported the impact of MetS on clinical outcomes in patients with coronary artery disease [11–13]. Although it has been elucidated that exercise decreases the prevalence of MetS [14–16], the beneficial effects of CR in patients with MetS, especially after CABG are still unclear. Milani and Lavie [17,18] reported that CR improved multiple metabolic derangements, however, the subjects consisted of patients with various diagnoses after major cardiac events. Shubair et al. [19] showed that CR resulted in a significant improvement in the cardiovascular risk profiles, including body weight, lipid profile, blood glucose, and exercise capacity, however, this study also consisted of patients with various diagnoses of coronary artery disease. Patients who need to undergo CABG show a high risk based on clinical findings, such as multi-vessel disease and diabetes [20]. It is clear that these clinical manifestations are associated with a poor outcome in the clinical setting [21,22]. Therefore, it is very important to investigate the efficacy of CR for improving metabolic parameters in patients after CABG.

It has been clearly established that exercise tolerance is a good predictor of the prognosis in patients with cardiovascular diseases [23,24]. In addition, muscular strength is also associated with all-cause mortality [25]. A report from the WHO suggested that increased muscle strength results in an improved long-term prognosis [26]. The present study did not include non-participating patients. It is possible that exercise tolerance might be improved by not only the natural course after CABG, but also the effect of CR. Indeed, Perk and Hedback reported that patients participating in CR following CABG showed a greater increase in work capacity and a more favorable effect on myocardial oxygen consumption compared with non-participating patients [27,28]. Our recent study also demonstrated that muscle strength of the lower limbs did not change in non-participating patients with coronary artery disease, including post CABG [9]. Therefore, we believe that CR, at least partly, brought about the amelioration of exercise tolerance and muscular strength, and may be an important strategy in patients with MetS after CABG.

Chronic inflammation plays an important role in the initiation and progression of atherosclerosis [2,5,29,30]. Indeed, circulating levels of hsCRP, which is one of the acute phase-reactant proteins in inflammatory reactions, are elevated in patients with coronary heart disease [26,29]. Moreover, high levels of hsCRP can predict mortality and future cardiac events in various patients with cardiovascular diseases [31]. Some previous studies have reported the improvement of hsCRP elevation in participants with CR [32,33]. The result of hsCRP reduction in patients with CR after CABG is consistent with previous results. No reports have investigated the changes of hsCRP comparing CR and non-CR groups in patients after CABG. Previous studies showed that the levels of hsCRP remained unchanged in the control group after percutaneous coronary intervention [34,35]. Eyileten et al. reported that hsCRP levels significantly decreased 1 month after CABG. However, the subjects in their study must be different from those of the present study. Because the mean levels of hsCRP in Eyileten’s study were relatively high (from $1.315 \pm 0.240$ to $0.725 \pm 0.189 \text{ mg/dL}$), suggesting that subjects who had ongoing acute inflammation...
were included [36]. Moreover, the levels of hsCRP at the baseline were significantly higher in patients with than in those without MetS after CABG (data not shown), suggesting that CR is a useful strategy to improve the inflammatory state even in MetS patients after CABG.

Limitations

There are several limitations to the present study. First, this is a small sample-sized study. Second, the supervised exercise in the outpatient clinic was performed only once or twice a week. Therefore, the protocol of the present study might not be sufficient to improve the metabolic status, such as TG and HDL-C levels. Third, the present study consisted of only subjects who participated in CR after CABG. We assessed the levels of serum lipids and hsCRP in 14 patients (12 males, 66 ± 8 years) with MetS, who did not participate in supervised CR after elective CABG in the outpatient clinic because of difficulty undergoing CR (a long distance from home to hospital) during the same period. Before and 6 months after CABG, no significant changes in TC (from 189 ± 26 to 208 ± 37 mg/dL, p = 0.11), LDL-C (from 112 ± 23 to 125 ± 34 mg/dL, p = 0.25), TG (from 214 ± 72 to 212 ± 97 mg/dL, p = 0.93), or hsCRP (from 0.22 ± 0.13 to 0.26 ± 0.22 mg/dL, p = 0.51) were observed. The results of this study need to be confirmed using a prospective and randomized study design involving patients participating and not participating in CR. However, we believe that the present study is a pioneering and valuable report promoting further investigations.

Conclusion

CR might have effects on not only the modification of metabolic risk factors, but also improving exercise tolerance and muscular strength in patients with MetS after CABG. Further studies with a control group are required to confirm these findings and to assess the efficacy of CR for improving the clinical prognosis in MetS patients after CABG.

Acknowledgments

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