Effects of Physical Training on the Recovery of the Autonomic Nervous Activity During Exercise After Coronary Artery Bypass Grafting

Effects of Physical Training After CABG

Junichiro Takeyama, MD*; Haruki Itoh, MD; Makoto Kato, MD; Akira Koike, MD; Keiichi Aoki, MD; Long Tai Fu, MD; Hiroshi Watanabe, MD; Masatoshi Nagayama, MD*; Takashi Katagiri, MD*

Analysis of heart rate variability (HRV) can identify patients at risk of sudden cardiac death after myocardial infarction. The present study examined the effect of 2 weeks of supervised aerobic exercise training on the recovery of the autonomic nervous activity, exercise capacity, and cardiac output (CO) after coronary artery bypass grafting (CABG). Twenty-eight patients were randomly divided into the training group or the control group and performed exercise tests at 1 week, 3 weeks, 3 months, 6 months and 1 year after CABG. The HRV was measured, and the high-frequency component of HRV was used as an index of parasympathetic nerve activity (PNA); the plasma norepinephrine concentration (NE) was used as an index of sympathetic nervous activity. Cardiac output was also measured. In the training group, peak VO2, peak CO and PNA during exercise had improved at 3 weeks, but there was no improvement in these indices in the control group. NE decreased 1 week after CABG in both groups. These results indicate that physical training soon after CABG improves not only the exercise capacity, but also PNA. (Jpn Circ J 2000; 64: 809-813)

Key Words: Aerobic exercise training; Coronary artery bypass grafting; Heart rate variability; Norepinephrine

Analysis of heart rate variability (HRV) is a noninvasive method of evaluating autonomic nervous system effects on the heart. It can identify patients at risk of sudden cardiac death after myocardial infarction (MI) independently of other risk factors, including clinical features, ventricular arrhythmias, ventricular late potentials and the left ventricular ejection fraction (LVEF).

Coronary artery bypass grafting (CABG) is an established treatment in patients with ischemic heart disease, but in post-CABG patients the status of sympathetic nervous activity (SNA) and parasympathetic nervous activity (PNA) is not fully understood. We used HRV analysis to investigate the effects of short-term supervised aerobic exercise training on the autonomic nervous system, exercise capacity and cardiac output (CO) at rest and during exercise in post-CABG patients. We also examined the difference between the time course of the recovery of SNA and that of PNA.

Methods

The study was approved by the Ethics Committee of the Cardiovascular Institute Hospital and all subjects gave informed consent.

(Received February 17, 2000; revised manuscript received July 19, 2000; accepted July 21, 2000) Cardiovascular Institute Hospital and *Third Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan Mailing address: Junichiro Takeyama, MD, Third Department of Internal Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-Ku, Tokyo 142-8666, Japan

Table 1  Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Training group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>58.8±5.3</td>
<td>61.7±8.7</td>
<td>NS</td>
</tr>
<tr>
<td>M/F</td>
<td>130</td>
<td>132</td>
<td>NS</td>
</tr>
<tr>
<td>AP/previous MI</td>
<td>3/10</td>
<td>1/10</td>
<td>NS</td>
</tr>
<tr>
<td>No. of grafts</td>
<td>2.8±1.8</td>
<td>2.7±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>62.5±12.7</td>
<td>61.6±11.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as the mean±SD. AP, angina pectoris; LVEF, left ventricular ejection fraction; MI, myocardial infarction.
All subjects were stable and were being treated with diuretics, nitrates, Ca antagonists and anti-coagulants. Angiotensin-converting enzyme inhibitors were used in 6 patients in the training group and in 8 patients in the control group. We excluded patients receiving β-blockers and those with arrhythmias (atrial fibrillation, frequent extrasystole). There were no significant differences in the age, number of grafts, LVEF or in the use of angiotensin-converting enzyme inhibitors between the 2 groups.

Protocol

The subjects underwent cardiopulmonary exercise tests with expired gas analysis and measurement of CO at 1 week after surgery, when they no longer had a fever and were able to walk at least 200 m without symptoms or significant ECG changes.

All patients in both groups began a rehabilitation program 1 week after CABG. In the training group, the exercise program consisted of 30 min of training on a cycle ergometer twice daily for 2 weeks. The exercise training was performed at the anaerobic threshold that was determined 1 week after CABG. One week later, the exercise test for a new exercise program was done, and patients did the training based on the new prescription for 1 more week. The patients in the control group were asked to walk 200 m 3 times daily; the walking distance was increased up to 500 m within 2 weeks. After 2 weeks of rehabilitation in the hospital, all patients underwent an exercise test and were then discharged. None of the subjects followed any special physical training program after discharge from the hospital.

Cardiopulmonary exercise tests were performed to evaluate the exercise capacity, CO and autonomic nervous activity at 1 week, 3 weeks, 3 months, 6 months and 1 year after surgery.

Cardiopulmonary Exercise Test

Cardiopulmonary exercise tests were performed with an electromagnetically controlled cycle ergometer (CPE-2000, MedGraphic Co, Minneapolis, MN, USA). After resting for 4 min on the ergometer, the subject began exercising with a 4-min warm-up at 20 W at 60 rpm; the work rate was increased by 1 W every 6 s until exhaustion. A 12-lead ECG and the HR were monitored throughout the test using the Stress Test System (ML-5000, Fukuda Denki, Tokyo, Japan). The cuff blood pressure was measured every minute with an automatic indirect manometer (Stress Test Blood Pressure Monitor STBP-780, Colin Denki, Aichi, Japan). Respiratory gas analysis was performed using the Aemo Monitor AE-280 (Minato Medical Science, Osaka, Japan), which consists of a zirconia O₂ analyzer, an infrared CO₂ analyzer and a hot-wire spirometer. The system was carefully calibrated before each study and O₂ uptake (VO₂), CO₂ output (VCO₂), and expired tidal volume were continuously measured on a breath-by-breath basis.

The anaerobic threshold was determined from the gas exchange data by the V-slope method using software developed at our institute that determines the turning point of the VO₂-VCO₂ relation curve using 2 linear regression lines. The peak O₂ was defined as the mean VO₂ during the last 30 s of each test.

Power Spectral Analysis and HRV

HRV data were analyzed by fast Fourier transformation. Spectral analysis of HRV was performed according to the methods described by Yamamoto and Hughson. Before the HRV spectra were analyzed, we screened 3 min of HRV data, excluding the first minute from the rest period and 20 W of the warm-up period, for extra or missing beats that could affect the results of spectral analysis. Abnormal intervals were corrected by either omitting (those <300 ms) or inserting beats (those with double or triple length of preceding intervals) with less than 2% of the total beats being corrected manually in this way. Spectral HRV was expressed as a low-frequency (LF: 0.04-0.15 Hz) component and a high-frequency (HF: 0.15-0.80 Hz) component; in this study the power of the HF component was used as an index of PNA.

Assay of Norepinephrine (NE)

Blood samples for NE were obtained at rest and the end of the 4-min warm-up. Samples were transferred immediately into ice-cold tubes containing ethylenediaminetetraacetic acid and centrifuged at 4°C. Plasma was separated and stored at –80°C until assayed. The plasma concentration of endogenous NE was determined using an HLA-725CA automated catecholamine analyzer (Toho, Tokyo, Japan), which consists of a high-performance liquid chromatography column with fluorescence detection using 1,2-diphenyl-ethylenediamine as the fluorescence derivation reagent. The plasma NE concentration was used as an index of SNA.

Measurement of CO

Cardiac output was measured at rest and at peak exercise by the dye dilution method with indocyanine green, using an ear photoelectric transducer. Analysis was performed by a special purpose computer (Cardiac Output Computer MLC-4200, Nihon-Koden, Tokyo, Japan), a method that is considered comparable to measuring CO during exercise.

Statistical Analysis

Data are expressed as the mean±SD. The statistical significance of differences were analyzed with unpaired t test and 2-way analysis of variance (ANOVA) followed by Tukey-Kramer’s test for between-group comparisons and Dunn’s test for individual comparisons of values at 1 week versus those at 3 weeks, 3 months, 6 months, and 1 year. A p value less than 0.05 was considered statistically significant.

Results

None of the 28 patients had any major complications, such as worsening of heart failure, worsening of ischemia, sudden cardiac death or other cardiac events, during the study.

Exercise Capacity

The anaerobic threshold increased significantly in the training group at 3 weeks after surgery compared with 1 week after surgery (from 10.6±1.6 to 11.9±1.6 ml min⁻¹ kg⁻¹, p=0.04). In the control group, the anaerobic threshold showed no increase at 3 months after surgery, and the eventual increase did not become significant until 6 months after surgery (from 11.6±1.3 to 13.1±1.3 ml min⁻¹ kg⁻¹, p=0.01). The change from baseline was significantly greater in the training group than in the control group at 3 weeks after surgery (1.5±1.2 vs -0.2±0.9 ml min⁻¹ kg⁻¹, p=0.02).

The peak VO₂ increased significantly at 3 weeks after surgery compared with 1 week after surgery in the training group only (from 13.1±1.7 to 16.1±2.0 ml min⁻¹ kg⁻¹, p=0.001). The control group exhibited a significant increase
in the peak VO₂ at 3 months after surgery compared with 1 week after surgery (from 13.7±2.5 to 17.2±2.8 ml.min⁻¹.kg⁻¹, p=0.003). The change from baseline was greater in the training group than in the control group at all measurement points.

There were no significant body weight changes throughout the study in either group (Table 2).

CO

The CO at rest showed no significant increase from 1 week to 1 year after surgery in either group and there was no significant difference between the groups. The peak CO increased significantly from 1 week to 3 weeks after surgery (from 10.6±2.4 to 13.4±2.1 L/min, p=0.01) and increased slightly thereafter in the training group. The control group showed no significant increase in the peak CO from 1 week to 1 year after surgery (Table 3). The change in CO from baseline was significantly greater in the training group than in the control group at 3 weeks after surgery (2.8±2.2 vs 0.1±1.5 L/min, p=0.02).

**Plasma NE Concentration**

The plasma NE concentration at rest decreased early after surgery (at 3 weeks) in both groups; there was no significant difference in the change in the NE concentration between the groups. In the overall study population, the plasma NE concentration decreased significantly at 3 weeks after surgery (1 week = 565±192, 3 weeks = 365±141, 3 months = 377±150, 6 months = 320±100, 1 year = 331±108 pg/ml, *p<0.05 vs 1 week).

The plasma NE concentration at 20 W of constant load exercise showed the same pattern as that of at rest. In the overall study population, the plasma NE concentration decreased significantly at 3 weeks after surgery (1 week = 917±450, 3 weeks = 509±236, 3 months = 494±225, 6 months = 442±177, 1 year = 439±189 pg/ml, *p<0.05 vs 1 week). The age-matched normal value (21 men and 3 women) of the NE concentration at 20 W of constant load exercise was 290±110 pg/ml in our laboratory.

**HRV**

The HF component at rest increased significantly at 3
months after surgery compared with 1 week after surgery in both groups (from 24.8±14.7 to 42.4±14.3 ms² in the training group, p=0.02; from 20.4±13.9 to 43.0±9.2 ms² in the control group, p=0.013). There was no significant difference between the groups. In the overall study population, the HF component increased significantly at 3 weeks after surgery (1 week=21.4±14.6, 3 weeks=35.1±19.4, 3 months=42.7±12.0, 6 months=49.1±20.4, 1 year=61.6±40.2 ms²), \( p<0.05 \) vs 1 week). The age-matched normal value (18 men and 2 women) of the HF component at rest determined in our laboratory was 159.8±96.0 ms².

The HF component at 20 W of constant load exercise increased significantly at 3 weeks after surgery compared with 1 week after surgery in the training group (from 9.6±6.2 to 21.0±19.9 ms², \( p=0.04 \)). In the control group, the HF component did not increase significantly until 3 months after surgery (from 8.8±7.5 to 18.5±12.7 ms², \( p=0.04 \)) (Table 4). The improvement from baseline was smaller in the control group than in the training group at all measurement points. In the overall study population, the HF component increased significantly at 3 months after surgery (1 week=9.2±8.2, 3 weeks=14.9±13.0, 3 months=24.3±19.0, 6 months=24.3±21.6, 1 year=26.4±20.7 ms², \( p<0.05 \) vs 1 week). The age-matched normal value (18 men and 2 women) of the HF component at 20 W of constant load exercise determined in our laboratory was 74.5±56.3 ms².

#### Discussion

A decrease in PNA in patients with ischemic heart disease may be associated with sudden cardiac death, which makes PNA a prognostic marker in these patients. SNA reflects the severity of heart failure and is closely associated with prognosis. The present study assessed SNA and PNA at rest and during 20 W of constant load exercise in patients after CABG by measuring the plasma NE concentration and HRV, and previous data supported the concept that physical training improves not only the exercise capacity but also PNA.

The measurement of HRV during exercise has been reported as useful for evaluating the autonomic nervous function during low-intensity exercise. In the present study, the ratio of the LF to HF components of HRV, which has been shown to be an index of SNA, showed no association with the plasma NE concentration, and this may have been partly a result of the short sampling period.

It has also been reported that the HF component is influenced by the ventilatory pattern, that is, a higher respiratory rate reduces the HF component, and a larger tidal volume increases it. In the present study, the respiratory rate tended to decrease slightly and the tidal volume tended to increase slightly at rest and at 20 W of exercise in both groups (Table 5); there were no significant differences in these parameters between the 2 groups at any measurement point. The ventilatory pattern might affect the value of the HF component, but the difference in the HF component between the present groups was not because of the ventilatory pattern.

The time courses of the recovery of SNA and PNA were different. In the overall study population, SNA improved soon after surgery, whereas PNA improved at 3 months after surgery.

Arterial and cardiopulmonary baroreflex control, both of which are reduced in patients with acute MI, gradually recovers during the chronic phase. Exercise training in young athletes increases the cardiopulmonary baroreflex control, and PNA has been shown to be decreased in sedentary healthy subjects. These results suggest that aerobic exercise training soon after CABG could correct the autonomic imbalance observed after this operation, probably by improving the baroreflex sensitivity. We also speculate that the effects of exercise training on autonomic nervous activity may not differ between the diseased state and the state of deconditioning without disease; however, these speculations will have to be tested in future studies.

In the training group the anaerobic threshold, peak VO₂, HF component during exercise and peak CO increased significantly at 3 weeks after surgery compared with the baseline values, whereas in the control group these indices did not improve. Moreover, the improvements of the peak VO₂ and the HF component in the training group persisted for months. The reason for this is unknown, but it is possible that the physical training before discharge encouraged patients to continue exercising after they left the hospital. No significant difference was noted between the groups in the change of the plasma NE concentration. The aerobic exercise training did not affect the recovery of SNA, even though SNA was activated during exercise.

We conclude that aerobic exercise training early after CABG was associated with early and long-term improvements in exercise capacity and PNA during exercise without affecting the recovery of SNA. The present data also indicate
that SNA improved soon after surgery, but PNA recovered later.

Acknowledgments

We thank Mr. Yohto Nakamura for technical assistance in measuring and evaluating HRV, and Mr. Tokujiro Ohuchi and Mr. Yugi Kawamoto for statistical assistance. We also thank Mr. Akihiko Tajima, Mrs. Naomi Harada and Miss Tomoko Maeda for technical assistance in performing the cardiopulmonary exercise tests.

References