ischemia occurs would slow the cardiac output response to the increasing work rate and simultaneously increase the O_2 deficit. This would be expected to increase the O_2 debt in recovery, the latter evidenced by a slowing of recovery $\dot{V}O_2$ kinetics. To investigate this hypothesis and to determine the sensitivity and specificity of gas exchange measurements to complement traditional tests to detect CAD, we determined the slope ratios of the increase in $\dot{V}O_2$ with respect to the increase in work rate ($\Delta\dot{V}O_2/\Delta WR$) above compared to below the anaerobic or ischemic threshold in patients with suspected angina and positive ECG changes suggestive of myocardial ischemia. Additionally, the $\dot{V}O_2$ kinetics during recovery from exercise, as evidence of an increased O_2 debt, was compared in CAD positive (+) and negative (–) patients. Thus a progressively increasing work rate test, in which gas exchange was measured, was used to provide evidence of impaired cardiac function at specific exercise levels in patients with suspected CAD.

Methods

Patients

Forty-two consecutive patients (average age of 62.9±9.1 ranging 38–77 years including 37 males and 5 females) with suspected effort-induced chest pain on exertion, and who exhibited significant ST depression (more than 1 mm at 60 ms after J point for the horizontal ST depression and at J point for the down-sloping depression)[10] in a treadmill exercise tolerance test (Bruce protocol) were entered into the study. Each patient underwent a CPET followed by exercise stress radio-isotope (RI) scintigraphy test and coronary angiography (CAG) within 2 weeks. Patients with previous myocardial infarction, left ventricular hypertrophy, dilated cardiomyopathy, valvular heart disease, anemia, and lung diseases (eg, obstructive or restrictive) were excluded. This study was approved by the ethical committee of The Cardiovascular Institute and was conducted according to the guidelines of the Declaration of Helsinki.

Cardiopulmonary Exercise Test

A symptom-limited CPET was performed on all patients, using an upright cycle ergometer (Corival 400; Lode BV; Groningen, The Netherlands). After a 4-min rest on the ergometer, exercise began with a 4-min warm-up at 0 W, 50 rpm, followed by 1-W incremental loading every 6 s. The ECG and heart rate (HR) were monitored throughout the test and recorded every 30 s by 12-lead exercise ECG (Stress System ML-4500; Fukuda Denshi Co Ltd; Tokyo, Japan). We determined the point of 1 mm ST depression (ST-dep) by the ST level trendgram. Cuff blood pressure was also measured every minute with an automatic indirect manometer (Stress Test Blood Pressure Monitor STBP-780; Nippon Colin Co Ltd, Aichi, Japan).

We measured the $\dot{V}O_2$, CO_2 output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}E$) on breath-by-breath basis using an expired gas analyzer AE-280S (Minato Medical Science Co Ltd, Osaka, Japan). The system was carefully calibrated before each study. The expired gas data obtained were converted into time-series data every 3 s. Then, an 8-point moving average was performed. From the expired gas analysis, the AT was determined by V-slope method.[11]

Peak $\dot{V}O_2$ was defined as the average value obtained during the last 30 s of incremental exercise. We measured $\Delta\dot{V}O_2/\Delta WR$ slopes for 2 min below and above the AT point and calculated the ratio of the above to the below AT slopes (slope ratio across AT). We also measured $\Delta\dot{V}O_2/\Delta WR$ below and above the ST depression of 1 mm along with the slope ratio between them (slope ratio across ST-dep). $\Delta\dot{V}O_2/\Delta WR$ during exercise was calculated by a linear fit of 2 min (40 points) below and 2 min above the AT and ischemic threshold.

The half time for $\dot{V}O_2$ to return to pre-exercise baseline ($T_{1/2}$) after exercise was calculated from the onset of recovery after exercise. This would reflect the size and rate of repayment of the O_2 debt.[12]

There were 3 patients who were ECG positive on the treadmill stress test, but did not show significant ST depression in the cardiopulmonary exercise test, by cycle ergometry. They were excluded from the study.

Stress Radioisotope Scintigraphy

Within 2 weeks after CPET, patients underwent stress RI scintigraphy using a treadmill with the Bruce protocol. From a bull's eye map, an area counting 2×standard deviation or less in comparison to a database prepared from 50 normal adults in our hospital was measured. The area of reduced ^{201}Thallium uptake was calculated as an extent score which reflects an area where myocardial blood flow is decreased.

CAG

Thirty-nine patients underwent CAG within 2 weeks after CPET. They were classified based on the results of the angiography as CAD+ or CAD– with or without significant stenosis (≥75%), respectively.[13] When patients showed normal coronary arteries, the provocation test for vasospasm, using acetylcholine, was performed. Two patients who diagnosed as vasospastic angina were excluded from the analysis. The left ventricular ejection fraction was measured by left ventriculography.

The medications, such as Ca antagonists, nitrates, and β-blockers, were all stopped 24 h before the CPET, RI scintigraphy, and CAG.

CPET was repeated 3–4 months later in 5 patients who had coronary artery bypass graft surgery (CABG) after the CAG. The same measurements were obtained.

Statistical Analysis

Statistical analysis was performed using SPSS statistical software (SPSS ver.11.0J, SPSS Japan Inc). Unpaired Student's t-tests were used to compare CAD+ or CAD– group means of CPET variables and patients' backgrounds.

Results

Two patients diagnosed as vasospastic angina were not included in this analysis. In total, therefore, the data from 37 patients were analyzed (33 males and 4 females, 60.6± 9.8 years).

Endpoint of Exercise

Most of all the patients in the CAD– group stopped the exercise test because of leg fatigue or SOB. In contrast, 16 of 18 patients in the CAD+ group stopped the test because of either chest pain or ST depression of more than 2 mm.

AT, Peak $\dot{V}O_2$

Figure 1 shows the typical $\dot{V}O_2$ kinetics and HR-$\dot{V}O_2$ curves during incremental exercise. The CAD– patient (case no. 9) showed a linear, non-changing increase in $\dot{V}O_2$

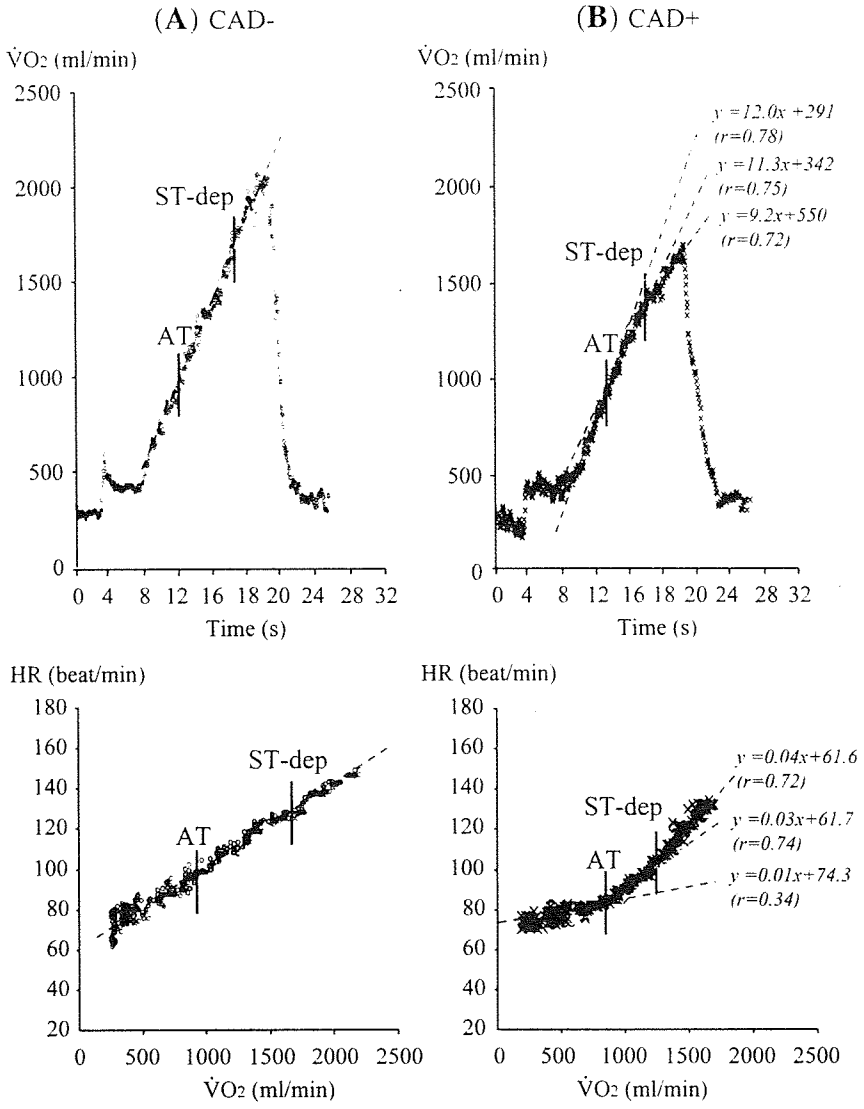

Figure 1. Oxygen uptake ($\dot{V}O_2$) kinetics (**Upper**) and heart rate (HR)-$\dot{V}O_2$ curves during exercise (**Lower**). In the coronary artery disease (CAD)– patients, $\dot{V}O_2$ increased linear to the work rate below and above anaerobic threshold (AT). However, $\dot{V}O_2$ increased more slowly above AT than below AT in CAD+ patients. The HR-$\dot{V}O_2$ curves became steeper in CAD+ patient in accordance with exercise intensity while it remained linear in CAD– patient above AT (**Lower**).

Table 1. Results of Cardiopulmonary Exercise Testing, Radio-Isotope Scintigraphy, and Cardiac Catheterization in Patients With and Without Significant Coronary Stenosis

	CAD– group(n=19)	CAD+ group (n=18)	P-values*
Age (year)	56.8±9.9	64.2±8.8	0.025
Heart rate at rest (beats/min)	71.6±13.1	71.3±7.6	0.934
Heart rate at peak (beats/min)	146.5±18.0	121.1±15.7	<0.001
Systolic blood pressure at rest (mmHg)	141.1±19.8	142.6±22.0	0.834
Systolic blood pressure at peak (mmHg)	221.4±17.4	187.2±28.7	<0.001
Oxygen uptake at AT ($ml \cdot min^{-1} \cdot kg^{-1}$)	13.0±2.4	12.1±1.5	0.261
Oxygen uptake at peak ($ml \cdot min^{-1} \cdot kg^{-1}$)	24.1±4.3	17.9±3.3	<0.001
Peak work rate (W)	122.3±26.0	82.8±20.2	<0.001
$T_{1/2}$ $\dot{V}O_2$ (s)	55.7±8.8	78.1±10.9	0.006
Total extent score	6.2±11.6	155.8±151.8	<0.001
No. of diseased vessels	0	1.9±0.9	
Ejection fraction by left ventriculography (%)	71.4±5.1	67.4±7.6	0.064

*P values by unpaired t-test.
CAD–, patient without significant coronary artery stenosis; CAD+, patient with significant coronary artery stenosis; AT, anaerobic threshold; $T_{1/2}$ $\dot{V}O_2$, half time recovery of $\dot{V}O_2$ after exercise.

relative to work rate below and above AT. The CAD+ patient (case no. 28) demonstrated same pattern of $\dot{V}O_2$ as CAD– patient below AT. However, the pattern showed a reduced rate of $\dot{V}O_2$ increase relative to work rate above AT and ST-dep. Also the CAD+ patient showed a non-linear steepening HR-$\dot{V}O_2$ curve, in contrast to the linear HR-$\dot{V}O_2$ curve typical of CAD– patient during increasing work rate exercise (**Figure 1 Lower**).

AT values averaged 13.0±2.4 and 12.1±1.5 $ml \cdot min^{-1} \cdot kg^{-1}$ for the CAD– and CAD+ groups, respectively, and these

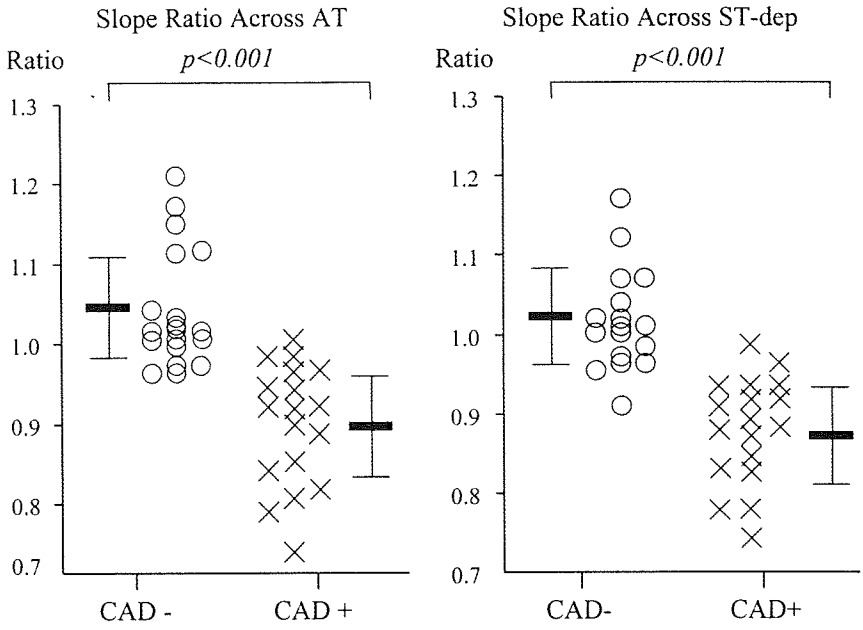

Figure 2. The ratio of $\Delta\dot{V}O_2/\Delta WR$ for 2 min below to above anaerobic threshold (AT) (**Left**) and ratio of $\Delta\dot{V}O_2/\Delta WR$ for 2 min below and above 1 mm ST depression point (ST-dep) (**Right**). There were no statistical difference between the $\Delta\dot{V}O_2/\Delta WR$ below and above AT in coronary artery disease (CAD)– group, whereas $\Delta\dot{V}O_2/\Delta WR$ above AT was significantly lower than that of below AT (P<0.001) in CAD+ group. Therefore, the slope ratio across AT in CAD+ group was significantly lower than that of CAD– group (P<0.001, **Left**). The $\Delta\dot{V}O_2/\Delta WR$ in the CAD– group for 2 min below ST-dep was not differrent from that of above ST-dep. In the CAD+ group, $\Delta\dot{V}O_2/\Delta WR$ above ST-dep was significantly lower than that of below ST-dep (P<0.001). The slope ratio across ST-dep in CAD+ group was significantly lower than that of CAD– group (P<0.001, **Right**).

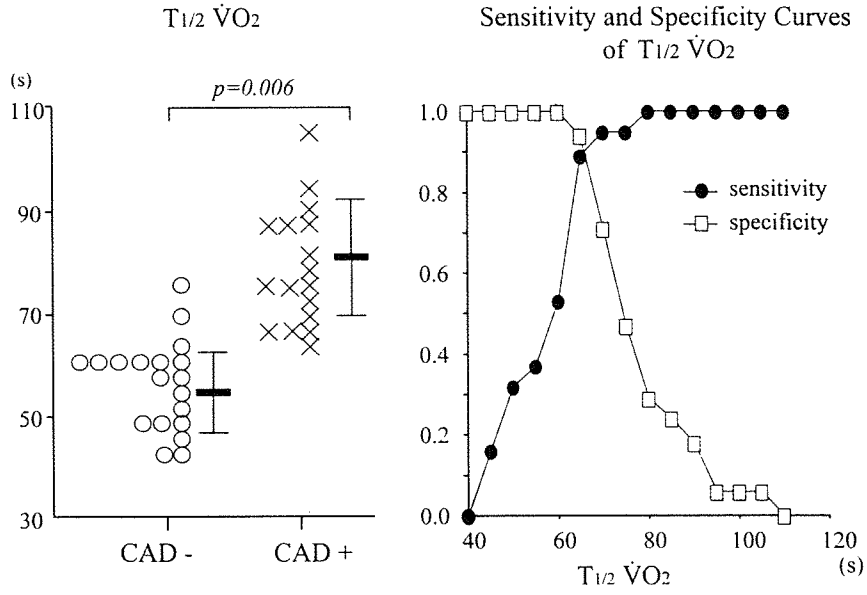

Figure 3. Half time of recovery of oxygen uptake ($T_{1/2}\ \dot{V}O_2$) in patients without (coronary artery disease (CAD)–) and with (CAD+) coronary artery stenosis (**Left**). Sensitivity and specificity curves of the $T_{1/2}\ \dot{V}O_2$ for CAD (**Right**). The $\dot{V}O_2$ kinetics after exercise was slower in the CAD+ group than that in the CAD– group. When we used 65 s as a cut-off value for CAD+ in $T_{1/2}\ \dot{V}O_2$, sensitivity was 89.4% and specificity was 94.4%.

values were not significantly different (**Table 1**). Peak $\dot{V}O_2$ values averaged 24.1±4.3 and 17.9±3.3 ml·min^{-1}·kg^{-1} for the CAD– and CAD+ groups, respectively (**Table 1**). Peak $\dot{V}O_2$ in the CAD+ group was significantly lower than that of the CAD– group.

$\Delta\dot{V}O_2/\Delta WR$ for 2 min Below and Above AT, and Ratio of $\Delta\dot{V}O_2/\Delta WR$ for 2 min Below to 2 min Above AT (Slope Ratio Across AT)

The $\Delta\dot{V}O_2/\Delta WR$ for the CAD– group for 2 min below AT was 10.7±1.0 ml·min^{-1}·W^{-1} and that for 2 min above AT was 11.1±0.9 ml·min^{-1}·W^{-1}. For the CAD+ group, $\Delta\dot{V}O_2/\Delta WR$ was 11.0±2.0 ml·min^{-1}·W^{-1} below AT, and 9.8±1.9 ml·min^{-1}·W^{-1} above AT. The $\Delta\dot{V}O_2/\Delta WR$ values of the 2 groups were similar below AT, whereas it decreased significantly above AT only in the CAD+ group (P<0.001). Therefore, the ratio of 2 min below to above AT was different in the 2 groups. **Figure 2** shows the slope ratio across AT was significantly lower in the CAD+ than CAD– group (1.03±0.07 vs 0.89±0.08, P<0.001, **Figure 2 Left**).

$\Delta\dot{V}O_2/\Delta WR$ for 2 min Below and Above ST-Dep, and the Slope Ratio Across ST-Dep

The $\Delta\dot{V}O_2/\Delta WR$ for the CAD– group for 2 min below ST-dep was 11.6±1.0 ml·min^{-1}·W^{-1} and that of for 2 min above ST-dep was 11.8±1.2 ml·min^{-1}·W^{-1}. For the CAD+ group, $\Delta\dot{V}O_2/\Delta WR$ was 10.4±1.8 ml·min^{-1}·W^{-1} below ST-dep, and 9.1±1.7 ml·min^{-1}·W^{-1} above ST-dep. There was no difference in $\Delta\dot{V}O_2/\Delta WR$ values between below ST-dep and above ST-dep in the CAD– group, whereas $\Delta\dot{V}O_2/\Delta WR$ above ST-dep was significantly lower than that of below ST-dep in the CAD+ group (P<0.001). The slope ratio across ST-dep was significantly lower in the CAD+ group than in the CAD– group (0.88±0.07 vs 1.02±0.06, P<0.001, **Figure 2 Right**).

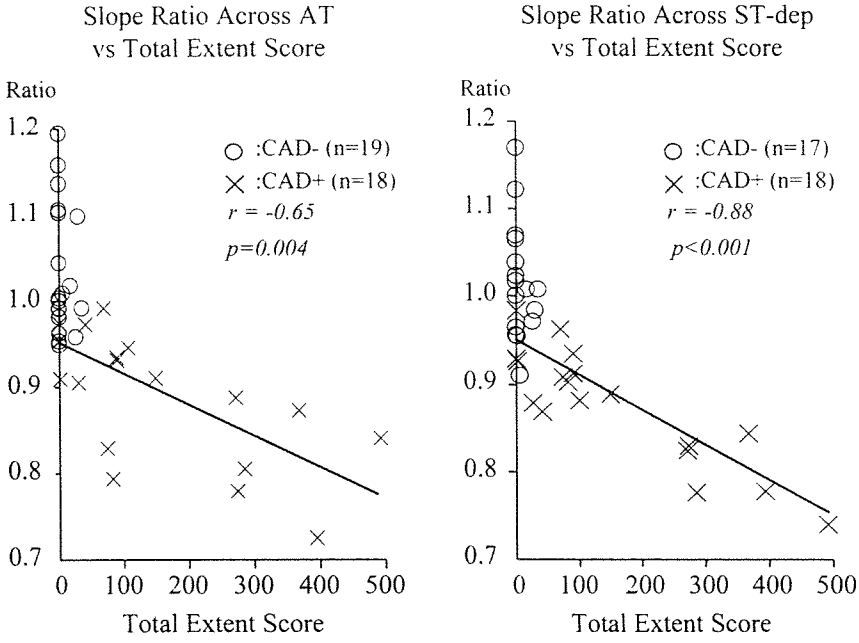

Figure 4. The slope ratios across anaerobic threshold (AT) and ST depression point (ST-dep) in relation to the total extent score. The total extent score calculated from the stress radio-isotope (RI) scintigraphy in CAD+ group showed a significant negative correlation to both of the slope ratio across AT (r=–0.65, P=0.004) and slope ratio across ST-dep (r=–0.88, P<0.001).

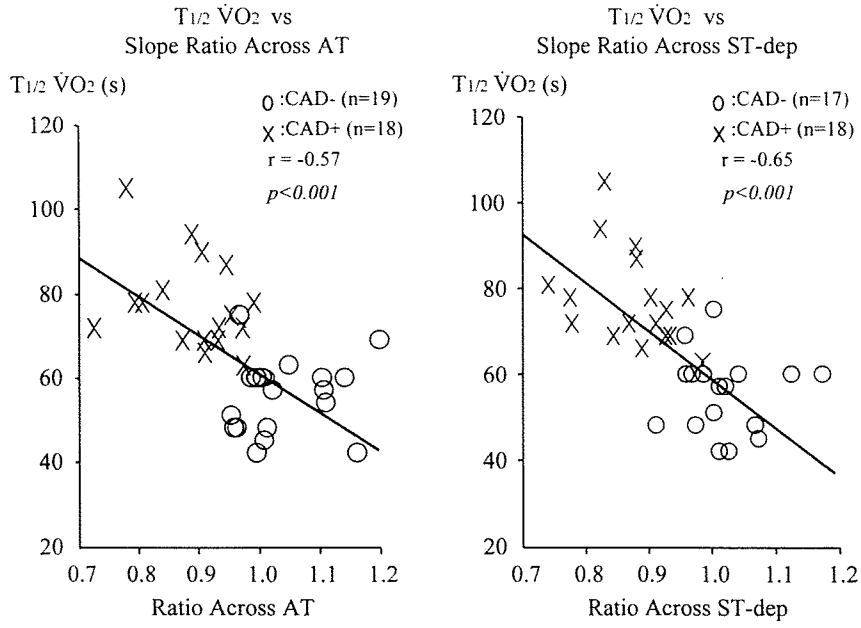

Figure 5. Half time of recovery of oxygen uptake ($T_{1/2}$ $\dot{V}O_2$) as related to the slope ratios of $\Delta\dot{V}O_2/\Delta WR$ across anaerobic threshold (AT) (**Left**) and ST depression point (ST-dep) (**Right**). There were significant correlations between $T_{1/2}$ $\dot{V}O_2$ and slope ratios across AT or ST-dep.

Table 2. Exercise Parameters Before and After the CABG (n=5)

	Pre CABG	Post CABG	P-values*
Ejection fraction by left ventriculography (%)	65.4±9.3	68.2±10.8	0.034
Oxygen uptake at AT ($ml \cdot min^{-1} \cdot kg^{-1}$)	11.9±1.5	12.4±2.5	0.057
Oxygen uptake at peak ($ml \cdot min^{-1} \cdot kg^{-1}$)	16.1±2.6	20.4±2.0	0.007
Peak work rate (W)	73.0±15.9	99.6±15.9	0.009
Peak O_2 pulse ($ml \cdot min^{-1} \cdot beat^{-1}$)	7.7±1.3	9.2±1.1	0.007
$T_{1/2}$ $\dot{V}O_2$ (s)	82.4±8.4	65.4±7.5	0.018
Slope above AT	8.9±1.5	10.9±0.5	0.038
$\Delta\dot{V}O_2/\Delta WR$ slope ratio across AT	0.85±0.07	1.01±0.05	0.011
Slope above ST-dep	7.7±1.3	10.6±0.4	0.009
$\Delta\dot{V}O_2/\Delta WR$ slope ratio across ST-dep	0.86±0.07	1.02±0.04	0.023

*P-values by unpaired t-test.
CABG, coronary artery bypass grafting; ST-dep, point of ST depression (1 mm). Other abbreviations see in Table 1.

O_2 Kinetics During Recovery Phase

$\dot{V}O_2$ kinetics in recovery phase of exercise ($T_{1/2}$ $\dot{V}O_2$) was significantly longer in the CAD+ compared to the CAD– group (78.1±10.9 s vs 55.7±8.8 s, P=0.006) (**Figure 3** and **Table 1**). $T_{1/2}$ $\dot{V}O_2$ showed a significant correlation with both the slope ratio across AT (r=–0.57 for CAD– group, P<0.001) and the slope ratio across ST-dep (r=–0.65 for CAD+ group, P<0.001; **Figure 5**).

Stress RI Scintigraphy

The total extent score calculated from the stress RI scintigraphy showed a significant positive correlation to $T_{1/2}$ $\dot{V}O_2$ (r=0.39 for CAD+ group, P=0.011). The total extent score also showed a significant correlation with both the slope ratio across AT (r=–0.65 for CAD+ group, P=0.004) and the slope ratio across ST-dep (r =–0.88 for CAD+ group, P<0.001; **Figure 4**).

Changes in O_2 Recovery Kinetics After the CABG

In 5 patients who underwent CABG (1.9±1.9 months after the CPET), we repeated the CPET 3–4 months (3.6±0.6 months) after the surgery and measured the $\dot{V}O_2$ kinetics. Because no patients showed significant ST depression after the surgery, we determined $\Delta\dot{V}O_2/\Delta WR$ for 2 min below and above ST-dep with the same analysis intervals as before the surgery. The $\Delta\dot{V}O_2/\Delta WR$ above AT and previous ST-dep point were improved. The slope ratios across AT and previous ST-dep point were also improved (**Table 2**) simultaneously with the improvement of $T_{1/2}$ $\dot{V}O_2$ (from 82.4±8.4 to 65.4±7.5).

Discussion

The failure of cardiac output to increase appropriately with work rate is commonly seen in patients with heart failure. This phenomenon reflects the failure for $\dot{V}O_2$ (as a result of limited increase in O_2 flow) to increase appropriately during exercise to meet the muscle O_2 requirement of the work rate. However, in patients with CAD, pumping function of the left ventricle and O_2 delivery is not disturbed until the myocardium has an inadequate O_2 supply to regenerate ATP. We found that $\Delta\dot{V}O_2/\Delta WR$ was decreased when myocardial ischemia developed in CAD+ patients. In this study, we excluded patients who had signs or symptoms of heart failure, and accordingly, there were no differences in AT between the 2 groups.

These findings are in agreement with previous reports[4–6] and support the concept that the decrease of $\Delta\dot{V}O_2/\Delta WR$ above the AT during exercise in CAD is because of the change in cardiac performance caused by myocardial ischemia. AT appears at a lower $\dot{V}O_2$ than ST-dep because myocardial ischemia occurs before the ECG change and ischemia affects the cardiac pumping function.[14,15]

It has been well documented that recovery $\dot{V}O_2$ is prolonged in patients with heart failure.[12,16] Pavia et al reported that $T_{1/2}$ $\dot{V}O_2$ was prolonged only in the severe heart failure patients and not in the normal individuals and CAD.[16] But their participants with CAD consisted of myocardial infarction and patients treated with coronary bypass surgery or percutaneous transluminal coronary angioplasty, and there was no evidence of ischemic changes during exercise. In our study, we found that there were significant negative correlations between recovery $T_{1/2}$ for $\dot{V}O_2$ and slope ratios across AT and ST-dep (**Figure 5**). This supports the physiological causality among the impaired pumping function of the heart caused by ischemia and the increased O_2 deficit during ischemic exercise. Also there was a significant negative correlation between the slope ratios and the extent score obtained by stress RI scintigraphy, which stands for the area of exercise induced myocardial ischemia.

The abnormal kinetics of $\dot{V}O_2$ during incremental exercise improved in 5 patients who underwent CABG surgery (**Table 2**). This supports the physiological relationship between myocardial ischemia and abnormal $\dot{V}O_2$ kinetics.

It is easier to measure the kinetics of $\dot{V}O_2$ in the recovery phase than during exercise because $\Delta\dot{V}O_2/\Delta WR$ above ST-dep might not be determined because of the short time of exercise duration. The $\dot{V}O_2$ decay in recovery is not affected by the exercise duration in an increasing work rate test[12,17] and is easily determined when patients perform at least 50% of maximum exercise. Another advantage for use of $T_{1/2}$ in recovery as a marker for myocardial ischemia is its sensitivity and specificity. When we employed 65 s as a cut-off value for CAD+, sensitivity was 89.4% and specificity was 94.4% (**Figure 3 Rright**). The age matched normal value of $T_{1/2}$ $\dot{V}O_2$ is 56.9±7.0 s (50–70 years, 60.2±5.3 years).

Study Limitations

We used the 'significant stenosis in coronary arteries by CAG' as a gold standard for CAD. However, more than 75% stenosis does not necessarily cause myocardial ischemia during exercise. Therefore we also measured the extent score using RI scintigraphy; however, it indicated the severity of ischemia caused by the maximum exercise, not during exercise.

Conclusions

We concluded that $\dot{V}O_2$ kinetics was slowed during increasing work rate exercise above the AT and in recovery in patients with regional myocardial ischemia. Presumably the change was consequent to the impaired increase in the cardiac output as work rate increased above the ischemic threshold of the myocardium. Accordingly, the $\dot{V}O_2$ with the slowed $\dot{V}O_2$ kinetics and the magnitude of the slowing reflected the severity of the ischemia. This phenomenon might be useful in differentiating false-positive from true-positive ECG changes during exercise testing for CAD.

Acknowledgment

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Disclosure

No authors have any conflicts of interest.

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ORIGINAL ARTICLE
Hypertension and Circulatory Control

Effects of Submaximal Exercise on Blood Rheology and Sympathetic Nerve Activity

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Background: To explore the acute effects of submaximal exercise on blood rheology and sympathetic nerve activity.

Methods and Results: The effects of exercise (20 or 80 Watts (W)) on blood rheology and sympathetic nerve activity were assessed in 10 healthy Japanese men. Blood sampling and heart rate variability (HRV) recording were performed during 20-min supine rest and standing ergometric exercise (20 W for 10 min, 80 W for 10 min) and recovery. Blood passage time across the microchannels (diameter, 7 μm) as a parameter of blood rheology, and the number of adhesive leukocytes on microchannel terraces as a parameter of leukocyte activation were measured. Sympathetic nerve activity was evaluated by plasma noradrenalin levels and the ratio of low-frequency (LF)/high-frequency (HF) by spectral analysis of HRV. Compared with values while supine at rest, significant increases in hematocrit, leukocyte count, noradrenalin level and blood passage time were seen after strenuous ergometer exercise at 80 W ($P<0.01$ each). The LF/HF ratio and nitric oxide metabolites tended to be increased with 80 W exercise.

Conclusions: Strenuous exercise dynamically alters blood rheological parameters, probably by changes in hematocrit and sympathetic nerve activity. (*Circ J* 2010; **74:** 730–734)

Key Words: Exercise; Leukocytes; Microcirculation; Rehabilitation; Sympathetic nerves

Exercise training has become an accepted therapeutic modality for patients with chronic heart failure and ischemic heart disease.[1–3] However, the effects of exercise on the rheological properties of blood have not received much research attention, despite the potential clinical importance. Limited evidence has recently suggested that acute coronary syndrome can occur during strenuous exercise, because of platelet activation, hemoconcentration and hypercoagulability.[4–8] Strenuous exercise is thought to activate blood cells by catecholamine stimulation and oxidative stress,[9–11] although increased shear stress during exercise upregulates endothelial nitric oxide synthetase (eNOS) expression at the transcriptional level, thereby increasing endothelium-derived nitric oxide (NO) production.[12] Endothelium-derived NO plays an important role in the regulation of vascular tone, inhibition of platelet aggregation, and prevention of leukocyte recruitment to the vessel wall.[13,14] In addition, changing to an upright posture leads to rapid pooling of blood in the lower extremities and shifts plasma into surrounding tissues. Exercise also decreases plasma volume by shifting plasma from the intravascular space to muscle tissues,[15,16] consequently leading to hemoconcentration.

Because of methodological limitations, the effects of exercise on blood rheology remain unclear. Kikuchi et al have developed optically assessable microchannels formed in a single-crystal silicon substrate for ex vivo studies of blood rheology.[17] The microchannel flow analyzer provides reliable quantitative blood rheological data for animals[14,18] and humans.[19] The aim of this study was to explore the acute effects of posture change and exercise on sympathetic nerve activity and blood rheology using the ex vivo microchannel flow analyzer.

Methods

Subjects

Subjects were 10 healthy, non-smoking Japanese male volunteers (age range, 27–47 years). They had normal findings on routine physical examination and standard laboratory tests (**Table 1**) and all gave written informed consent prior to enrolment. All subjects fasted for 5 h and abstained from drinking beverages containing alcohol or caffeine for ≥12 h

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Table 1. Baseline Characteristics of the Healthy Male Subjects

	Mean±SD
Age (years)	41.7±10.1
Height (cm)	171.1±6.4
Weight (kg)	65.8±7.8
White blood cells (/μl)	5,648±1,341
Hematocrit (%)	42.6±2.3
Platelets (×10³/μl)	245.2±39.5
Total cholesterol (mg/dl)	195.3±29.2
HDL (mg/dl)	50.2±8.1
Triglycerides (mg/dl)	98.5±50.4
Fasting blood sugar (mg/dl)	91.7±8.7
Serum creatinine (mg/dl)	0.79±0.15
Anaerobic threshold (ml·kg⁻¹·min⁻¹)	15.5±3.8
Peak $\dot{V}O_2$ (ml·kg⁻¹·min⁻¹)	31.7±4.1
Work load at AT (W)	69±14
Work load at AT-1 min (W)	59±14

HDL, high-density lipoprotein; AT, anaerobic threshold; W, Watts.

before the study. All studies were performed in an air-conditioned room at 24°C in Saitama Medical Center, Jichi Medical University.

Protocol

The study protocol was approved by the Ethical Committee of Jichi Medical University.

In a pilot study, all subjects underwent a cardiopulmonary exercise test to determine workload and oxygen consumption at the anaerobic threshold (AT), with an electronically braked cycle ergometer (Ergometer 2320, Minato Medical Science, Osaka, Japan) using an incremental 20 Watts (W)/min ramp at a constant heart rate of 60 beats/min in the upright position. Their mean work load at AT was 69±14 W and AT-1 min was 59±14 W. As the cardiopulmonary reaction to exercise is delayed by approximately 1 min, the real work load at AT was supposed to approximately 59 W. Consequently, we set the ergometric exercise work rate at 20 W under AT and at 80 W as strenuous exercise beyond the AT.

All subjects arrived at the laboratory room at 13.00 h. Ambulatory ECG (SM-28, SM-30, SM-60; Fukuda Denshi, Tokyo, Japan) was used to assess heart rate variability (HRV). Subjects were asked to remain at rest while supine for the first 20 min, then a 20-gauge catheter was inserted into the left cephalic vein for blood sampling. Blood was drawn carefully without stasis through the catheter. The initial 2 ml of blood was discarded, then 5 ml blood was taken into a syringe (5 ml) containing heparin sodium (50 units/L ml blood) for assessment of hemorheology, followed by another 10 ml of blood for measurement of hematocrit, blood cell counts, noradrenalin (NA) and NO metabolites (nitrite, nitrate), which was immediately placed in ice-cooled tubes containing ethylenediaminetetraacetic acid-2Na (1 mg/ml) and the contents were centrifuged at 4°C for 10 min at 3,000 g. Plasma samples were immediately frozen and stored at −80°C until assay.

After blood sampling, saline drip infusion at 20 ml/h through the venous catheter was started and continued for anticoagulation in the catheter during the study. Subjects rested while supine for 20 min, then while standing for another 10 min, after which they then performed ergometric exercise at 20 W for the third 10-min period, as the work load under the AT, using an electronically braked cycle ergometer (Ergometer 2320; Minato Medical Science) at a constant rate of 60 rpm in an upright position, followed by ergometric exercise at 80 W for the fourth 10-min period, as the work load beyond the AT, and finally recovery while standing for the last 10 min. At the end of each phase, blood sampling was repeated through the catheter. Blood pressure was recorded each minute by the manchette method (STBP-780; NIPPON COLIN, Aichi, Japan). At the end of the each phase, the subjects were asked to indicate their level of physical fatigue using the Borg scale (6–20 point scale).[20,21]

Table 2. BP, HR and Borg Scale (6–20 Point Scale) at Each Phase of the Study

	Rest	20 W exercise	80 W exercise
Systolic BP (mmHg)	124±9	133±16	174±22
Diastolic BP (mmHg)	76±8	86±12	87±7
HR (beats/min)	79±11	100±13	140±17
Borg scale		8.4±0.9	15.3±1.3

BP, blood pressure; HR, heart rate.

Blood Kinetics Through Narrow Microchannels Ex Vivo

Immediately after blood sampling, the passage time of 0.1 ml of blood through the narrow microchannels (8700-parallel; equivalent diameter, 7 μm; channel length, 20 μm; Kowa, Tokyo, Japan) under constant suction of 20 cm H_2O was determined using a microchannel flow analyzer (Kowa) as an ex vivo rheological parameter.[17–19] Saline passage time was determined before each blood measurement for calibration. Microscopic images of blood passing through the micro ditches were monitored on a television screen with a charge-coupled device camera. Images were stored on a digital videocassette recorder (WV-DR9; Sony, Tokyo, Japan) for off-line analysis. The video vertical frame rate of the camera was 30 frames/s. Overall magnification on the TV monitor was approximately ×900. An investigator who was unaware of the subjects' backgrounds selected 5 still images at 30–33 s for off-line VTR analysis. The number of adhesive leukocytes on the microchannel terrace and the percentage of microchannels obstructed were then counted. At ex vivo hemorheological analysis, some microchannels were obstructed by blood cells because of rheological worsening, and there was "no reflow". To minimize unevenness, passage times greater than 120 s (showing obstruction of almost all microchannels) were considered as 120 s.

Measurement of Plasma Levels of NA and NO Metabolites

Assays for plasma NA level were conducted according to established methods (SRL, Tokyo, Japan).[22] NO metabolites (nitrite, nitrate) in plasma were measured using an NO analyzer (ENO-20; Eicom, Tokyo, Japan), as described previously;[14,23,24] the minimum detectable concentration of nitrite or nitrate was 0.01 mmol/L.

Evaluation of HRV

Qualifying recorded tapes were subsequently analyzed to measure HRV using validated HRV software (TM-2025-15; A&D, Tokyo, Japan). We assessed frequency domain variability with spectral analysis using the fast Fourier transformation method. The power spectrum of HRV was divided into a low-frequency (LF) band of 0.04–0.15 Hz and a high-frequency (HF) band of 0.15–0.40 Hz. Sympathetic nerve activity was shown by the ratio LF/HF.[25]

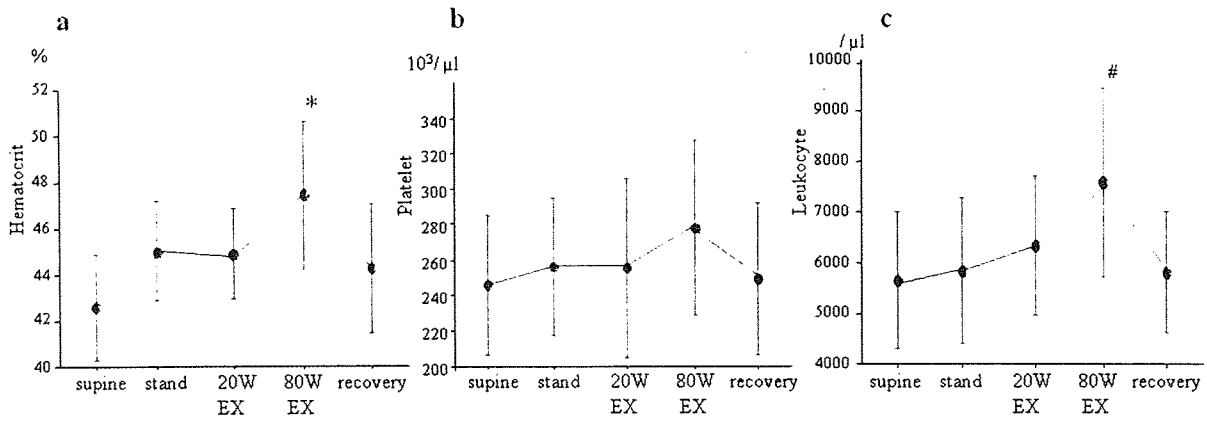

Figure 1. Serial changes in hematocrit (**a**), platelet count (**b**) and leukocyte count (**c**) before and after exercise. After strenuous ergometer exercise at 80 Watts (W), hematocrit (42.6±2.2% to 47.4±3.2%, **a**) and leukocyte count (5,648±1,341/μl to 7,584±1,860/μl, **c**) were significantly increased compared with values at rest while supine, but platelet count was not. *P=0.0001 vs while supine; #P=0.005 vs while supine. EX, exercise.

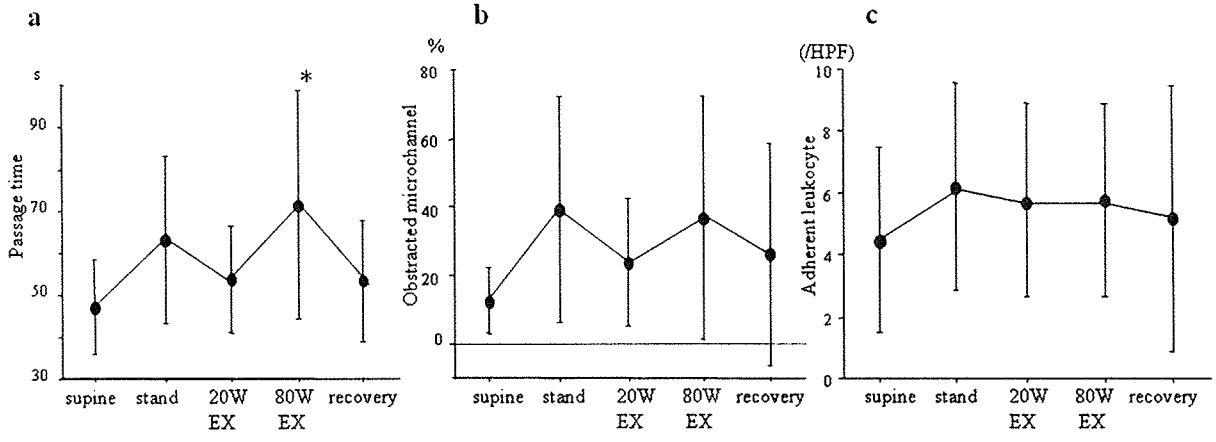

Figure 2. Serial changes in the passage time of 0.1 ml of whole blood through the microchannels (**a**), percentage of microchannels obstructed (**b**), and number of adherent leukocytes on the terrace (**c**). Passage time for 0.1 ml of whole blood through the narrow microchannels was significantly increased after 10 min of 80 Watts (W) exercise (71.3±27.0 s, **a**) compared with at rest while supine (47.1±11.4 s, P=0.004). The number of obstructed microchannels tended to be increased while standing and with 80 W exercise as compared with resting while supine (**b**). The number of adherent leukocytes on the terrace was unchanged through all study phases (**c**). *P=0.004 vs supine. HPF, high power field; EX, exercise.

Statistical Analysis

Data are presented as mean±standard deviation. Mean values were compared among serial data using analysis of variance, followed by Bonferroni/Dunn's multiple comparison test. Probability values of $P<0.05$ were considered indicative of statistical significance. All statistical analyses were performed using StatView version 5.0 software (SAS Institute, Cary, NC, USA).

Results

Blood pressure, heart rate and Borg scale at the end of each phase are shown in **Table 2**. After the end of 10 min of 80 W ergometric exercise, blood pressure rose to 174±22 mmHg and the Borg scale was 15.3±1.3 (hard).

Effects of Posture Change on Hemorheological Parameters

Posture change from supine to standing tended to increase the hematocrit (**Figure 1a**), whole blood passage time through the microchannels (**Figure 2a**) and NA concentration (**Figure 3a**).

Effects of Exercise on Hematocrit, Leukocyte and Platelet Counts

After strenuous ergometer exercise at 80 W, hematocrit (42.6±2.2% to 47.4±3.2%, P=0.0001, **Figure 1a**) and leukocyte count (5,648±1,341/μl to 7,584±1,860/μl, P=0.005, **Figure 1c**) were significantly increased compared with values at rest while supine, but platelet count was not.

Effects of Exercise on Hemorheological Parameters

The passage time of 0.1 ml of whole blood through the narrow

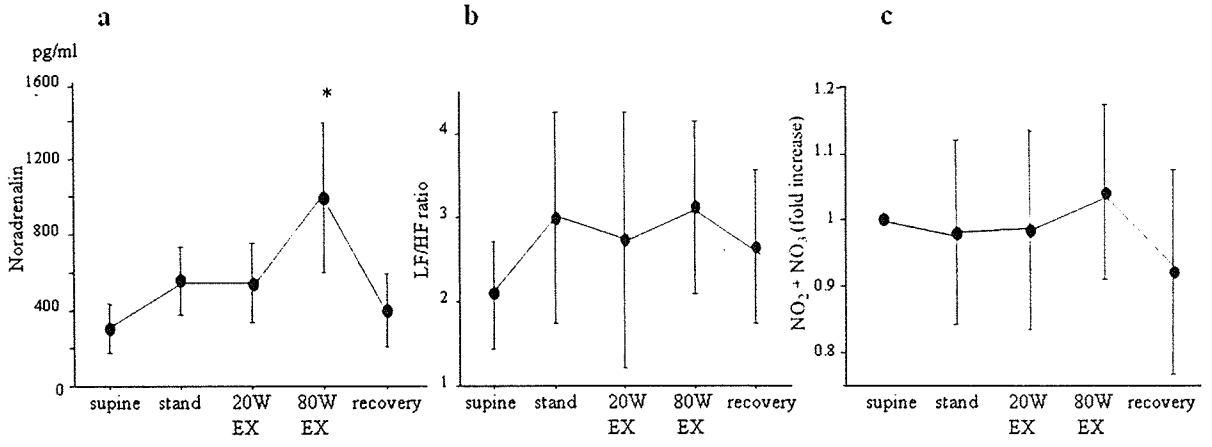

Figure 3. Serial changes in plasma levels of noradrenalin (**a**), low-frequency to high-frequency (LF/HF) ratio (**b**) and nitric oxide (NO) metabolites (**c**). Plasma levels of noradrenalin were significantly increased after 80 Watts (W) exercise (994±391 pg/ml, **a**) compared with resting while supine (306±130 pg/ml, P<0.0001 vs 80 W exercise). LF/HF ratio and NO metabolites also tended to increase at the end of 80 W exercise (**b**, **c**). *P=0.0001 vs supine. EX, exercise.

microchannels was significantly increased after 10 min of 80 W exercise (71.3±27.0 s) compared with the value at rest while supine (47.1±11.4 s, P=0.004, **Figure 2a**). The number of obstructed microchannels tended to be increased while standing and with 80 W exercise compared with resting while supine (**Figure 2b**). The number of adherent leukocytes on the terrace was unchanged through all the study phases (**Figure 2c**).

Effects of Exercise on Sympathetic Nerve Activity and NO Metabolites

Plasma levels of NA were significantly increased after 80 W exercise (994±391 pg/ml, **Figure 3a**) compared with resting while supine (306±130 pg/ml, P<0.0001). The LF/HF ratio and NO metabolites also tended to be increased with 80 W exercise (**Figures 3b, c**).

Discussion

The present data indicate that strenuous, seated ergometer exercise induced hemoconcentration and sympathetic nerve activation, thus transiently worsening hemorheological parameters even in healthy men, although NO production tended to be increased. We believe that the exercise work rates at 20 W and 80 W were appropriate as light exercise under the AT and strenuous exercise over the AT, because averaged Borg scales at 20 W and 80 W ergometer exercise were 8.4 (very light) and 15.3 (hard), respectively.

Dynamic Changes in Blood Rheology by Posture Change and Exercise

Posture change and exercise induce a shift in water from the intravascular space to the extravascular space such as muscle and the interstitial spaces.[15,16] The resulting hemoconcentration caused by this water shift increases blood viscosity and worsens hemorheological parameters, although eNOS activity may be enhanced by the increased shear stress during exercise. Standing and strenuous exercise increase sympathetic nerve activity and catecholamine spillover, leading to activation of platelets and leukocytes both in vitro and in vivo.[9-11] Strenuous exercise is rapidly followed by an increase in blood cell count, not only by hemoconcentration, but also by altered hemodynamic conditions; that is, increased flow and shear forces within the circulation would be expected to lead to recruitment of both sequestered red blood cells in various circulatory beds and of leukocytes from the marginal pool.[26-28]

Leukocyte Activation, Sympathetic Nerve Activity and NO

No significant increase in the number of adhesive leukocytes was seen after exercise in the healthy men. Previous reports have shown that strenuous exercise contributes to hemorheological deterioration as a proinflammatory factor.[29,30] The most likely causes of the inflammatory response after strenuous exercise are generalized muscle damage and oxidative stress.[10,31] Leukocytes activated in this manner may block microvascular circuits[32] and result in further oxidative stress. In patients with ischemic heart disease, leukocyte activation may represent the most important factor in hemorheological deterioration. Exercise at 80 W for 10 min might not reach the level required to activate leukocytes in healthy subjects. Serum levels of NO metabolites tended to be increased after exercise, but this change was not significant. Exercise increases the production of NO from the endothelium following increases in shear stress, particularly in the vessels of the working muscles. At the same time, exercise increases the formation of reactive oxygen species.[33,34] The bioavailability of endothelial NO mainly depends on the balance between eNOS activity and inactivation of NO by reactive oxygen species. We are currently unable to determine which of these factors represent the most important contributors to the observed changes, because we did not assess reactive oxygen species or endothelial function using plethysmography or ultrasound techniques.

Study Limitations

This study used healthy volunteers as subjects. Patients with ischemic heart disease or other lifestyle disease (eg, diabetes mellitus, hypertension, dyslipidemia) may show different results, and warrant examination in future studies.

Conclusion

Strenuous exercise dynamically alters blood rheology, probably by changes in plasma volume and sympathetic nerve activity. Water supply should be taken into consideration to improve rheological status during exercise, particularly in patients with ischemic cardiovascular disease.

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ORIGINAL ARTICLE
Cardiac Rehabilitation

Effects of Phase III Cardiac Rehabilitation on Mortality and Cardiovascular Events in Elderly Patients With Stable Coronary Artery Disease

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Background: Cardiac rehabilitation (CR) has numerous benefits, including reduction of mortality and cardiovascular events, in patients with coronary artery disease (CAD). However, the long-term effect of phase III CR in elderly patients with stable CAD is still unknown.

Methods and Results: The 111 elderly male CAD patients (≥65 years), including 37 subjects participating in supervised CR for 6 months and 74 age-matched controls, were analyzed. The patients were followed for up to 3,500 days, until the occurrence of death or 1 of the following major adverse cardiovascular events (MACE): cardiovascular death, acute coronary syndrome, refractory angina requiring revascularization, admission for congestive heart failure, or stroke. All-cause mortality tended to be lower in the CR group than in the Control group (14% vs 28%, P=0.081). The MACE incidence was significantly lower in the CR group than in the Control group (30% vs 62%, P=0.001). Multivariate Cox proportional hazard analysis showed that the MACE incidence was significantly lower in the CR group than in the Control group [adjusted hazard ratio 0.43 (95% confidence interval 0.20–0.91), P=0.027].

Conclusions: Phase III CR has the beneficial effect of reducing cardiovascular events even in elderly patients with stable CAD. (*Circ J* 2010; **74:** 709–714)

Key Words: Cardiovascular events; Cardiac rehabilitation; Coronary artery disease; Elderly patients; Prognosis

The elderly population has grown rapidly in Japan, resulting in a remarkable increase in the number of patients with coronary artery disease (CAD).[1,2] The elderly people have a 2- to 3-fold higher incidence of acute myocardial infarction (MI) than the younger population,[3–5] and they also tend to have more complications associated with prolonged hospital stays, low physical activity and hence, substantially higher fatality rates after a CAD event.[4,6] Because of these high rates of morbidity and mortality, primary and secondary prevention programs are important strategies not only for modifying cardiovascular risk factors, but also for improving the mortality and quality of life of elderly patients with CAD.[7,8]

Cardiac rehabilitation (CR) programs consist of exercise training, medical counseling, education about cardiovascular diseases, and psychosocial support. The comprehensive treatment has significant benefits on exercise capacity, coronary risk factors, and health-related quality of life (HRQOL).[4–12] In addition, CR reduces all-cause mortality and cardiovascular events; however, its use in patients with CAD is still low.[13–17] In general, CR programs consist of 3 stages: acute stage (phase I), subacute stage (phase II), and the chronic stage (phase III) at least 6 months after a major cardiovascular event. Most CR programs have been performed for phase I and phase II, however, phase III CR has not often been instituted in Japan, especially, because it was not covered by Japanese health insurance until March 2006. Moreover, most previous studies included very few older persons,[18–21] so limited data were available regarding the efficacy of phase III CR, especially in elderly patients with stable CAD.

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Table 1. Baseline Characteristics of the Study Subjects

	CR group (n=37)	Control group (n=74)	P value
Age (years)	69.6±3.4	70.1±4.2	NS
Body mass index (kg/m^2)	23.8±2.8	23.2±2.6	NS
Hypertension (%)	19 (51)	50 (68)	NS
Diabetes mellitus (%)	16 (43)	31 (42)	NS
Dyslipidemia (%)	25 (66)	40 (54)	NS
Current smoker (%)	3 (8)	13 (18)	NS
Myocardial infarction (%)	21 (57)	44 (59)	NS
PCI (%)	15 (41)	30 (41)	NS
CABG (%)	15 (41)	32 (43)	NS
Diseased vessels			
1 (%)	14 (38)	20 (27)	NS
2 (%)	10 (27)	25 (34)	
3 (%)	11 (30)	28 (38)	
LMT (%)	2 (5)	6 (8)	NS
Ejection fraction (%)	64.9±13.5	65.2±13.8	NS
Time from last CVE	1,982±1,729	1,288±2,136	NS
Total cholesterol (mg/dl)	186.0±22.4	182.1±28.8	NS
Triglyceride (mg/dl)	132.4±74.3	136.6±79.4	NS
LDL-cholesterol (mg/dl)	109.3±21.8	108.5±27.8	NS
HDL-cholesterol (mg/dl)	50.2±10.8	46.2±10.5	NS
FBS (mg/dl)	104.0±31.1	104.3±22.0	NS
Hemoglobin A_{1c} (%)	6.0±1.0	5.9±1.1	NS
Medications			
Antiplatelets (%)	37 (100)	71 (96)	NS
CCB (%)	19 (51)	39 (53)	NS
β-blockers (%)	17 (46)	26 (35)	NS
ACEI/ARB (%)	12 (32)	24 (32)	NS
Statin (%)	9 (24)	20 (27)	NS
Sulfonylurea (%)	3 (8)	9 (12)	NS
Insulin (%)	2 (5)	3 (4)	NS

Values are mean value±SD or number and percentage in parentheses.
CR, cardiac rehabilitation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVE, cardiovascular event; LDL, low-density lipoprotein; HDL, high-density lipoproten; FBS, fasting blood glucose; CCB, calcium-channel blocker; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin 1 receptor blocker.

Therefore, in the present study we assessed the effects of phase III comprehensive CR on the morbidity and mortality of cardiovascular diseases in elderly male Japanese patients with CAD.

Methods

Subjects

The study group consisted of 111 elderly male patients (≥65 years) with stable CAD attending the outpatient clinic at Juntendo University Hospital in 1999–2001: 37 patients underwent supervised phase III CR for 6 months as participants of the Juntendo Cardiac Rehabilitation Program (J-CARP), which has been described previously.[9,10] We recruited 39 subjects in the J-CARP study; however, 1 patient dropped out and 1 patient was lost to follow-up, so finally, 37 patients were enrolled as the CR group in this study. As the Control group, we randomly screened 120 stable CAD patients, using medical records, who were outpatients during the same period of the CR program. Patients with ongoing congestive heart failure (CHF), liver dysfunction (aspartate aminotransferase ≥40 IU/L), renal dysfunction (creatinine ≥2.0 mg/dl), or systemic disease, including malignancy and collagen disease, were excluded, so finally, 74 patients were selected as age-matched controls. All patients had been referred at least 6 months after a major coronary event such as acute coronary syndrome (ACS), coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI). None of the subjects had previously undergone CR. Subjects received full verbal and written explanations of the nature and purpose of this study, and gave their written informed consent. The study was approved by the Ethical Committee of Juntendo University.

Rehabilitation Protocol

In the CR group, subjects participated in an outpatient phase III CR program once weekly for 6 months, as described previously.[9,10] Briefly, this program included exercise therapy and a dietary and education program. The supervised exercise session consisted of a 10-min warm-up of stretching, 40–60 min of intermittent aerobic exercise, and then resistance training such as sit-ups, squats, push-ups and back kicks and front raises using the patient's own weight. The exercise session was concluded with an approximately 10-min cool down. The intensity of exercise was prescribed individually at the anaerobic threshold (AT) as obtained by a treadmill test using expiratory gas analysis and a rating of 12–13 on the Borg's standard perceived exertion scale. Subjects were

Table 2. Changes in Body Mass Index, Lipid Profiles, Fasting Glucose, and Hemoglobin A_{1c} Levels

	CR group (n=37)		Control group (n=74)	
	At baseline	After 6 months	At baseline	After 6 months
Body mass index (kg/m^2)	23.8±2.8	23.3±2.6*	23.2±2.6	23.4±2.3
Total cholesterol (mg/dl)	186.0±22.4	182.3±26.3	182.1±28.8	184.2±27.6
Triglyceride (mg/dl)	132.4±74.3	113.4±54.3#	136.6±79.4	143.7±61.0
LDL-cholesterol (mg/dl)	109.3±21.8	100.3±37.6	108.5±27.8	107.4±25.0
HDL-cholesterol (mg/dl)	50.2±10.8	50.4±11.9	46.2±10.5	46.6±10.9
FBS (mg/dl)	104.0±31.1	96.1±15.4#	104.3±22.0	105.7±17.3
Hemoglobin A_{1c} (%)	6.0±1.0	5.9±1.0	5.9±1.1	5.9±0.9

Values are mean value±SD. *P<0.05 compared with at baseline; #P<0.05 compared with the Control group after 6 months.
Abbreviations see in Table 1.

Table 3. Prevalence of All-Cause Death and Cardiovascular Events

	CR group (n=37)	Control group (n=74)	P value
Death (%)	5 (14)	21 (28)	0.081
Cardiovascular death (%)	1 (3)	8 (11)	0.140
MACE* (%)	11 (30)	46 (62)	0.001
ACS (%)	5 (14)	16 (22)	0.304
PCI (%)	6 (16)	20 (27)	0.205
CABG (%)	1 (3)	7 (9)	0.194
CHF (%)	1 (3)	9 (12)	0.100
Stroke (%)	1 (3)	6 (8)	0.269
Cancer (%)	6 (16)	8 (11)	0.434

*Combined with cardiovascular death, ACS, PCI, CABG, CHF, and stroke.
MACE, major adverse cardiovascular events; ACS, acute coronary syndrome. Other abbreviations see in Table 1.

encouraged to perform home-based aerobic and resistance exercise twice weekly. In addition, subjects were instructed to follow the phase II diet of the American Heart Association at the beginning and every 2 months of the study. An education program was usually provided for each subject by physicians, nurses, and dietitians, regarding ischemic heart disease, risk factors, exercise and dietary instructions. In addition, individual counseling for physical and psychological conditions was provided every visit. The Control group received the standard outpatient care. Medical treatment was unchanged during the 6 months in both groups. After 6 months, the subjects were treated with a standard care protocol conducted by each physician in charge of the 2 groups.

Measurements

In both groups, we assessed body mass index (BMI), serum lipid profiles, glucose, and hemoglobin A_{1c} (HbA_{1c}) at baseline. Serum lipid profiles, including total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were determined by standard methods using an auto-analyzer after 12h of fasting at baseline and after 6 months. Levels of low-density lipoprotein cholesterol were calculated with Friedewald's equation using the concentrations of TC, HDL-C, and TG.

Follow-up

After the initial assessment, the subjects were followed for up to 3,500 days until the occurrence of 1 of the following events: all-cause death or major adverse cardiovascular events (MACE), including cardiovascular death, ACS, refractory ischemia requiring PCI or CABG, admission for CHF, and stroke.

Statistical Analysis

The results are expressed as the mean value±standard deviation. Baseline characteristics of the CR and Control groups were compared using Student's t-test for continuous variables and the chi-square test for categorical variables. Time-to-event data was estimated by the Kaplan-Meier method and analyzed with the log-rank test. The Cox proportional hazards method was used for the multivariate analysis. A value of P<0.05 was considered to be significant.

Results

Baseline Characteristics and Changes in BMI, Lipid Profiles, Fasting Glucose, and HbA_{1c} After 6 Months

The baseline characteristics at enrollment are shown in **Table 1**. There were no significant differences between the CR and Control groups in age, BMI, the rates of hypertension (HT), diabetes mellitus (DM), dyslipidemia or smoking history, or in the other clinical profiles. The concomitant use of medications was also identical between the 2 groups. After 6 months, BMI had significantly decreased in the CR group (from 23.8±2.8kg/m^2 to 23.3±2.6kg/m^2, P<0.05) (**Table 2**). The levels of TG (113.4±54.3mg/dl vs 143.7±61.0mg/dl, P<0.05) and fasting glucose (96.1±15.4mg/dl vs 105.7±17.3mg/dl, P<0.05) were significantly lower in the CR group than in the Control group (**Table 2**).

Parameters Before and After Supervised CR

In the CR group, the values of peak $\dot{V}O_2$, peak heart rate (HR), peak speed, AT, AT-HR and AT-speed were 22.5±3.3ml·kg^{-1}·min^{-1}, 114±10beats/min, 6.3±0.9km/h, 12.2±2.1ml·kg^{-1}·min^{-1}, 87±10beats/min, and 3.5±0.8km/h, respec-

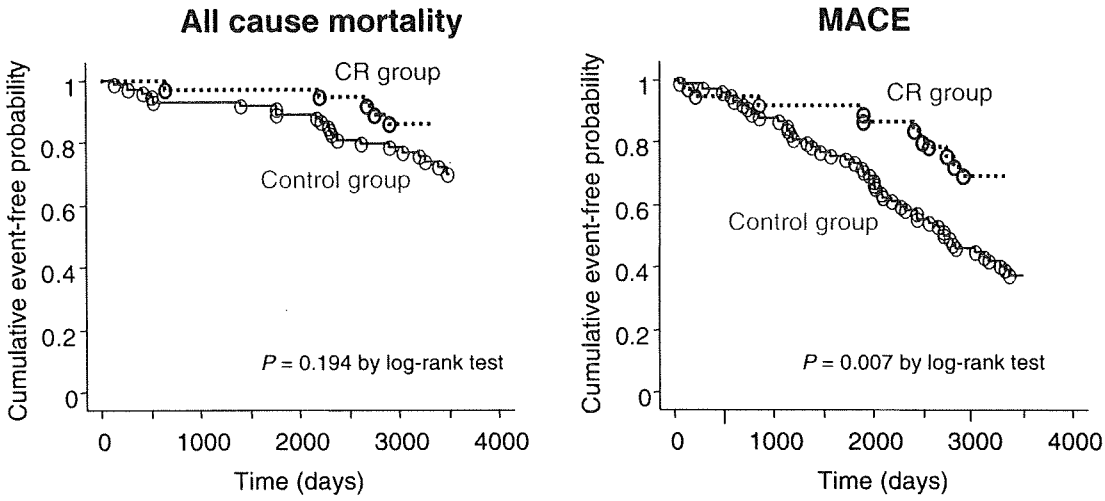

Figure. Kaplan-Meier curves for all-cause mortality and major cardiovascular events in the cardiac rehabilitation group and control group. CR, cardiac rehabilitation; MACE, major adsverse cardiovascular events combined with cardiovascular death, acute coronary syndrome, refractory ischemia requiring percutaneous coronary intervention or coronary artery bypass grafiting, congestive heart failure, and stroke.

Table 4. Relationships Between CR and Adjusted Risk of Total Mortality and MACE

	n	Total mortality			MACE		
		N (%)	HR (95%CI)	P value	N (%)	HR (95%CI)	P value
Control group	74	21 (28)	1.00		46 (62)	1.00	
CR group	37	5 (14)	0.65 (0.19–2.27)	0.505	11 (30)	0.43 (0.20–0.91)	0.027

Cox proportional hazard model adjusted for age, body mass index, hypertension, diabetes, dyslipidemia, smoking history, diseased vessels, and ejection fraction.
Combined with acute coronary events, PCI, CABG, CHF, and stroke.
HR, hazard ratio; CI, confidence interval. Other abbreviations see in Tables 1,3.

tively. In the CR group, all subjects completed the supervised program for 6 months, and 36 patients (97%) continued home exercise 3 times weekly during that period. After 6 months, the values of peak $\dot{V}O_2$, peak HR, peak speed, AT, AT-HR and AT-speed were 23.3±3.2 ml·kg^{-1}·min^{-1}, 121±16 beats/min (P<0.01 vs baseline), 7.0±0.8 km/h (P<0.01 vs baseline), 12.4±2.1 ml·kg^{-1}·min^{-1}, 88±10 beats/min, and 4.2±0.9 km/h (P<0.01 vs baseline), respectively.

Incidence of All-Cause Death and Cardiovascular Events

The incidence of all-cause mortality and of cardiovascular events in the CR and Control groups are presented in **Table 3**. All-cause death tended to be lower in the CR group than in the Control group (14% vs 28%, P=0.081). The MACE incidence was significantly lower in the CR group than in the Control group (30% vs 62%, P=0.001). The incidence of each of cardiovascular death, ACS, refractory ischemia requiring PCI or CABG, admission for CHF, stroke, and cancer did not significantly differ between the 2 groups.

Figure shows the survival curves for all-cause mortality and MACE between the CR and Control groups. Kaplan-Meier analysis demonstrated that the CR group had a significantly lower rate of MACE, but not of all-cause death, during the entire follow-up period (P=0.007, P=0.194, respectively). Multivariate Cox proportional analysis adjusted for age, BMI, HT, DM, dyslipidemia, smoking history, diseased vessels, and ejection fraction, showed that the MACE incidence was significantly lower in the CR group than in the Control group (adjusted hazard ratio 0.43, 95% confidence interval 0.20–0.91, P=0.027) (**Table 4**).

Discussion

In this study, the MACE incidence was significantly lower in the CR group than in the Control group for long-term follow-up of ≤3,500 days even in elderly patients with stable CAD. To the best of our knowledge, this is the first report to demonstrate the efficacy of phase III CR for reducing cardiovascular events in elderly and stable CAD patients.

Comprehensive CR has numerous beneficial effects, including not only improvement of exercise capacity, muscle strength, cardiac risk factors, and HRQOL, but also reducing mortality in CAD patients. We and other groups have shown that these benefits of CR even affect elderly patients with CAD.[9,10,22–24] However, most of the previous studies were observational and assessed the phase II period.[22–24] Naylor et al[25,26] and Clark et al[27] showed that comprehensive discharge planning and home follow-up intervention improved clinical outcomes in elderly patients with CAD, but their reports were based on educational programs without a structured exercise component in the phase II period. Recently, Suaya et al reported that CR participants decreased their 5-year mortal-

ity, among elderly patients of US Medicare beneficiaries who were hospitalized for coronary conditions or cardiac revascularization procedures.[21] Most of the subjects were thought to be recruited during the phase II period, such as after acute MI and coronary revascularization. In addition, detailed clinical conditions, such as lipid profiles, data of glucose tolerance, ejection fraction, severity of coronary lesions, and medical treatment, were not clarified, because the origin of the data was the Medicare database.[21] Therefore, we believe that the present study is important, because we investigated the effects of CR on mortality and cardiovascular events in elderly patients in the phase III period.

The precise mechanisms by which CR improves the clinical outcome, even in elderly patients with stable CAD, have not fully been elucidated. Exercise-based training has direct effects on the cardiovascular system, including improvement of oxygen demand, endothelial function, autonomic nerve balance, coagulation system, and inflammatory state.[20] Moreover, comprehensive CR may have indirect effects, such as improvements in the risk factors for atherosclerotic disease.[20] In the present study, BMI significantly decreased in the CR group, and the levels of TG and fasting glucose were significantly lower in the CR group than in the Control group. Indeed, we have already demonstrated in a study of randomized design that CR reduced fat weight without a reduction in lean body weight, as well as the levels of TC in older patients with CAD.[10] The CR group maintained exercise capacity, although peak $\dot{V}O_2$ significantly decreased in the Control group.[10] In addition, the CR group significantly improved muscle strength, flexibility and HRQOL scores calculated by SF-36.[9,10] These direct and indirect effects may have lead to the reduction in cardiovascular events in the subjects of this study.

Although this study reported that the MACE incidence was significantly lower in the CR group than in the Control group, all-cause mortality and cardiovascular death were not significantly different between the 2 groups. This result may be caused by the small sample size. Indeed, a recent study demonstrated that the mortality rate was 34% lower in CR users than nonusers in propensity-based matching of 70,040 subjects.[21] In the present study, the adjusted hazard ratio by multivariate Cox proportional method was 0.65, which was not statistically significant for total mortality in the CR group, compared with the Control group, which suggests that the impact of CR on reducing mortality might be identical in this different cohort. Another possibility is the short period of follow-up. The prognosis for these study subjects may be relatively better than in a previous study, which demonstrated 24.6% mortality at 5 years, even in the non-CR group.[21]

Study Limitations

There are several potential limitations to the present study. First, as described, this study had a small sample. Second, all subjects were male. Third, the supervised exercise session at the clinic was performed only once weekly with at least two home exercise sessions. Therefore, the protocol of this study might not be sufficient to improve the incidence of clinical events such as cardiovascular death, development of new lesions, and admission for CHF. Fourth, the CR group consisted only of subjects who accepted to participate in a formal CR program. Therefore, there may be some selection bias and the study group may not be representative of all elderly patients with CAD. However, the baseline characteristics were identical, including age, BMI, frequency of coronary risk factors, ejection fraction, severity of diseased vessel, and concomitant use of medications, between the 2 groups in this study. In the CR group, 21 patients (57%) undertook habitual exercise, including walking, golf, tennis, and stretching. We did not have precise data of prevalence of regular exercise in the Control group; however, 29 patients (58%) undertook habitual exercise among 50 consecutive elderly patients with CAD who were admitted to our division. Therefore, the prevalence of habitual exercise between the 2 groups may be identical. We believe that the present study is a pioneering and valuable report promoting further investigations. In addition, we did not evaluate physical activity in detail. We assessed the continuance of home-based exercise in the CR group after 1 year of the CR program. Nearly 70% of subjects had continued home exercise, including walking and stretching (data not shown). This high prevalence of continuing home-based exercise may be an explanation for the reduction in cardiovascular events in the CR group. We need to clarify this point in the next step.

Conclusion

A phase III comprehensive CR program significantly improved clinical prognosis, even in elderly patients with stable CAD. Further large sample studies of then elderly population are required to confirm these findings.

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ORIGINAL ARTICLE

Relationship between exercise tolerance and muscle strength following cardiac rehabilitation: Comparison of patients after cardiac surgery and patients with myocardial infarction

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KEYWORDS
Cardiac rehabilitation;
Valvular heart disease;
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Summary
Background and purpose: Previous studies have demonstrated that cardiac rehabilitation (CR) improves exercise tolerance and muscle strength in patients with myocardial infarction (MI) and in patients after cardiac surgery. However, the association between exercise tolerance and muscular strength following CR and the comparison of relationships among various disease categories has not been fully examined. The purpose of the present study was to assess the relationship between exercise tolerance and muscle strength following CR in patients after cardiac surgery and patients with MI.
Methods and results: One hundred and four patients who participated in CR for 6 months were enrolled [post-cardiac valve surgery (VALVE), $n = 28$; post-coronary artery bypass grafting (CABG), $n = 42$; post-acute MI, $n = 34$]. The exercise tolerance, thigh/calf circumferences, and muscle strength were measured before and after CR. At the baseline, the thigh circumference was significantly smaller in the VALVE

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group than in the MI group. There were significant positive correlations between peak $\dot{V}O_2$ and muscle torques of the lower muscles in all groups. After 6 months, peak $\dot{V}O_2$ and muscle torque were significantly increased in all groups ($p < 0.001$). A positive significant correlation between percent increases in peak $\dot{V}O_2$ and muscular strength was observed in the VALVE group ($r = 0.51$, $p < 0.01$), but not in the other groups. In addition, the changes in peak $\dot{V}O_2$ and calf circumference after CR were significantly higher in the VALVE group than in the MI group.

Conclusions: These data suggest that exercise intolerance in patients after heart valve surgery may in part depend on decreased muscular strength. Further studies are needed to assess whether the strategy of increasing muscular strength of lower limb by programmed resistance training could be effective for improving exercise intolerance in patients after heart valve surgery and symptomatic patients with heart failure.

Introduction

Cardiac rehabilitation (CR) has been applied to patients receiving open-heart surgeries such as cardiac valvular surgery and coronary artery bypass grafting (CABG), and patients with ischemic heart disease following myocardial infarction (MI). It has been clearly established that CR reduces mortality and morbidity in patients with chronic heart failure [1,2].

Physical deconditioning is frequently observed in patients after cardiac surgery and in patients with MI [3,4]. These patients often have skeletal muscle abnormalities including demand-perfusion mismatch, muscle atrophy, shifts in the muscle fiber type, and metabolic dysfunction [5]. Indeed, skeletal muscle strength is closely correlated with exercise tolerance, in patients with chronic heart failure [6]. Previous studies have clearly demonstrated that CR improves exercise tolerance and muscle strength in patients with MI and in patients after cardiac surgery. However, the association between exercise tolerance and muscular strength following CR and the comparison of relationships among various disease categories has not been fully examined. The purpose of the present study was to assess the relationship between exercise tolerance and muscle strength before and after CR in patients who had cardiac valve surgery, CABG, or acute MI.

Methods

Patients

One hundred and four patients who participated in CR for 6 months at Juntendo University Hospital between February 2002 and April 2005 were enrolled. They were divided into three groups: patients after valve surgery (VALVE) ($n = 28$), after CABG ($n = 42$), and with acute MI ($n = 34$). Preoperative diagnoses in the VALVE group were as follows: six patients with aortic stenosis, nine with aortic regurgitation, 11 with mitral regurgitation, and two with aortic and mitral regurgitation. Ten patients were in New York Heart Association functional classification I, 15 patients were in class II, and three patients were in class III. Written informed consent was obtained from each patient before participation. This study was approved by the Ethical Committee of Juntendo University Hospital.

Study protocol

All patients performed a symptom-limited cardiopulmonary exercise test using an electronically braked upright ergometer (Corival 400, Lode B.V., Groningen, Netherlands). After a period of resting, warm-up was performed for a few minutes at 20 W, followed by ramp loading (15 W/min) until patients felt fatigued. Heart rate and rhythm were monitored continuously by a 12-lead electrocardiographic system (Marquette CASE 8000, GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA), and blood pressure was assessed every minute throughout the test. The respiratory gas exchange was measured by the breath-by-breath method using a gas analyzer system (Vmax-29S, SensorMedics Co., Yorba Linda, CA, USA). Oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation, and the respiratory exchange ratio were measured. Peak $\dot{V}O_2$ was determined as highest $\dot{V}O_2$ achieved during exercise. The anaerobic threshold was measured by the V-slope method. To measure the isokinetic muscle strength of the quadriceps and hamstrings, we used the Cybex-770

Table 1 Baseline characteristics.

	VALVE	CABG	MI
N	28	42	34
Sex (male/female)	22/6	40/2	28/6
Age (year)	56 ± 13	61 ± 8	60 ± 11
Body mass index (kg/m^2)	21.6 ± 2.6	23.3 ± 2.8*	24.0 ± 2.6*
Hypertension, *n* (%)	13 (46)	25 (60)	18 (53)
Dyslipidemia, *n* (%)	4 (14)	28 (67)**	22 (65)**
Diabetes, *n* (%)	2 (7)	21 (50)**	13 (38)**
Ejection fraction (%)	57.3 ± 17.5	56.9 ± 16.7	53.4 ± 12.3

Values are expressed mean ± SD. Examination of statistical significance was followed by Scheffe test or chi-square test. VALVE, cardiac valve surgery group; CABG, coronary artery bypass grafting group; MI, acute myocardial infarction group.
* $p < 0.05$ denotes statistically significant difference from the value of VALVE.
** $p < 0.01$ denotes statistically significant difference from the value of VALVE.

isokinetic dynamometer (Lumex Co., Ronkonkoma, NY, USA), as we described previously [7–9]. Patients were tested in a seated position with hip flexion. Stabilization straps were applied to the trunk, waist, and thigh. The range of motion during testing was set between 0° and 90° of knee flexion. All patients performed three consecutive repetitions of knee extension and flexion movements at an angular velocity of 60° per second. The highest value was regarded as the peak torque. The peak torques of the knee extensor and flexor muscles were adjusted by body weight according to the following formula: strength (Nm) × 100/body weight (kg), since it is well known that the peak muscle power is closely associated with body weight [10]. The circumferences of thigh and calf were also measured. These measurements were performed after surgery or acute MI onset (from 4 to 11 days) and 6 months after rehabilitation in the same manner.

Exercise session

Supervised exercise training, which was composed of warm-up, aerobic exercise, resistance training, and cool-down sessions, was performed once or twice a week for 6 months, as we described previously [7–9]. In brief, warm-up and cool-down sessions consisted of 12 types of stretching. Aerobic exercise, including a treadmill, cycle ergometer, and walking on in-room tracks, was prescribed on the basis of heart rate at the anaerobic threshold (maximum of 20 min/each). The total aerobic exercise time was approximately 60 min. Resistance training consisted of four types of training (sit-ups, diagonal arm and leg lifts, squats, and push-ups) using the patients' own weight. Resistance training was gradually added to the exercise program at least a month after the beginning of participation. In addition to the supervised exercise, patients were encouraged to perform home-based aerobic exercise, more than 20 min at 11–13 of rating perceived exertion on the Borg scale twice a week.

Statistical analysis

The mean ± SD was calculated for all continuum values. The paired *t*-test was used to compare the data within each group before and after exercise training. For two and three group comparisons, the significance levels were calculated by an unpaired *t*-test and a one-way analysis of variance followed by Scheffe's test, respectively. Linear regression analysis was used to determine the correlations between changes in peak $\dot{V}O_2$ and muscle torque. $p < 0.05$ was defined as significant.

Results

Baseline characteristics

At the baseline, the body mass index was significantly lower in the VALVE group than the CABG and MI groups (CABG: 23.3 ± 2.8 kg/m^2, MI: 24.0 ± 2.6 kg/m^2, VALVE: 21.6 ± 2.6 kg/m^2; CABG vs. VALVE, $p < 0.05$; MI vs. VALVE, $p < 0.05$) (Table 1). The prevalence of dyslipidemia (CABG: 67%; MI: 53%; VALVE: 14%; CABG vs. VALVE, $p < 0.01$; MI vs. VALVE, $p < 0.01$) and that of diabetes (CABG: 50%, MI: 38%, VALVE: 7%; CABG vs. VALVE, $p < 0.01$; MI vs. VALVE, $p < 0.01$) were significantly higher in the CABG and MI groups than in the VALVE group. There were no significant differences in the number of supervised training sessions in each group (VALVE: 28.0 ± 12.3; CABG: 30.4 ± 12.6; and MI: 26.4 ± 13.7 sessions).