Oxygen Uptake Kinetics During and After Exercise are Useful Markers of Coronary Artery Disease in Patients With Exercise Electrocardiography Suggesting Myocardial Ischemia

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Background: The aim of the current study was to determine if the slowed exercise oxygen uptake (V̇O₂) kinetics, which is developed by myocardial ischemia, would be accompanied by delayed recovery V̇O₂ kinetics in patients with coronary artery disease (CAD).

Methods and Results: Thirty-seven patients with significant ST depression during treadmill exercise underwent cardiopulmonary exercise testing with cycle ergometer. Measurements performed are the ratios of change in increase in oxygen (O₂) uptake relative to increase in work rate (ΔV̇O₂/ΔWR) across anaerobic threshold (AT) and 1 mm ST depression point (ST-dep), the time constants of V̇O₂ during recovery (T₁/₂ V̇O₂), stress radio-isotope scintigraphy and coronary angiography. Patients were divided into CAD positive (CAD+) and CAD negative (CAD−) groups, based on coronary angiography. In CAD+, ΔV̇O₂/ΔWR decreased above AT and ST-dep, in contrast to CAD− patients. The T₁/₂ V̇O₂ in CAD+ (103.1±13.0 s) was greater than that of CAD− (76.5±8.7 s) and showed negative correlations to the ratios of ΔV̇O₂/ΔWR across AT and ST-dep. These parameters improved in the patients who underwent coronary bypass surgery.

Conclusions: Exercise and recovery V̇O₂ kinetics were slowed when myocardial ischemia was provoked by exercise. Measurement of exercise and recovery V̇O₂ kinetics improve the accuracy of the exercise electrocardiogram diagnosis of CAD.

Key Words: Coronary artery disease; Exercise recovery; Oxygen uptake kinetics; ΔV̇O₂/ΔWR; T₁/₂ V̇O₂

Exercise electrocardiogram (ECG) is widely used to diagnose and evaluate the severity of patients with coronary artery disease (CAD). However, ischemia detected from the change in the ST segment of the ECG during exercise, is said to be not highly sensitive or specific. A meta-analysis on sensitivity and specificity found 68%±16% in sensitivity and 77%±17% in specificity.¹ For this reason, nuclear medicine stress test² or stress echocardiography by exercise or dobutamine³ are used in combination in daily clinical practice. The present study is designed to increase the sensitivity and specificity for detection of myocardial ischemia by non-invasive cardiopulmonary exercise testing (CPET) in which changes in gas exchange occur consequent to exercise-induced myocardial dyskinesis, which accompanies myocardial ischemia.

Editorial p ????

Recent reports have shown the usefulness of CPET for detecting myocardial ischemia in CAD patients.⁴⁻⁶ We⁴ and others⁵,⁶ found that oxygen uptake (V̇O₂) failed to continue to increase linearly with increasing work rate above the anaerobic threshold (AT) or ischemic threshold during an increasing work rate CPET in CAD patients. When the left ventricular wall becomes hypokinetic, akinetic or even dyskinetic secondary to ischemia, the decreased stroke volume prevents oxygen (O₂) transport to increase at a rate sufficient to supply the muscles with the O₂ needed to regenerate the high energy phosphate (adenosine triphosphate (ATP)) needed by the skeletal muscles to sustain muscle contraction, aerobically. Thus V̇O₂ fails to increase appropriately for the increasing work rate. Because V̇O₂ is a product of cardiac output times the arterial-venous O₂ difference, its altered kinetics reflects altered cardiac function during exercise.

V̇O₂ kinetics at the beginning of exercise and recovery⁷ reflect abrupt early changes in cardiac output at these 2 functional states, and both are slow to change in patients with congenital heart disease⁸ and heart failure.⁹ We hypothesized that the work rate above which myocardial...
ischemia occurs would slow the cardiac output response to the increasing work rate and simultaneously increase the O2 deficit. This would be expected to increase the O2 debt in recovery, the latter evidenced by a slowing of recovery VO2 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 VO2 with respect to the increase in work rate (ΔVO2/ΔWR) above compared to below the anaerobic or ischemic threshold in patients with suspected angina and positive ECG changes suggestive of myocardial ischemia. Additionally, the VO2 kinetics during recovery from exercise, as evidence of an increased O2 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) 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 Denki 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 VO2, CO2 output (VCO2) and minute ventilation (VE) 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 VO2 was defined as the average value obtained during the last 30 s of incremental exercise. We measured ΔVO2/ΔWR 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 ΔVO2/ΔWR below and above the ST depression of 1 mm along with the slope ratio between them (slope ratio across ST-dep). ΔVO2/ΔWR 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 VO2 to return to pre-exercise baseline (T1/2) after exercise was calculated from the onset of recovery after exercise. This would reflect the size and rate of repayment of the O2 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 201Thallium 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.11.0F, 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 VO2
Figure 1 shows the typical VO2 kinetics and HR−VO2 curves during incremental exercise. The CAD− patient (case no. 9) showed a linear, non-changing increase in VO2.
Myocardial Ischemia Affects Exercise $\dot{V}$O$_2$ Kinetics

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·min$^{-1}$·kg$^{-1}$ for the CAD– and CAD+ groups, respectively, and these 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

![Figure 1](https://example.com/f1.png)

**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 |
|---------------------------------|---------------------|--------------------|
| **Age** (year)                  | CAD– group(n=19)    | CAD+ group (n=18)  | P-values* |
| 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±5.7          | <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·min$^{-1}$·kg$^{-1}$) | 13.0±2.4           | 12.1±1.5           | 0.261     |
| Oxygen uptake at peak (ml·min$^{-1}$·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$\frac{1}{2}$: $\dot{V}$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$\frac{1}{2}$: $\dot{V}$O$_2$, half time recovery of $\dot{V}$O$_2$ after exercise.
the CAD− and CAD+ groups, respectively (Table 1). Peak VO₂ in the CAD+ group was significantly lower than that of the CAD− group.

**ΔVO₂/ΔWR for 2 min Below and Above AT, and Ratio of ΔVO₂/ΔWR for 2 min Below to 2 min Above AT (Slope Ratio Across AT)**

The ΔVO₂/ΔWR 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, ΔVO₂/ΔWR 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 ΔVO₂/ΔWR 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).

**ΔVO₂/ΔWR for 2 min Below and Above ST-Dep, and the Slope Ratio Across ST-Dep**

The ΔVO₂/ΔWR for the CAD− group for 2 min below ST-dep was 11.6±1.0 ml·min⁻¹·W⁻¹ and that for 2 min above ST-dep was 11.8±1.2 ml·min⁻¹·W⁻¹. For the CAD+ group, ΔVO₂/ΔWR 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 ΔVO₂/ΔWR values between below ST-dep and above ST-dep in the CAD− group, whereas ΔVO₂/ΔWR 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 in CAD+ group was significantly lower than that of CAD− group (P<0.001, Figure 2 Right).

**O₂ Kinetics During Recovery Phase**

VO₂ kinetics in recovery phase of exercise (T 1/2 VO₂) 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 Figure 2 Right).
Myocardial Ischemia Affects Exercise $\dot{V}O_2$ Kinetics

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 $\Delta\dot{V}O_2/\Delta W_R$ 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)

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

*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.
Table 1). T1/2 VO2 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 T1/2 VO2 (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 O2 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 VO2 kinetics. Because no patients showed significant ST depression after the surgery, we determined ΔVO2/ΔWR for 2 min below and above ST-dep with the same analysis intervals as before the surgery. The ΔVO2/ΔWR 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 T1/2 VO2 (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 VO2 (as a result of limited increase in O2 flow) to increase appropriately during exercise to meet the muscle O2 requirement of the work rate. However, in patients with CAD, pumping function of the left ventricle and O2 delivery is not disturbed until the myocardium has an inadequate O2 supply to regenerate ATP. We found that ΔVO2/ΔWR 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 reports1,4,6 and support the concept that the decrease of ΔVO2/ΔWR above the AT during exercise in CAD is because of the change in cardiac performance caused by myocardial ischemia. AT appears at a lower VO2 than ST-dep because myocardial ischemia occurs before the ECG change and ischemia affects the cardiac pumping function.1,4,15

It has been well documented that recovery VO2 is prolonged in patients with heart failure.12,16 Pavia et al reported that T1/2 VO2 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 T1/2 for VO2 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 O2 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 VO2 during incremental exercise improved in 5 patients who underwent CABG surgery (Table 2). This supports the physiological relationship between myocardial ischemia and abnormal VO2 kinetics.

It is easier to measure the kinetics of VO2 in the recovery phase than during exercise because ΔVO2/ΔWR above ST-dep might not be determined because of the short time of exercise duration. The VO2 decay in recovery is not affected by the exercise duration in an increasing work rate test1,2,17 and is easily determined when patients perform at least 50% of maximum exercise. Another advantage for use of T1/2 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 Right). The age matched normal value of T1/2 VO2 is 56.9±7.0 s (50–70 years, 60±25.3 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 VO2 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 VO2 with the slowed VO2 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.

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Disclosure
No authors have any conflicts of interest.

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Myocardial Ischemia Affects Exercise VO₂ Kinetics


