Cardiac Output--O\textsubscript{2} Uptake Relation During Incremental Exercise in Patients With Previous Myocardial Infarction

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**Background.** The cardiac output--O\textsubscript{2} uptake (Vo\textsubscript{2}) relation, which is thought to be linear and predictable in normal humans, has not been clarified in cardiac patients. We evaluated the relation between cardiac output and Vo\textsubscript{2} during the incremental exercise test in patients with previous myocardial infarction.

**Methods and Results.** Twenty-two patients (age, 58.1±8.0 years) with previous myocardial infarction performed a symptom-limited exercise test on a cycle ergometer. Vo\textsubscript{2} was calculated from the expired gas analysis, and cardiac output was measured by a computerized cadmium telluride detector every 10 seconds during exercise. The ratio of increase in Vo\textsubscript{2} to the increase in work rate (ΔVo\textsubscript{2}/ΔWR) below and above the anaerobic threshold (AT) was 11.1±3.6 and 11.1±2.9 ml/min/W, respectively, showing no significant difference. However, the ratio of increase in cardiac output to increase in work rate (ΔCO/ΔWR) below the AT was 50.1±26.6 ml/min/W and was significantly decreased to 11.8±25.3 ml/min/W above the AT (p=0.0002). The decreased ΔCO/ΔWR above the AT primarily would be due to silent myocardial ischemia produced by exercise, as there was the presence of \textsuperscript{201}TI redistribution in 15 of 16 patients in whom myocardial \textsuperscript{201}TI scintigraphy with dipyridamole or exercise stress testing was evaluated. ΔCO/ΔVo\textsubscript{2}, which has been reported to be approximately 5.5 in normal subjects, was only 4.4±2.6 at work rates below the AT and was decreased to 1.1±2.3 at work rates above the AT.

**Conclusions.** The relation between cardiac output and Vo\textsubscript{2} during exercise in patients with previous myocardial infarction differs profoundly from that reported in normal subjects. These findings must be considered when we noninvasively estimate the change in cardiac output during exercise by obtaining Vo\textsubscript{2} in patients with coronary artery disease. (*Circulation* 1992;85:1713–1719)

**KEY WORDS** • anaerobic threshold • exercise testing • cadmium telluride

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It has generally been assumed that O\textsubscript{2} uptake (Vo\textsubscript{2}) increases linearly with work rate below Vo\textsubscript{2max} during the incremental exercise test.\textsuperscript{1,2} The ratio of the increase in Vo\textsubscript{2} to the increase in work rate (ΔVo\textsubscript{2}/ΔWR) has also been described as not differing between cardiac patients and normal subjects;\textsuperscript{3} thus, it has been considered that Vo\textsubscript{2} during exercise would be predicted from the work rate without the analysis of respiratory gas. However, ΔVo\textsubscript{2}/ΔWR was recently found to decrease according to the severity of heart failure.\textsuperscript{4–6} It was also noted that the ΔVo\textsubscript{2}/ΔWR decreases only at work rates above the anaerobic threshold (AT), when the transport of O\textsubscript{2} to the working muscles is reduced.\textsuperscript{7}

The relation between cardiac output and Vo\textsubscript{2} during exercise is an important subject and has been analyzed in normal subjects by numerous physiologists.\textsuperscript{8–11} In 1977, Faulkner et al\textsuperscript{11} reported that the cardiac output--Vo\textsubscript{2} relation is linear and predictable in a wide variety of normal humans. Since then, the slope of the regression line (ΔCO/ΔVo\textsubscript{2}) has been believed to be approximately 5.5 in normal subjects.\textsuperscript{8–10,11}

Vo\textsubscript{2} is equal to cardiac output×arterial–mixed venous O\textsubscript{2} difference (C\textsubscript{a–v}O\textsubscript{2}). If the ΔVo\textsubscript{2}/ΔWR is decreased in cardiac patients compared with normal subjects, this decrease might be secondary to the decrease in the ratio of the increase in cardiac output to the increase in work rate (ΔCO/ΔWR). These decreases in ΔVo\textsubscript{2}/ΔWR and ΔCO/ΔWR in cardiac patients might also affect the assumed relation between cardiac output and Vo\textsubscript{2}.

The relation between cardiac output and Vo\textsubscript{2} during exercise is very important when we noninvasively evaluate cardiac performance during exercise by respiratory measurements in cardiac patients. However, there has been no study to our knowledge that clarified the cardiac output--Vo\textsubscript{2} relation in cardiac patients during incremental exercise testing. Recently, we reported that left ventricular ejection fraction initially increased but reached a peak value at the AT and then fell below resting levels during incremental exercise in patients with chronic heart disease, probably because of myocardial ischemia.\textsuperscript{12} Thus, ΔCO/ΔWR above the AT would be reduced compared with that below the AT in pa-

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tients with coronary artery disease when they are measured independently.

We hypothesized that \( \Delta CO/\Delta \dot{V}O_2 \) is decreased in patients with previous myocardial infarction, especially at work rates above the AT because of the decrease in \( \Delta CO/\Delta W\). To test this hypothesis, we selected patients with previous myocardial infarction because they usually have decreased left ventricular function at rest, which would be more apparent during exercise because of exercise-induced myocardial ischemia. We determined \( \Delta \dot{V}O_2/\Delta W\), \( \Delta CO/\Delta W\), and \( \Delta CO/\Delta \dot{V}O_2 \) below and above the AT, measuring the \( \dot{V}O_2 \) and cardiac output continuously during the incremental exercise test.

Methods

Study Patients

Twenty-two patients with previous myocardial infarction, 19 men and three women ranging in age from 44 to 69 years, were evaluated (Table 1). None of the patients had a myocardial infarction within 1 month preceding enrollment in the study. At the time of the study, all patients were clinically stable and in sinus rhythm. Patients whose exercise tolerance was extremely low, i.e., whose AT occurred at low work rates (less than 40 W) and/or within 20 W of the maximum work rate, were excluded to obtain enough window to calculate \( \Delta \dot{V}O_2/\Delta W\), \( \Delta CO/\Delta W\), and \( \Delta CO/\Delta \dot{V}O_2 \) below and above the AT. All medications were withheld for 24 hours before the study.

Exercise Protocol

A symptom-limited exercise test with an upright, electromagnetically braked cycle ergometer (Siemens-Elema 930B, Siemens Elema AB, Solna, Sweden) was used. After a 4-minute rest on the ergometer, exercise began with a 4-minute warm-up at 20 W, 60 rpm, followed by a 1-W increase in the work rate every 6 seconds (ramp pattern). The heart rate and a 12-lead electrocardiogram were monitored throughout the test by System ML-8000 (Fukuda Denshi Co., Ltd., Tokyo). Cuff blood pressure was measured every minute with an automatic indirect manometer (STBP-680F, Collin Denshi, Aichi, Japan). To calibrate subsequent measurements, cardiac output during the rest period preceding exercise was measured by the dye dilution method with indocyanine green, using an ear photoplethysmographic transducer, and the output was analyzed by a cardiac output computer (MLC-4200, Nihon-Kohden Corp., Tokyo).

Table 1. Physical Characteristics, Left Ventricular Ejection Fraction at Rest, Maximum Work Rate, Location of Infarct, and Angiographic Data

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<th>Weight (kg)</th>
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Mean: 58.1 160.7 60.3 35.9 102.8

SD: 8.0 7.2 7.8 8.5 20.8

LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; M, male; F, female; Ant, anterior; Inf, inferior; Lat, lateral.

Left ventricular ejection fraction was measured at rest in the sitting position. Significant coronary stenosis was defined as ≥75% reduction in luminal diameter of coronary vessels. Coronary angiography was not evaluated in patient 7.
### Table 2. Hemodynamic Data for Each Patient at Rest and at Peak Exercise

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<th>VO2 (ml/min)</th>
<th>CO (l/min)</th>
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Mean 79.0 131.5 81.2 13.8 241.4 4.5 829.6 140.5 193.4 972 1,282.5 8.5 1,545.5
SD 12.3 18.6 10.0 1.4 34.0 1.1 226.4 19.6 26.7 17.7 252.3 2.2 427.8

HR, heart rate; bpm, beats per minute; BPS, systolic blood pressure; BPD, diastolic blood pressure; Hb, hemoglobin; VO2, O2 uptake; CO, cardiac output.
O2 transport was calculated assuming that 1 g hemoglobin can combine with 1.39 ml O2 and that arterial O2 saturation is 95%.

**Measurements of Cardiac Output and VO2 During Exercise**

The detailed methods used in this study have been reported previously.12 A computerized cardiac monitoring system (RRG-607, Aloka Co., Ltd., Tokyo) was used to continuously monitor left ventricular function. This system consists of a cadmium telluride detector (A-116, Radiation Monitoring Devices, Boston), a preamplifier unit, a portable data acquisition unit, and a central processing unit (personal computer PC-9801, NEC Corp., Tokyo). After the patient's red blood cells were labeled with 30 mCi 99mTc by the semi-in vivo method, the cadmium telluride detector was positioned over the left ventricular region by a vest designed specifically to hold the detector in place. The left ventricular region of interest was chosen as the position with the maximal ratio of stroke counts (end-diastolic counts minus end-systolic counts) to average counts (end-diastolic counts plus end-systolic counts divided by 2).15

The microcomputer calculated the counts over the left ventricular region of interest during the cardiac cycle at 50-msec intervals throughout the exercise test.16 As previously described,12 the left ventricular ejection fraction was calculated using 70% of the end-diastolic counts as the background activity, as

\[ \text{EF} = \frac{SC}{(0.3 \times EDC)} \]

where EF is ejection fraction, SC is stroke count (end-diastolic count minus end-systolic count), and EDC is end-diastolic count.

Stroke volume at rest was calculated from the cardiac output measured by the dye dilution method and was used to calculate the absolute values of stroke volume from the ejection fraction derived by the radioactive counting technique. Accordingly, stroke volume during exercise was calculated from stroke count by measuring the change from rest. After the test, cardiac output (stroke volume × heart rate) throughout the test was determined using 10-second averaging. From our experience, this determination of cardiac output during exercise is quite reproducible in patients with previous myocardial infarction when the same exercise test is repeated at 1–2-month intervals.

VO2, CO2 output (VCO2), and the rate of respiratory air flow were measured at rest (while the patient was seated on the ergometer) and throughout the exercise period with an Aerobic Processor 391 (Nihon Denki Sanei, Tokyo) for six patients (patients 1–6 in Tables 1 and 2) or the Respirometer RM-300 (Minato Medical Science, Tokyo) for 16 patients (patients 7–22 in Tables 1 and 2). Aerobic Processor 391 consists of a mixing
chamber (2.5 l), a polarograph O₂ analyzer, infrared CO₂ analyzer, and a hot wire spirometer. The Respiromoniter RM-300 consists of a hot wire flowmeter and gas analyzer (MG-360, Minato Medical Science) that contains a sampling tube, filter, suction pump, O₂ analyzer of zirconium element, and infrared CO₂ analyzer. The system was carefully calibrated before each study. Gas exchange and flow measurements were corrected for ambient temperature, barometric pressure, and water vapor. From these measurements, VO₂, VCO₂, and minute ventilation (VE) were calculated every 10 seconds.

AVO₂/AWR, ACO/AWR, and AVO₂/WR were determined by the V-slope method in addition to the following conventional criteria: 1) VO₂/VCO₂ increases after being stable or decreasing while the VE/VCO₂ remains constant or is decreasing; 2) the gas exchange ratio, which was stable or slowly rising, begins to increase more steeply.

Calculations of AV0₂/ΔWR, ΔCO/ΔWR, and ΔCO/ΔVO₂

For the calculations of AV0₂/ΔWR, ΔCO/ΔWR, and ΔCO/ΔVO₂, a three-point moving average of the 10-second data was used. AV0₂/ΔWR below and above the AT was calculated by least-squares linear regression from the data between 60 seconds after start-up to the AT point and between the AT point to 20 seconds before the end of the ramp test, respectively, assuming that the regression line passes through the AT point for both the VO₂ and the work rate. The first 60 seconds and the last 20 seconds of the VO₂ response (the transitional periods) were excluded from the calculation, as previously described by Hansen et al. After this exclusion, 181±75 (mean±SD) and 223±60 seconds of data were obtained for analysis below and above the AT, respectively. ΔCO/ΔWR and ΔCO/ΔVO₂ were also calculated using the same method.

Statistical Analysis

All data are given as mean±SD. Comparisons of AV0₂/ΔWR, ΔCO/ΔWR, and ΔCO/ΔVO₂ below and above the AT were made by the paired t test. Differences were considered significant at the level of p<0.05.

Results

Heart rate, systolic blood pressure, diastolic blood pressure, VO₂, and cardiac output at rest and at peak exercise are shown in Table 2. VO₂ and cardiac output were 241.4±34.0 ml/min and 4.5±1.1 l/min, respectively. All patients were able to perform the incremental exercise test without chest pain, although most of them exhibited ST segment depression during the exercise. The maximum work rate was 102.8±20.8 W (Table 1).

Figure 1 shows the AT determined by the V-slope method in one representative subject (patient 1 in Table 1). AT was easily determined in all subjects by respiratory gas measurements.

Figure 2 shows the response of VO₂ of 22 patients during the incremental exercise test, in which each patient's AT is aligned at the point labeled "0" for both VO₂ and work rate. The mean slope of VO₂ (ΔVO₂/ΔWR) below and above the AT was 11.1±3.6 and

Discussion

In 1987, Hansen and colleagues analyzed the relation between the increase in VO₂ and the increase in work rate.
during incremental cycle ergometer exercise in 54 normal men and 51 patients with circulatory disorders. They suggested that a reduction in ΔVO₂/ΔWR indicates cardiovascular dysfunction. Hansen et al.\(^7\) also noted that in contrast to work rates below the AT, the ΔVO₂/ΔWR above the AT is influenced by the rate of work rate increase. It was previously reported that ΔVO₂/ΔWR decreases only at the work rates above the AT, when O₂ transport to the working muscles is decreased by an increase in carboxyhemoglobin and that this decrease might be proportional to the amount of anaerobic energy production.\(^7\)

Although we assumed that ΔVO₂/ΔWR above the AT must be lower than that below the AT in patients with coronary artery disease, there was no significant difference in the ΔVO₂/ΔWR below and above the AT in this study. The explanations for this finding might include the following: 1) While lactate will increase detectably in the blood and create a significant metabolic acidosis above the AT, the decrease in ΔVO₂/ΔWR would be very difficult to detect unless a very clear reference slope for the condition of nonanaerobic metabolism were available. 2) When the rate of work rate increase is relatively slow, such as 10 W/min, ΔVO₂/ΔWR above the AT might be similar to that below the AT, as previously described by Hansen et al.\(^7\) 3) Even though the rate of increase in the cardiac output above the AT is much lower than that below the AT, this decrease might be compensated for by widening of C(a−v)O₂ or increased O₂ extraction ratio so that the decrease in VO₂ might be undetectable.

Calculated arterial O₂ transport ranged from 828 to 2,417 ml/min (Table 2), and systemic O₂ extraction ratio was an average of 86% at peak exercise. Similar high extraction ratio in cardiac patients has also been reported by Wilson et al.\(^23\) In their study, systemic O₂ extraction ratio was 83% at maximum exercise in cardiac patients with reduced maximal VO₂, although it was 74% in the patients with normal maximal VO₂. High O₂ extraction, which might be attributed to the blood flow diversion from other organs to the exercising muscle groups, may account for the decrease in ΔCO/ΔVO₂ above the AT, i.e., preservation of ΔVO₂/ΔWR despite the marked decrease in ΔCO/ΔWR above the AT.

From several studies in normal subjects,\(^10,24,25\) it was postulated that cardiac output increases linearly according to the increase in VO₂ from low to high levels of work intensity. Faulkner et al.,\(^11\) who thoroughly reviewed these reports, concluded that the cardiac output–VO₂ relation is not significantly affected by age or weight, and that the slope (ΔCO/ΔVO₂) ranges from 5.0 to 5.9. In 1986, Yamaguchi et al.\(^8\) reported that this slope ranges from 5.5 to 10.3 in normal untrained men and is independent of both the subject’s physical characteristics and the resting cardiac output.

In the present study, we measured ΔCO/ΔWR below and above the AT independently and found that ΔCO/ΔWR above the AT is significantly lower than that below the AT. This decrease in cardiac output affected the relation between cardiac output and VO₂. The mean value of ΔCO/ΔVO₂ below the AT was 4.4±2.6 and was apparently lower than those reported in normal subjects.\(^8,10,11,24\) Furthermore, ΔCO/ΔVO₂ decreased to 1.1±2.3 at work rates above the AT. A similar phenomenon can be found in the report of Yamaguchi et al.,\(^8\) in which one normal subject with VO₂max of 3 l/min (shown in Figure 2) failed to show an increase or actually had a decrease in cardiac output above the VO₂ of 1.7 l/min.

The increase in heart rate with respect to the increase in VO₂ (ΔHR/ΔVO₂) below and above the AT was also calculated in 14 patients whose heart rates were continuously measured and recorded during exercise. ΔHR/ΔVO₂ was 64.9±24.3 below the AT and was significantly increased to 73.2±25.7 beats/l above the AT (p=0.024 by paired t test). This finding contrasts to those reported in normal subjects.\(^26–28\) In normal subjects, it has been reported that ΔHR/ΔWR (i.e., ΔHR/ΔVO₂) is lower at work rates above the AT compared with that below the

![Figure 3](http://circ.ahajournals.org/content/103/16/1717/F3)

**Figure 3.** Plot shows cardiac output (CO) response to the 10 W/min ramp test for each patient plotted with respect to patient’s anaerobic threshold. Each patient’s anaerobic threshold is aligned at point labeled “0” for both CO and work rate (WR). ΔCO/ΔWR below and above the anaerobic threshold are calculated independently by least-squares linear regression for each patient. Mean slopes are represented by a solid line.

![Figure 4](http://circ.ahajournals.org/content/103/16/1717/F4)

**Figure 4.** Plot shows relation between cardiac output (CO) and O₂ uptake (VO₂) during the 10 W/min ramp test for each patient. Each patient’s anaerobic threshold is aligned at point labeled “0” for both CO and VO₂. ΔCO/ΔVO₂ below and above the anaerobic threshold are calculated independently by least-squares linear regression for each patient. Mean slopes are represented by a solid line.
AT. 28 Decreased ΔCO/ΔVO2 above the AT despite the increase in ΔHR/ΔVO2 in our patients must be due to the insufficient increase in stroke volume.

Myocardial 201TI scintigraphy with dipyridamole or exercise stress testing was evaluated in 16 patients, and the presence of 201TI redistribution was found in 15. 201TI redistribution is defined as the total or partial resolution of initial postdipyridamole or postexercise defects when assessed by repeat imaging 2.5–4 hours after tracer administration. 29 As 201TI rapidly washes out of normal myocardial zones, redistribution is thought to be the presence of the ischemic segment perfused by the stenotic vessel. Therefore, the decreases in ΔCO/ΔWR and ΔCO/ΔVO2 above the AT in our patients primarily would be due to silent myocardial ischemia produced by exercise, although the role of depressed left ventricular function at rest is presumably secondary to prior infarction. The deterioration of left ventricular function during exercise might also be attributed to the increased preload and/or failure of systemic vasodilatation to produce sufficient afterload reduction during exercise. 12

It has been reported that aging does not affect the VO2–work rate, 2–5 or cardiac output–VO2, 11 relations. Thus, there would be no influence of aging on our findings, although the mean age was relatively high (58.1 years) in the present study. Heart rate at peak exercise was 86.2±11.6% of the age-predicted maximal heart rates 20 in the present study. This might be due to inability or unwillingness of the subject to exercise to maximum. If they had actually reached their maximal heart rates or maximal VO2, there might have been more decrease in the ratio of ΔCO/ΔVO2 in the work rate above the AT.

It was recently reported that the nuclear detector, a portable nonimaging device, is useful for the beat-to-beat assessment of left ventricular function during the incremental exercise test. 31–33 An excellent correlation between the left ventricular ejection fraction measured with a cadmium telluride detector and that recorded with the gamma camera or contrast ventriculography has been noted by several investigators. 32, 34 However, there is a limitation that should be considered in the evaluation of the data obtained by this technique. We used a fixed percent (70%) of end-diastolic counts as background activity to calculate the ejection fraction. 12, 33, 35 Background activity might increase during exercise, especially in patients with congestive heart failure. Thus, using a fixed percentage of end-diastolic counts might lead to the underestimation of stroke volume and cardiac output. However, in a previous study, 12 we noted that the increase in background counts during the symptom-limited incremental exercise test from the reference detector placed over the right anterior chest is small, even in patients with congestive heart failure. Because a change in the background activity would have only a small effect on the absolute value of cardiac output, we do not think that this problem affected the cardiac output–work rate relation and the cardiac output–VO2 relation described in the present study.

In our recent report, 12 we demonstrated that the left ventricular ejection fraction gradually increased as work rate increased, reached its highest value at the very point of the AT (neither below nor above the AT), and then decreased even though the work rate was still increased. Therefore, the AT must be exactly the point at which the decrease in the slopes of ΔCO/ΔWR and ΔCO/ΔVO2 occur during exercise. AT determination provides a method to detect an extremely important demarcation point in the work rate spectrum of patients with coronary artery disease.

It has been described that the relation between cardiac output and VO2 during exercise is linear and that the regression equation or the nomogram can be used to predict cardiac output in normal subjects. 11 However, we found that the relation between cardiac output and VO2 during exercise is not linear and that the ratio of ΔCO/ΔVO2 in patients with previous myocardial infarction is apparently lower than that reported in normal subjects, especially at work rates above the AT. This observation should be considered when we noninvasively estimate the change in cardiac output during exercise by obtaining VO2 in patients with coronary artery disease.

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