Early Aerobic Training Increases End-Tidal CO₂ Pressure During Exercise in Patients After Acute Myocardial Infarction

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Background End-tidal CO₂ partial pressure (PETCO₂) has been suggested as a noninvasive index reflecting cardiac output under constant ventilation. The aim of this study was to examine whether PETCO₂ does reflect cardiac output, even during exercise, in patients with acute myocardial infarction (AMI) undergoing exercise training early after onset.

Method and Results Patients aged 47–73 years were randomly assigned to either a training group (n=18) or a control group (n=18) 1 week after the onset of AMI. Those in the training group performed exercise training under supervision at the anaerobic threshold level for 2 weeks, while patients in the control group followed a conventional walking regimen. In the training group, but not in the control group, PETCO₂ at the respiratory compensation point increased significantly from 39.1±3.5 to 41.1±3.7 mmHg (p<0.01). Similarly, the cardiac index at peak exercise increased only in the training group (from 6.04±0.98 to 7.31±0.97 L/min per m², p<0.01). These 2 measurements correlated well both before and after the study period. Peak oxygen uptake and anaerobic threshold were increased only in the training group.

Conclusions Aerobic exercise training early after the onset of AMI significantly increased PETCO₂ during exercise, which may reflect an improvement in cardiac output during exercise in response to physical training via a decreased ventilation–perfusion mismatch. (Circ J 2004; 68: 778–783)

Key Words: Cardiac output; End-tidal CO₂ pressure; Exercise; Myocardial infarction

It has been suggested that exercise training improves the cardiac output response to exercise in patients with previous myocardial infarction¹ but individual evaluation has been limited partly because of the invasiveness and difficulties inherent in the method used to measure cardiac output. If the response of cardiac output during exercise could be estimated noninvasively, it would be of practical use in evaluating the therapeutic effects of training in patients with various heart diseases.

End-tidal CO₂ pressure (PETCO₂) is a noninvasive index obtained from respiratory gas monitoring. Variations in PETCO₂ have been shown to reflect changes in cardiac output and pulmonary blood flow in animals and humans under constant ventilation.^{2–9} It has been reported that PETCO₂ is influenced by changes of heart rate (presumably cardiac output) in patients with a pacemaker.¹⁰ Compared with normal subjects, patients with a pulmonary embolism have a low PETCO₂, probably because of increased physiological dead space attributable to decreased pulmonary blood flow.¹¹ It has also been shown that patients with cardiac disease have an abnormally low PETCO₂ during exercise, especially those with an impaired response of cardiac output during exercise¹² or with decreased peak

oxygen uptake ($\dot{V}O_2$).¹³ Taking all these findings together, PETCO₂ might be a good estimate of cardiac output in cardiac patients over a wide range of conditions. In the present study, we measured PETCO₂ and cardiac output during exercise in patients undergoing aerobic training started early after the onset of acute myocardial infarction (AMI).

Methods

Study Patients

Thirty-six patients (35 men, 1 woman) were randomly assigned to either a training group (n=18) or a control group (n=18) 1 week after the onset of AMI. The 13 patients (70 %) in the training group and 12 patients (67 %) in the control group underwent successful percutaneous coronary intervention before entering the study. There were

Table 1 Characteristics of the Patients With AMI

	Training group (n=18)	Control group (n=18)
M/F	17/1	18/0
Age (years)	58.6±4.5	60.0±7.9
Site of infarction (n)		
Anterior	9	7
Inferior	6	7
Postero-lateral	3	4
Stenotic lesions (n)	1.2±0.6	1.6±1.0
Peak CK (IU/L)	2,529±2,145	2,061±1,519

Values are mean±SD.

AMI, acute myocardial infarction; CK, creatine kinase.

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Table 2 Cardiac Index and Respiratory Gas Variables During Exercise

	Rest	AT	RCP	Peak
<i>Training group</i>				
Cardiac index (L/min per m ²)				
1 week	2.85±0.63			6.04±0.98
3 week	2.69±0.48			7.31±0.97**
$\dot{V}O_2$ (ml/min per kg)				
1 week	4.1±0.5	12.8±2.0	16.3±2.3	17.0±2.8
3 week	3.9±0.5	14.0±2.2**	19.4±2.6**	20.1±2.9**
$\dot{V}E/\dot{V}CO_2$				
1 week	51.6±6.1	35.7±3.7	35.0±4.1	35.8±4.1
3 week	51.6±4.9	33.7±3.2**	33.1±3.5**	35.1±3.8
Gas exchange ratio				
1 week	0.86±0.05	0.94±0.06	1.01±0.08	1.03±0.08
3 week	0.86±0.04	0.96±0.07	1.05±0.07**	1.12±0.10**
<i>Control group</i>				
Cardiac index (L/min per m ²)				
1 week	2.71±0.55			5.98±1.35
3 week	2.61±0.53			6.51±1.81
$\dot{V}O_2$ (ml/min per kg)				
1 week	3.8±0.4	12.1±2.2	15.6±3.4	16.2±3.3
3 week	3.5±0.4**	12.2±1.7	16.1±2.6	16.9±3.4
$\dot{V}E/\dot{V}CO_2$				
1 week	53.3±7.3	36.4±6.3	36.5±6.5	37.9±5.8
3 week	53.8±5.4	36.0±4.4	35.5±3.8	37.2±3.7
Gas exchange ratio				
1 week	0.85±0.04	0.95±0.06	1.01±0.06	1.05±0.09
3 week	0.88±0.04	0.96±0.05	1.04±0.05*	1.08±0.07

Values are mean ± SD.

AT, anaerobic threshold; RCP, respiratory compensation point; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen uptake.

* $p < 0.05$ vs 1 week, ** $p < 0.01$ vs 1 week.

no inter-group differences in age, sex, site of infarction, number of stenotic lesions, or maximum concentration of creatine kinase at the time of enrollment (Table 1). We excluded patients with pulmonary congestion, dyspnea at rest, serious arrhythmia, left ventricular aneurysm, valvular lesions or primary lung disease. All patients were hospitalized, and conventional medications were prescribed during the study period. The Ethics Committee of the Cardiovascular Institute approved the study protocol, and informed consent was obtained from all patients.

Study Protocol

One week after the onset of AMI, when the patients could successfully walk at least 200 m without any significant ST changes or blood pressure abnormality, they underwent cardiopulmonary exercise testing with measurement of their cardiac output. The training group then started 30 min of supervised bicycle exercise with a constant workload at the anaerobic threshold level, twice daily for 1 week. After the first week of training, the exercise intensity was increased to a new anaerobic threshold level that was determined at the second exercise testing. Meanwhile, the control group performed walking exercise according to the conventional rehabilitation protocol. They started walking 200 m along a corridor in the hospital 3 times a day, 1 week after the onset of AMI. The walking distance was gradually increased up to 500 m by the end of the study period. The patients from both groups underwent a final cardiopulmonary exercise testing 3 weeks after the onset of AMI.

Exercise Testing

The patients performed a symptom-limited exercise test on an electromagnetically braked upright cycle ergometer (CPE-2000, Med Graphics Co, Minneapolis, MN, USA).

After resting for 4 min on the ergometer, they started exercising at a workload of 20 watts for a 4-min warm-up period. The workload was increased by 1 watt every 6 s. Throughout the test, the electrocardiogram and heart rate were monitored continuously using the Stress Test System (ML-5000, Fukuda Denshi, Tokyo, Japan). Blood pressure was also measured every min with an automatic indirect manometer (STBP-780, Colin, Aichi, Japan). All patients stopped exercising because of leg fatigue, dyspnea, or significant ST changes.

Expired Gas Analysis Expired gases were monitored continuously using an expired gas analyzer (Aeromonitor AE-280S, Minato Medical Science, Osaka, Japan), which was carefully calibrated before each measurement. Respiratory parameters, including $\dot{V}O_2$, carbon dioxide output ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$) were measured on a breath-by-breath basis. The data was interpolated to every 3 s after correction for the functional residual capacity and then an 8-point moving average was applied. The ratios of $\dot{V}E$ to $\dot{V}O_2$ ($\dot{V}E/\dot{V}O_2$) and $\dot{V}E$ to $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$), the respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$), and $PETCO_2$ were computed simultaneously and displayed together with the heart rate and $\dot{V}O_2$ on the monitor of a personal computer. The anaerobic threshold was determined mainly by the V-slope method¹⁴ and was also identified by the following conventional criteria:¹⁵ (1) $\dot{V}E/\dot{V}O_2$ increases after being stable or decreasing while $\dot{V}E/\dot{V}CO_2$ remains constant or decreases, and (2) the respiratory exchange ratio, which has been stable or slowly rising, begins to increase more steeply. Peak $\dot{V}O_2$ was calculated by averaging the values of the final 30 s. The respiratory compensation point was determined at the point where $PETCO_2$ started to decrease.

Measurement of Cardiac Output At rest and peak exercise, cardiac output was measured in all patients by the dye

Fig 1. End-tidal CO₂ partial pressure (PETCO₂) and minute ventilation ($\dot{V}_E$) during exercise in the training and control groups. The values at rest, 20, 30, 40 watts, anaerobic threshold, respiratory compensation point, and peak exercise are plotted sequentially from left to right. Values are means $\pm$ SD. * $p < 0.05$ vs 1 week (W), ** $p < 0.01$ vs 1 W.

dilution method using an earpiece with a densitometer (MCL-4200, Nihon Koden, Tokyo, Japan). Indocyanine green (5 mg) was injected through a 20-gauge plastic cannula inserted into the antecubital vein. The resting cardiac output was measured twice and expressed as an average of the 2 measurements. For the cardiac output at peak exercise, indocyanine green was injected when the subject was judged to be reaching the maximum exercise level by the degree of symptoms and/or the change in the respiratory gas variables. The subject was encouraged to continue the incremental exercise until the completion of the cardiac output measurement.

Statistics

Data are expressed as means $\pm$ SD. Inter-group differences were compared by the unpaired t-test. The time-course changes in ventilatory parameters were analyzed by analysis of variance for repeated measures followed by the Fisher's test. A p value < 0.05 was considered significant.

Results

All patients in both groups accomplished the 2-week rehabilitation program without developing any major complications, including symptoms suggesting a new ischemia or arrhythmia, or the need for further interventional procedures. In the training group, the workload during exercise training was set at 32 ± 9 W for the first week and increased

to 40 ± 8 W for the second week. Heart rate during exercise training was 100 ± 12 beats/min for the first week and 99 ± 13 beats/min for the second week. In the initial testing, significant ST changes were observed in 2 patients from the training group and in 1 patient from the control group. However, in the final testing, a significant ST change was observed in only 1 patient from the control group.

Exercise Capacity and Cardiac Output

In both groups, the workload at peak exercise increased significantly during the 2 weeks of the follow-up period: from 73.3 ± 15.3 to 92.9 ± 16.2 W ($p < 0.01$) in the training group, and from 75.9 ± 19.0 to 83.9 ± 23.6 W ($p < 0.01$) in the control group. However, the magnitude of the increase was greater in the training group: 19.6 ± 13.0 W in the training group vs 8.0 ± 10.0 W in the control group ($p < 0.01$). Both the peak $\dot{V}O_2$ and $\dot{V}O_2$ at the anaerobic threshold increased significantly in the training group, but not in the control group (Table 2). Cardiac index at peak exercise increased significantly only in the training group (from 6.04 ± 0.98 to 7.31 ± 0.97 L/min per m², $p < 0.01$). The magnitude of the increase in the cardiac index at peak exercise was greater in the training group than in the control group: 1.27 ± 0.92 vs 0.47 ± 1.06 L/min per m² ($p < 0.01$), respectively.

Ventilatory Parameters

PETCO₂ during incremental exercise was increased at 3 weeks in the training group: from 39.1 ± 3.5 to $41.1 \pm$

Fig 2. Relationship between end-tidal CO₂ partial pressure (PETCO₂) at the respiratory compensation point and the cardiac index at peak exercise (peak CI) for each patient: 1 week (W) (Left panel) and 3 W (Right panel) after the onset of AMI.

3.7 mmHg at the respiratory compensation point ($p < 0.01$) (Fig 1). In the control group, however, there was no significant change in PETCO₂ during the 2 weeks of the follow-up period. $\dot{V}E$ during exercise did not change during the 2 weeks of the follow-up period in either group.

Relationship Between Ventilatory Parameters and Cardiac Index

As shown in Fig 2, PETCO₂ at the respiratory compensation point positively correlated with the cardiac index at peak exercise both at 1 week ($r = 0.42$, $p = 0.01$) and at 3 weeks ($r = 0.54$, $p = 0.0007$). Fig 3 shows the relation between the change in PETCO₂ at the respiratory compensation point and that of cardiac index at peak exercise during the 2 weeks of the follow-up period for all the patients. There was a weak, but significant positive correlation between the 2 indices. In Fig 4, the mean value of PETCO₂ at the respiratory compensation point is plotted as a function of the cardiac index at peak exercise for each group. The PETCO₂ with respect to cardiac index showed a right and upward shift from 1 week to 3 weeks only in the training group.

Discussion

It is known that PETCO₂ increases from a resting value to the point of the anaerobic threshold during incremental exercise, and after a transient stable (or slowly rising) period, PETCO₂ starts to decrease from the respiratory compensation point!¹⁶ The present study showed that the level of PETCO₂ during exercise was increased by physical training for 2 weeks in patients after AMI. The increase in PETCO₂ at the respiratory compensation point observed in the training group was associated with a greater increase in cardiac output at peak exercise.

Basically, PETCO₂ obtained by respiratory gas analysis is assumed to reflect the level of arterial CO₂ partial pressure (PaCO₂), but in fact PETCO₂ is slightly lower than PaCO₂ at rest. It exceeds PaCO₂ during exercise because of the increased rate of CO₂ delivery to the lungs, associated with the high rate of CO₂ production in the exercising muscles!¹⁷ The ventilation perfusion (V/Q) mismatch is also a factor influencing PETCO₂. It has been reported that the failure of pulmonary blood flow (cardiac output) to increase appropriately during exercise in cardiac patients aggravates

Fig 3. Relationship between the change of end-tidal CO₂ partial pressure (PETCO₂) at the respiratory compensation point [Δ PETCO₂ (3 W–1 W)] and that of cardiac index [Δ Peak CI (3 W–1 W)] during the 2 W of follow-up for each patient. W, week.

this V/Q mismatch (high ventilation/perfusion) and the pulmonary dead space, leading to a decrease in PETCO₂!¹³

In the present study, we noted that exercise training significantly increased PETCO₂ during exercise, suggesting an improvement of the V/Q mismatch. The increase in PETCO₂ can occur by raising the set point of PaCO₂ and/or hypoventilation; however, $\dot{V}E$ during incremental exercise did not appreciably change during the follow-up period. Therefore, the increase in PETCO₂ observed in the training group is probably related to the improvement of the V/Q mismatch caused by the increasing cardiac output response to exercise, rather than to the change in the ventilatory pattern. These results are consistent with our previous report in 2000, in which we found that patients with cardiac disease have an abnormally low PETCO₂ at rest and during

Fig4. Changes in the relationships between end-tidal CO₂ partial pressure (PETCO₂) at the respiratory compensation point and the cardiac index at peak exercise (peak CI) from 1 week (W) to 3 W after the onset of AMI. Average values and SD are shown for the training group (Left panel) and the control group (Right panel). **p<0.01 vs 1 W.

exercise, and that PETCO₂ correlates with cardiac output during exercise.¹²

We found that supervised aerobic exercise training started early after AMI, but not the conventional walking training, increased the exercise capacity, such as peak $\dot{V}O_2$ and the anaerobic threshold. These results are consistent with previous studies reporting the effects of physical training on exercise capacity in patients with AMI.^{1,18–26} although training was initiated later in most of those studies. We also found that the increase in cardiac output at peak exercise was greater in the training group, which is also consistent with previous reports.^{1,27} Because the increase in PETCO₂ after training was noted even during a mild level of exercise, we assume that the exercise training increased cardiac output not only at peak exercise but also during submaximal exercise. Our present findings substantiate the safety and effectiveness of aerobic exercise training at the anaerobic threshold level started early after the onset of AMI. Moreover, our present findings strongly suggest that the improvement of cardiac output during exercise attained by exercise training can be evaluated non-invasively by measuring PETCO₂.

In conclusion, aerobic exercise training started early after AMI increased PETCO₂ during exercise, and this increase was associated with an increase in the cardiac output. The increase in PETCO₂ probably reflects an improvement of the cardiac output during exercise in response to physical training via a decreased ventilation–perfusion mismatch.

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