O₂ Extraction During Exercise Determines Training Effect After Cardiac Rehabilitation in Myocardial Infarction

Issei Uchida, MD; Hiroshi Takaki, MD*; Yoshio Kobayashi, MD; Yoshiaki Okano, MD; Toru Satoh, MD; Tatsuaki Matsubara, MD**; Yoichi Goto, MD

Correlations between baseline hemodynamic and oximetric variables during an invasive exercise test and an improvement in peak oxygen uptake (peak $\dot{V}O_2$) after exercise training (ET) were examined in 20 patients who participated in a cardiac rehabilitation program after acute myocardial infarction (AMI). Peak $\dot{V}O_2$ significantly increased by $23 \pm 21\%$ ($p < 0.01$) after ET and the improvement best correlated with the change in O₂ extraction fraction ([arterial O₂ content – venous O₂ content]/arterial O₂ content) during an exercise test before ET ($r = -0.61$, $p < 0.01$). Exercise capacity was improved to a greater extent by ET in patients with a smaller increase in O₂ extraction fraction during an exercise test before ET. Thus, O₂ extraction fraction during an exercise test before ET may be a useful predictor of the improvement in exercise capacity after ET in post-AMI patients. (*Circ J* 2002; 66: 891–896)

Key Words: Acute myocardial infarction; Cardiac rehabilitation; Exercise capacity; Exercise training; Oxygen extraction fraction

Cardiac rehabilitation with exercise training (ET) for patients after acute myocardial infarction (AMI) improves exercise capacity, reduces coronary risk factors, improves quality of life, reduces subsequent hospitalization costs and reduces major coronary artery disease events including fatal MI, sudden death, and all-cause mortality!^{1–6} It is a general notion that the magnitude of the improvement in exercise capacity after ET differs among individuals, but despite many reports on the benefits of cardiac rehabilitation with ET, the determinants of the improvement in exercise capacity have not been well documented. For example, Fioretti et al⁷ and Digenio et al⁸ reported that left ventricular (LV) systolic function, such as ejection fraction, did not correlate with the improvement in exercise capacity after ET.

Therefore, the present study examined whether or not an improvement in exercise capacity is determined by, or predicted from baseline variables obtained before ET. To this end, we performed left and right heart catheterization during a supine exercise test at the beginning of 3 months of ET and correlated the hemodynamic and oximetric variables with the post-training improvement in exercise capacity.

Methods

Patients

Twenty male post-AMI patients agreed to participate in

the study. The baseline clinical characteristics are shown in Table 1: all patients were clinically stable and did not have claudication, old cerebral infarction, post-infarction angina, or silent myocardial ischemia. Although 2 patients had residual coronary stenotic lesions, no ischemia was detected by exercise thallium scintigraphy. No patient had significant valvular heart disease or lung disease. All medication dosages remained stable during the study. All patients gave written informed consent to this study protocol.

Protocol

Cardiac Rehabilitation Program Patients were enrolled

Table 1 Clinical Characteristics of the AMI Patients

	<i>n</i>
Age (years)	60±10
AMI site	
Anterior	12
Inferior	8
Prior MI	3
Residual stenosis	2
Exercise-induced ischemia	0
MVD	2
LVEF (%)	46±11 (range, 27–62)
Diabetes mellitus	8
Hyperlipidemia	8
Hypertension	5
Medication	
Aspirin	20
Nitrates	15
Ca-blocker	11
ACEI	3
-blocker	0
Digoxin	0
Diuretics	0

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; MVD, multi-vessel disease.

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Division of Cardiology, Department of Medicine, National Cardiovascular Center and *Department of Cardiovascular Dynamics, National Cardiovascular Research Institute, Suita and **Department of Internal Medicine, Nagoya University School of Medicine, Nagoya, Japan

Mailing address: Yoichi Goto, MD, Division of Cardiology, Department of Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: ygoto@hsp.ncvc.go.jp

in the National Cardiovascular Center Cardiac Rehabilitation Program.⁹ The program started approximately 2 weeks after the onset of AMI and continued for 3 months. Patients exercised for approximately 1 h 5 times a week: 2–3 times in hospital under supervision and the remaining 2–3 times at home. Exercise consisted of aerobic dance and stationary bicycle riding in hospital and brisk walking at home. The training heart rate (HR) was determined according to Karvonen's equation ($k=0.5-0.6$): training HR = (peak HR – rest HR) $\times k$ + rest HR, where peak and rest HR were obtained in a symptom-limited exercise test at the beginning of the 3-month program.

Exercise Test All subjects underwent a symptom-limited cardiopulmonary exercise test at the beginning and end of the 3-month cardiac rehabilitation, using a bicycle ergometer in the upright position with workload beginning at zero watt and increasing by 15 W every minute (ramp mode) to a symptom-limited maximum. Twelve-lead electrocardiography (ECG) was monitored and blood pressure was measured with a sphygmomanometer every minute. Expired gas analysis was performed continuously with a respiromonitor AE-280 (Minato Products, Tokyo, Japan). Oxygen uptake ($\dot{V}O_2$) was measured on a breath-by-breath basis. Data were averaged over contiguous 30-s intervals, except at peak exercise, when 15 s averaging was used to improve time resolution. We defined peak $\dot{V}O_2$ (ml/min) as the $\dot{V}O_2$ value averaged during the last 15 s of the symptom-limited exercise test. All patients safely completed the exercise test at their maximum without anginal pain or ischemic ECG changes.

Cardiac Catheterization Cardiac catheterization was performed approximately 1 week after starting the cardiac rehabilitation program (ie, 3–4 weeks after the onset of AMI). On the day before the catheterization study, all patients underwent a non-invasive rehearsal cardiopulmonary exercise test to familiarize them with the bicycle ergometer exercise and respiratory gas analysis in the supine position.

On the day of the study, patients did not take their drugs and fasted for at least 3 h. While supine, an 8Fr opti-thermodilution Swan-Ganz catheter was introduced into the right pulmonary artery through the right antecubital vein. Pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure were measured, and cardiac output (CO) was measured by the thermodilution method. Both coronary arteriography and left ventriculography were performed with an 8Fr Sones catheter inserted through the right brachial artery. Significant stenotic coronary lesions were defined as $\geq 75\%$ reduction of luminal diameter. LV volume and LVEF were determined from left ventriculography in the right anterior oblique (30 degree) projections by the area-length method.¹⁰

Hemodynamic and Oximetric Measurements After measuring the hemodynamic parameters at rest, a symptom-limited incremental bicycle exercise test was performed using an electromagnetically braked bicycle ergometer (Simens-Elema 930B, Simens-Elema, Solna, Sweden) in the supine position. During the exercise test, LV pressure and systemic aortic pressure (AoP) were monitored using an 8Fr double-tip, high fidelity pressure sensor catheter (Sentron 811-810S, Sentron Ink, The Netherlands), which was placed in the left ventricle. PAP and mixed venous oxygen saturation (SvO_2) were measured using an 8Fr opti-thermodilution Swan-Ganz catheter that was placed in the main pulmonary artery trunk. We also measured arterial blood oxygen saturation (SpO_2) continuously using a Biox

Fig 1. Comparison of peak oxygen uptake before and after 3-month exercise training. $\dot{V}O_2$ indicates oxygen uptake.

III pulse oximeter (Omeda, Louisville, Kentucky, USA). According to our previously described exercise test protocol,^{11,12} the exercise test began with a 1-min warm up at 0 W, 60 rpm, followed by incremental loading (15 W/min) until subjective symptomatic limitation. The ECG, HR were continuously monitored throughout the exercise test. PAP, AoP and LV pressure were monitored and recorded at a paper speed of 50–100 mm/s. CO was measured by thermodilution method every minute during the exercise test.

Data Analysis

Hemodynamic variables were calculated by a computer in the hospital's catheterization laboratory system (Toshiba, Tokyo, Japan), and also confirmed visually on the recorded chart. The oxygen (O_2) extraction fraction was calculated as (arterial O_2 content – venous O_2 content) / arterial O_2 content. The improvement in exercise capacity achieved by ET was defined as the difference in peak $\dot{V}O_2$ between the 2 non-invasive cardiopulmonary exercise tests conducted before and after the 3-month ET program. To determine the predictors of an improvement in exercise capacity, correlations between the increase in peak $\dot{V}O_2$ achieved by ET and the hemodynamic and oximetric variables at rest and during the exercise test at the beginning of ET were examined.

Statistics

Comparisons of data before and after ET were performed using paired Student's *t* tests. To determine correlations between variables, linear regression analysis was performed using the least square method. Probability values less than 0.05 were considered statistically significant. All data were presented as mean $\pm$ SD.

Results

All patients completed the 3-month cardiac rehabilitation program with ET. Fig 1 compares peak $\dot{V}O_2$ before and after the program. Peak $\dot{V}O_2$ significantly increased by $23 \pm 21\%$ from $1,224 \pm 271$ (20.0 ± 3.8 ml $\cdot$ min $^{-1} \cdot$ kg $^{-1}$) to $1,520 \pm 380$ ml/min (24.8 ± 4.9 ml $\cdot$ min $^{-1} \cdot$ kg $^{-1}$) ($p < 0.01$) after cardiac rehabilitation.

Table 2 summarizes the baseline hemodynamic and oximetric variables at rest and during peak exercise in the exercise test at the beginning of ET. All variables significantly changed in response to exercise.

Table 3 summarizes the correlation coefficients between the increase in peak $\dot{V}O_2$ and baseline hemodynamic

Table 2 Baseline Hemodynamics and Oximetric Variables at Rest and at Peak Exercise

	Rest	Peak exercise	p value
Heart rate (beats/min)	75±10	124±14	<0.01
LVSP (mmHg)	118±17	151±21	<0.01
LVEDP (mmHg)	13±7	32±7	<0.01
mAoP (mmHg)	85±12	108±14	<0.01
mPAP (mmHg)	12±4	35±6	<0.01
CO (L/min)	6.3±1.3	12.3±2.8	<0.01
SvO ₂ (%)	77.0±4.6	49.8±6.1	<0.01
O ₂ extraction fraction (dimensionless)	0.21±0.05	0.49±0.06	<0.01

CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure; mAoP, mean aortic pressure; mPAP, mean pulmonary artery pressure; O₂ extraction fraction, (arterial oxygen content-venous oxygen content)/arterial oxygen content; SvO₂, venous oxygen saturation.

Table 3 Correlation Coefficients Between the Improvement in Peak $\dot{V}O_2$ and Initial Hemodynamic and Oximetric Variables at Rest and at Peak Exercise

Variables	At rest		At peak exercise	
	r	p value	r	p value
Heart rate	0.13	NS	0.27	NS
LVSP	0.10	NS	-0.11	NS
LVEDP	0.23	NS	-0.40	NS
mAoP	0.27	NS	0.11	NS
mPAP	-0.033	NS	-0.22	NS
Ejection fraction	0.43	NS	—	—
CO	0.083	NS	0.45	<0.05
SvO ₂	-0.03	NS	0.42	<0.05
O ₂ extraction fraction	0.03	NS	-0.44	<0.05
Peak $\dot{V}O_2$	—	—	0.03	NS

Abbreviations as in Table 2.

Table 4 Correlation Coefficients Between the Improvement in Peak $\dot{V}O_2$ After Exercise Training and Changes in the Hemodynamic and Oximetric Variables During the Exercise Test Before Exercise Training

	r	p value
Δ Heart rate	0.21	NS
Δ LVSP	0.10	NS
Δ LVEDP	-0.54	<0.05
Δ mAoP	-0.13	NS
Δ mPAP	-0.19	NS
Δ CO	0.45	<0.05
Δ SvO ₂	0.60	<0.01
Δ O ₂ extraction fraction	-0.61	<0.01

Each delta (Δ) indicates the change in the respective variable from rest to peak exercise in the exercise test before exercise training. Other abbreviations as in Table 2.

and oximetric variables. The improvement in peak $\dot{V}O_2$ after ET did not significantly correlate with any hemodynamic or oximetric variables at rest. As for the variables during exercise, the improvement in peak $\dot{V}O_2$ after ET significantly correlated with CO, SvO₂, and O₂ extraction fraction at peak exercise, but not with HR, LV systolic pressure, LV end-diastolic pressure (EDP), mean AoP, or mean PAP at peak exercise. In addition, the improvement in peak $\dot{V}O_2$ after training did not correlate with peak $\dot{V}O_2$ before training.

Table 4 summarizes the correlation coefficients between the improvement in peak $\dot{V}O_2$ after ET and the changes in hemodynamic and oximetric variables during the exercise test (from rest to peak exercise) at the beginning of ET. The improvement in peak $\dot{V}O_2$ after ET significantly correlated with the change in O₂ extraction fraction during the baseline exercise test (r=-0.61, p<0.01), followed by the change in SvO₂ (r=0.60, p<0.01), the change in LVEDP (r=-0.54,

p<0.05), and the change in CO (r=0.45, p<0.05). Fig 2 shows the correlations between the improvement in peak $\dot{V}O_2$ after ET and the changes in O₂ extraction fraction, SvO₂, LVEDP and CO in the baseline exercise test. There was no significant correlation between the improvement in peak $\dot{V}O_2$ after ET and the changes in heart rate, LV systolic pressure, mean AoP, or mean PAP during the baseline exercise test.

Discussion

The major findings in the present study are that (1) the improvement in peak $\dot{V}O_2$ after the 3-month ET program well correlated with the change in O₂ extraction fraction and the change in SvO₂ (both p<0.01), and weakly correlated with the change in LVEDP, the change in CO, peak CO, peak SvO₂, and peak O₂ extraction fraction (all p<0.05) during the exercise test at the beginning of the ET,

Fig 2. Scatterplots of individual values for distribution between the improvement in peak oxygen uptake ($\dot{V}O_2$) after 3-month exercise training and the change in hemodynamic and oximetric variables in the baseline exercise test for all 20 subjects. Each delta (Δ) indicates the change in the respective variable from rest to peak exercise in the exercise test before exercise training. CO, cardiac output; EDP, end-diastolic pressure; O_2 extraction fraction, (arterial oxygen content – venous oxygen content)/arterial oxygen content; SvO_2 , venous oxygen saturation.

whereas (2) the improvement did not significantly correlate with any of the hemodynamic or oximetric variables at rest. These findings suggest that the improvement in exercise capacity after ET can be best predicted by the change in O_2 extraction fraction in the baseline exercise test.

Previous Studies

In previous studies of ET in patients with coronary artery disease, indexes of cardiac function at rest have not been found to correlate with either exercise capacity¹³ or an improvement in exercise capacity after ET.^{7,8,14} Hammond et al,¹⁵ van Dixhoorn et al¹⁶ and Heldal et al¹⁷ have reported that the training effect can be predictable from baseline clinical data, baseline fitness, and cardiac status, but they did not evaluate the correlation between an improvement in exercise capacity after ET and hemodynamic or oximetric variables during exercise before ET. In the present study, we measured arteriovenous oxygen content (A- $\dot{V}O_2$) difference and LV pressure directly during an exercise test at the beginning of ET.

Wilson et al reported that patients with heart failure who were able to increase CO during an initial exercise test showed a significant improvement in exercise capacity with ET, whereas those who were unable to increase CO during the initial exercise test did not.¹⁸ They concluded that the level of circulatory dysfunction primarily determined the improvement in exercise capacity after ET. However, they did not measure the A- $\dot{V}O_2$ difference during exercise or evaluate the actual correlation between the improvement in peak $\dot{V}O_2$ and the changes in variables obtained in the exercise test. Thus, predictors of the improvement in exercise capacity after ET have not been sufficiently described.

Present Study

In the present study, we measured both hemodynamic and oximetric variables during the baseline exercise test and related these variables to the improvement in peak $\dot{V}O_2$ achieved in the subsequent 3-month cardiac rehabilitation. We have found that the increase in O_2 extraction fraction from rest to peak exercise in the baseline exercise test correlated best with the improvement in peak $\dot{V}O_2$ after ET, which indicates that the improvement in exercise capacity achieved in cardiac rehabilitation can be predicted by the baseline exercise test. Although Wilson et al reported that the CO response to exercise can identify responders (>10% increase in peak $\dot{V}O_2$) and nonresponders in cardiac rehabilitation, the difference in response rate between the 2 groups (9 of 21 patients [43%] vs 1 of 11 patients [9%], $p=0.04$) was not very large.¹⁸ This small difference may be explained by the present result that the correlation between the increase in CO during exercise and the improvement in peak $\dot{V}O_2$ after ET was not very close ($r=0.45$).

Determinants of Training Effect

It is generally accepted that exercise capacity in cardiac patients is mainly determined by peripheral factors such as skeletal muscle function, muscle bulk, and endothelial vasodilatory capacity rather than the central (cardiac) factors.^{19,20} In contrast, the determinants of an improvement in exercise capacity after ET (ie, training effect) have not been fully clarified, although it has been repeatedly demonstrated that LV systolic function is not the major determinant.^{7,8,14} Recently, Wilson et al proposed a new framework in which patients with exercise intolerance fall into 2 groups: those with a normal CO response to exercise whose exercise capacity would improve after ET and those with a reduced CO response who would not.¹⁸ This framework reasonably assumes that the former group represents patients with skeletal muscle deconditioning and the latter represents those with circulatory (cardiac) dysfunction.

However, Anker et al demonstrated that in cachectic heart failure patients, peak leg blood flow significantly correlates with peak $\dot{V}O_2$, whereas in non-cachectic heart failure patients, age and skeletal muscle strength, but not peak leg blood flow, correlate with peak $\dot{V}O_2$.²¹ This finding indicates that peak blood flow is a critical determinant of exercise capacity in very severe patients (in whom the increase in O_2 extraction fraction during exercise would be very large), whereas other factors such as age and muscle strength are the determinants of exercise capacity in milder cases (patients in whom the increase in O_2 extraction fraction during exercise would be small). In addition, blood flow toward tissues and organs other than the exercising muscles during exercise varies depending on the severity of cardiac dysfunction,¹⁹ indicating that the whole body CO response to exercise is not necessarily proportionate to the nutrient flow perfusing the exercising muscles. These points may explain why CO response showed only a modest correlation with the training effect in the present study.

Then, why did the change in O_2 extraction fraction during exercise show a better correlation with the training effect than the CO response in the present study? Yoshioka et al have demonstrated that changes in O_2 extraction fraction occurs earlier during exercise, followed by changes in CO, suggesting that the O_2 extraction fraction primarily and more sensitively reflects skeletal muscle metabolism than CO during exercise.¹⁹ Studies using ³¹P-magnetic resonance spectroscopy have demonstrated that in patients with heart

failure with exercise intolerance, high energy phosphate metabolism and the intracellular pH of skeletal muscles deteriorate earlier during exercise than in normal subjects, indicating that skeletal muscle metabolism is one of the primary determinants of exercise capacity^{22,23}. Furthermore, the latter study²³ has demonstrated that exercise training improves skeletal muscle oxidative metabolism without change in blood flow. Taken together, these findings suggest that, compared with CO response, O₂ extraction fraction during exercise may more sensitively and directly reflect skeletal muscle metabolism, which would determine the magnitude of an improvement in exercise capacity after exercise training.

Clinical Implications

The result of the present study may have a great clinical implication because one can predict the magnitude of the effect of ET before actually starting the training. Namely, patients showing a small increase in O₂ extraction fraction in the initial exercise test will gain a large improvement in exercise capacity after training and hence should be encouraged to actively participate in an ET program.

On the other hand, patients showing a large increase in O₂ extraction fraction in the initial exercise test would be expected to gain only small improvement in exercise capacity after the usual ET program and hence require different approaches to improve their exercise capacity, such as local skeletal muscle training^{24,25} or selective respiratory muscle training.²⁶

Moreover, if a noninvasive measurement for oxygen extraction fraction or SvO₂ during exercise becomes available in the future, the present findings will greatly contribute to predicting the training effect (ie, identifying good and poor responders) of a conventional cardiac rehabilitation program, thereby facilitating the stratification of participants to the appropriate exercise modality or protocol.

Study Limitations

The first limitation of the present study is that the number of enrolled patients was not large and that a control sedentary group without exercise training was not studied. Therefore, to confirm the present findings, prospective studies with a large number of patients and with a control group are necessary.

A second limitation is that the change in O₂ extraction fraction during exercise can be measured at present only with an invasive method. Although the present results suggest that the change in SvO₂ during exercise can be used as a substitute for the change in O₂ extraction fraction because of their similar correlation coefficients ($r=0.60$ and -0.61) for the improvement in peak $\dot{V}O_2$, the measurement of SvO₂ during exercise is also invasive. An easily applicable, noninvasive techniques that reflects skeletal muscle metabolism during exercise, such as ³¹P-magnetic resonance spectroscopy^{22,23} is desirable.

Conclusion

Exercise capacity improves to a greater extent by ET in patients with a smaller increase in O₂ extraction fraction during a baseline exercise test. O₂ extraction fraction during exercise may be a useful predictor for the improvement in exercise capacity after ET in post-AMI patients.

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