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Effects of Exercise Training on the Recovery of the Autonomic Nervous System and Exercise Capacity After Acute Myocardial Infarction

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This study investigated the effects of aerobic exercise training on the early phase of the recovery process following acute myocardial infarction (AMI) in terms of the autonomic nervous system, cardiac function and exercise capacity. Twenty-eight patients in the first week after the onset of AMI were assigned randomly to either a training group or a control group. The training group performed aerobic exercise for 2 weeks. Cardiopulmonary exercise testing was performed 3 times during the 3 months after the onset. Heart rate variability, plasma norepinephrine (NE) levels, and cardiac index (CI) during exercise were measured. In the training group, plasma NE level and ΔCI (peak CI−rest CI) were significantly improved from 1 to 3 weeks after the onset, and the high frequency of heart rate variability and peak oxygen uptake were significantly increased up to 3 months after the onset. In the control group, the plasma NE level and the ΔCI during the 1–3 weeks post-AMI, the high frequency of heart rate variability and the peak oxygen uptake showed a tendency to improve up to 3 months after the onset. These results indicate that sympathetic nervous activity improves soon after the onset of AMI, in conjunction with improvement in cardiac function, and that this improvement is not affected by exercise training. In contrast, the recovery of parasympathetic nervous activity requires a longer period, along with the recovery of exercise capacity, which is facilitated by even short-term aerobic exercise training. (*Jpn Circ J* 1999; **63:** 843–848)

Key Words: Autonomic nervous system; Exercise training; Heart rate variability; Myocardial infarction

Several studies have shown a decreased heart rate (HR) response during exercise in patients with coronary artery disease and heart failure[1–3] Diminished HR variability could be a useful prognostic indicator after myocardial infarction (MI) and have a predictive value independent of conventional noninvasive measurements, such as exercise time, late potential, or detection of ventricular ectopy by Holter monitoring[4–6] Parasympathetic nervous activity is suppressed and sympathetic nervous activity is accentuated after acute MI (AMI)[1,2] However, the detailed time course of the recovery process of this autonomic nervous imbalance in patients in the acute phase of MI is not clear.

Aerobic exercise training improves exercise capacity in healthy subjects[6,7] and even in patients with AMI[8–11] Recent studies have shown that physical training improves autonomic nervous activity and decreases the incidence of cardiac events or sudden death not only in patients with AMI, but also in those with chronic heart failure[12,13] and that physical training may increase parasympathetic nervous activity even in healthy subjects[6,7] However, little information is available about the effect of exercise training on the recovery process of the autonomic nervous system and on exercise capacity in the early phase after AMI. We designed this study to investigate the detailed time courses of the recovery process of both parasympathetic and sympathetic nervous activity, as well as cardiac function reserve, during exercise and to clarify the effects of early physical training on the recovery course of those functions in patients with AMI.

Methods

Subjects

Twenty-eight patients (59.0±6.0 years old, mean±SD) were enrolled in the study 1 week after the onset of AMI. The diagnosis of AMI was made on the basis of chest pain persisting for at least 30 min, an ST-segment elevation of at least 0.1 mV in at least 2 contiguous leads and elevation of serum creatine kinase-MB (CK-MB) to more than twice the upper limit of the normal range. Their clinical characteristics, including age, site of infarction, ejection fraction, and mean peak creatine kinase level, are summarized in Table 1. During the acute phase, prior to entering the study, 25 patients underwent direct percutaneous transluminal coronary angioplasty and/or percutaneous transluminal coronary revascularization and 3 underwent conservative therapy. We excluded patients with severe heart failure or arrhythmia (atrial fibrillation, bundle branch block, frequent extrasystole) or with ST depression more than 0.2 mV during an exercise test. During the investigation, medications were not changed in order to prevent any influ-

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Table 1 Patient Characteristics

	Training group	Control group	
Age (years)	59±7	58±7	NS
Sex (M/F)	14/2	12/0	NS
Site of infarction			
Anterior	2	0	
Anteroseptal	5	8	
Inferior	6	3	NS
Lateral	2	1	
Posterior	1	0	
LVEF (%)	63±8	62±12	NS
CK max (IU/L)	2445±2261	2427±1824	NS

Resulis are expressd as mean±SD or number of paticnts.
LVEF, left ventricular ejection fraction; CK, creatine kinase; NS, not significant; training group vs control group.

ence on the exercise response. The study was approved by the hospital ethics committee of The Cardiovascular Institute Hospital, and after detailed explanation of the study protocol, informed consent was obtained from all subjects.

Study Protocol

All patients enrolled in this study underwent cardiopulmonary exercise testing with expired gas analysis 1 week after the onset of AMI. Cardiac output was measured by the dye dilution method. The patients were randomly assigned to either a training or a control group. The training group consisted of 14 men and 2 women, the control group 12 men. The training group performed supervised exercise training using a cycle ergometer at the anaerobic threshold level for 30 min, twice daily for 2 weeks. In the control group, only walking exercise was permitted according to a conventional rehabilitation protocol. Then, 3 weeks after the onset of AMI, patients in both groups underwent cardiopulmonary exercise tests to evaluate exercise capacity, cardiac output, and autonomic nervous activity during exercise. They were discharged after completion of each rehabilitation program for the acute phase of MI. They performed the same tests again at 3 months after the onset.

Exercise Testing

Symptom-limited exercise testing using a ramp protocol (1 W/6 s) with a cycle ergometer (CPE 2000, MedGraphics Co, Minneapolis, MN, USA) was performed at 1 week, 3 weeks, and 3 months after the onset of AMI. After a 4-min rest on the cycle ergometer, exercise began with a 4-min warm up at 20 W followed by continuous load increase of 10 W/min. HR, ST–T changes, and arrhythmia were monitored by 12-lead electrocardiogram using a model ML-5000 Stress Test System (Fukuda Denshi, Tokyo, Japan) throughout the tests. Blood pressure was also measured at 1 min intervals by the cuff method using an automatic manometer (STBP-780, Colin Denshi, Aichi, Japan).

Ventilatory Gas Analysis

Ventilatory gas exchange was measured on a breath-by-breath basis with a gas analyzer (Aerometer AE-280s, Minato Medical Science Co, Osaka, Japan). The system was carefully calibrated before each study. Oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and minute ventilation ($\dot{V}E$) were measured on a breath-by-breath basis throughout the testing. From these measurements, the ventilatory equivalent for $\dot{V}O_2$ was calculated as $\dot{V}E/\dot{V}O_2$ and that for CO_2 as $\dot{V}E/\dot{V}CO_2$, and the gas exchange ratio as $\dot{V}CO_2/\dot{V}O_2$. These parameters were simultaneously displayed on a monitor of a personal computer (PC-9821, NEC, Tokyo, Japan). The anaerobic threshold was determined by the following conventional criteria: (1) $\dot{V}E/\dot{V}O_2$ increased after being constant or decreased while $\dot{V}E/\dot{V}CO_2$ remained constant or decreased and (2) the gas exchange ratio, which had been stable or slowly rising, began to increase more steeply. Peak $\dot{V}O_2$ was calculated by averaging the values recorded during the final 30 s of a ramp exercise.

Time Constant of $\dot{V}O_2$

To determine $\dot{V}O_2$ kinetics at the beginning of exercise, the time constant was calculated from the start of exercise with single exponential kinetics using least square nonlinear regression analysis; the resting value was designated as its baseline and the $\dot{V}O_2$ at the end of the warm-up period as its asymptote.

Blood Sampling

Plasma norepinephrine (NE) level, which could represent sympathetic nervous activity, was measured at the end of the warm-up. The sampled blood was ice-cooled immediately and centrifuged at 3000 rpm for 10 min at 4°C, thereby separating the plasma, which was frozen and stored at −70°C until the day of analysis. Norepinephrine was extracted by alumina absorption and then measured by high-pressure liquid chromatography.

Power Spectral Analysis of Heart Rate Variability

Spectral analysis of the HR variability was performed according to the methods of Yamamoto and Hughson[14] and the data were analyzed by Fast Fourier Transform. Spectral HR variability was expressed as low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.8 Hz) components. HF was used as an index of parasympathetic nervous activity in this study. The power spectrum data of the continuous time sequence of R–R intervals were calculated after 3 min of resting, during warming-up with the exception of the first minute, and then every 2 min during incremental exercise.

Cardiac Output

The cardiac index (CI) was measured at rest and during exercise by the dye dilution method using a dye densitometer (MCL-4200, Nihon Koden, Tokyo, Japan).[15] A catheter was placed in the left brachial vein, and indocyanine green (5 mg) was injected from the catheter during the resting control state, the warm-up state, and the peak exercise state. The change in CI (ΔCI) from resting to peak exercise was calculated as an index of cardiac output reserve.

$$\Delta CI = (\text{peak value}) - (\text{resting value})$$

Statistical Analysis

The mean values of parameters in the 2 groups were compared by unpaired Student's t test. The time course changes of the ventilatory parameters and cardiac output during exercise were analyzed by one-way ANOVA of repeated measurements. When this test was significant, a post-hoc test (Fisher's PLSD) was used to compare each measurement. A value of $p<0.05$ was considered significant. HF data are expressed as mean±SE. The other data are expressed as mean±SD.

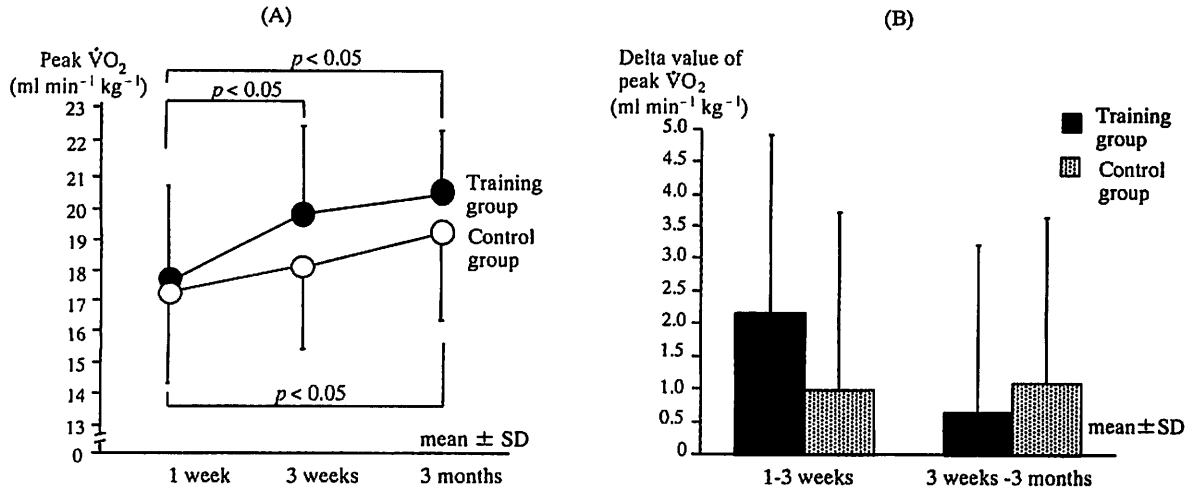

Fig 1. (A) Serial change in peak oxygen uptake ($\dot{V}O_2$) and (B) the delta value of $\dot{V}O_2$ from 1 week to 3 months after the onset of acute myocardial infarction (AMI) in the training and control groups. Peak $\dot{V}O_2$ increased significantly in the training group from 1 to 3 weeks post-AMI.

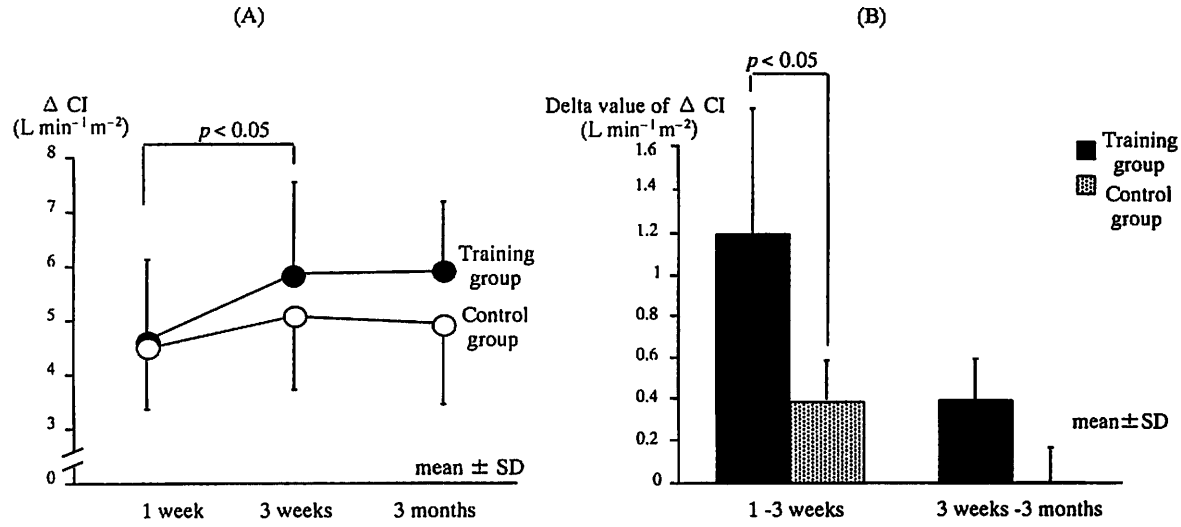

Fig 2. (A) Changes in the cardiac index (ΔCI) from 1 week to 3 months after the onset of acute myocardial infarction (AMI) in the training and control groups and (B) the relationship between delta values of these groups. ΔCI increased significantly in the training group, and the change in ΔCI in the training group was greater than that in the control group from 1 to 3 weeks post-AMI.

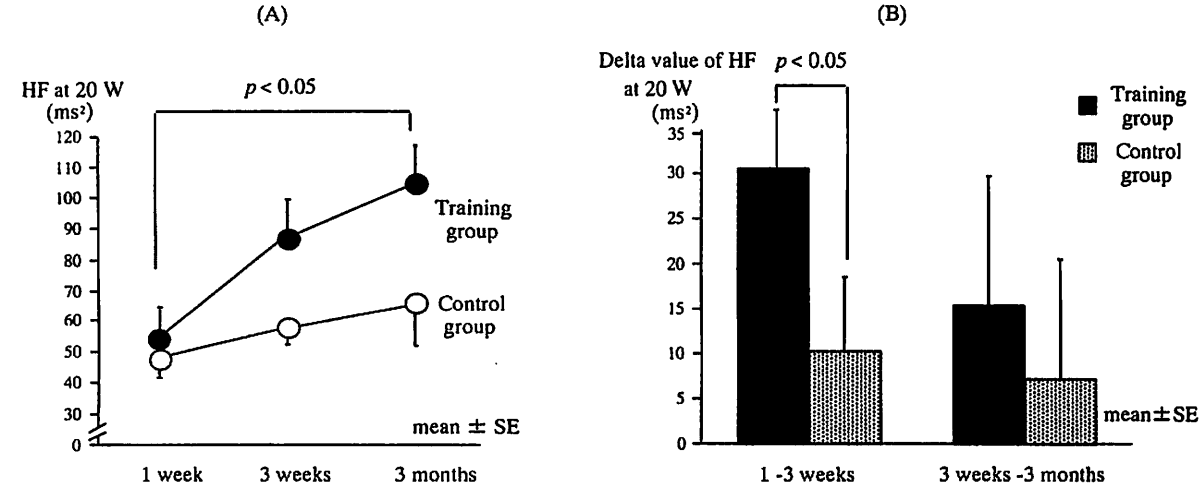

Fig 3. (A) The change in high frequency (HF) and (B) the delta value of HF at 20 W from 1 week to 3 months after the onset of acute myocardial infarction (AMI) in the training and control groups. HF increased in both groups from 1 week to 3 months post-AMI, but significantly so in the training group.

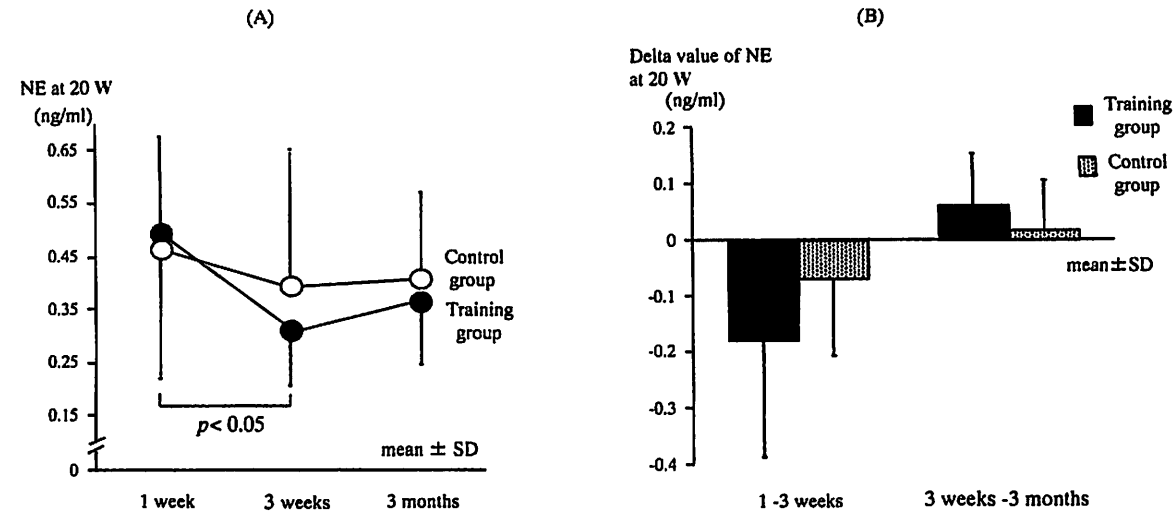

Fig 4. (A) The change in the blood concentration of norepinephrine (NE) and (B) the delta value of NE at 20 W from 1 week to 3 months after the onset of acute myocardial infarction (AMI) in the training and control groups. NE level decreased in both groups from 1 to 3 weeks post-AMI, but significantly so in the training group.

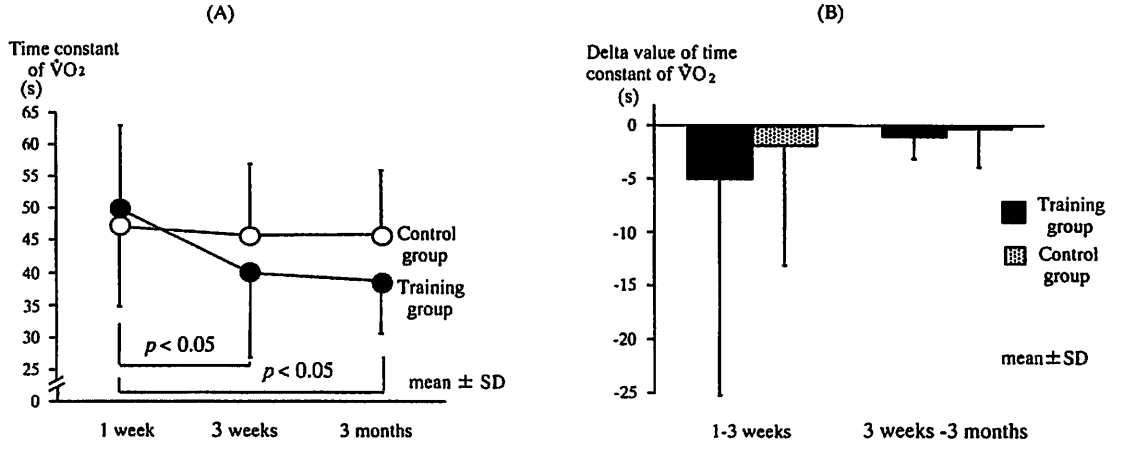

Fig 5. (A) Change in and (B) delta value of the time constant of $\dot{V}O_2$ from 1 week to 3 months after the onset of acute myocardial infarction (AMI) in the training and control groups. The time constant of $\dot{V}O_2$ was significantly shortened from 1 to 3 post-AMI in the training group.

Results

During the study period, none of the patients suffered from major complications, such as worsening of heart failure, sudden cardiac death or any other cardiac event.

Change in Peak Exercise Capacity

Peak $\dot{V}O_2$ increased from 1 week to 3 months after the onset of MI in both the training and control groups. The increase from 1 to 3 weeks was significant in the training group (17.6±3.1 to 19.8±2.9 ml min^{-1} kg^{-1}, $p<0.05$), whereas no significant change was noted in the control group. From 1 to 3 weeks, the mean delta value of peak $\dot{V}O_2$ in the training group was greater than that in the control group (2.2±2.8 vs 1.0±1.8 ml min^{-1} kg^{-1}), although this difference was not statistically significant (Fig 1). Peak work rates (W/kg) in the training group were 74.6±16.7 at 1 week, 90.5±16.2 at 3 weeks and 93.5±18.0 at 3 months W/kg, and 72.3±14.9 at 1 week, 80.8±16.7 at 3 weeks and 86.1±19.3 at 3 months W/kg in the control group. It increased significantly from 1 to 3 weeks in the training group ($p<0.05$), whereas significant change was noted in the control group from 1 week to 3 months ($p<0.05$).

Change in Cardiac Index

From 1 to 3 weeks post-AMI, ΔCI increased significantly in the training group (4.6±1.5 to 5.8±1.7 ml min^{-1} m^{-2}, $p<0.05$), but not in the control group (Fig 2). The change in ΔCI from 1 to 3 weeks post-AMI was significantly higher in the training group than in the control group (1.2±0.9 vs 0.4±0.4 ml min^{-1} m^{-2} $p<0.05$). There was no significant difference in ΔCI between the groups in the period from 3 weeks to 3 months post-AMI.

HF During Exercise at 20 Watts

HF increased in both the training and control groups, and this increase from 1 week to 3 months post-AMI was significant in the training group (55±8 to 106±31, $p<0.05$ vs 48±6 to 66±14 ms^2 in the control group). The delta value of HF at 20 W from 1 to 3 weeks post-AMI was significantly higher in the training group (30±6 vs 10±8 ms^2, $p<0.05$), whereas the values obtained from 3 weeks to 3

months post-AMI were not statistically different between the groups (Fig 3).

Plasma Norepinephrine Level at 20 Watts

Although both groups showed decreases in plasma NE at 20 W exercise during the 1–3 weeks post-AMI period, the decrease was only significant in the training group (from 0.5±0.2 to 0.3±0.1 ng/ml, $p<0.05$). The decrease in NE level did not differ significantly between groups throughout the study (Fig 4).

Time Constant of $\dot{V}O_2$

The time constant of $\dot{V}O_2$ was significantly shortened from 1 to 3 weeks post-AMI in the training group (49.8±13.0 to 40.0±13.3, $p<0.05$), whereas it did not change significantly in the control group. The delta value of the time constant of $\dot{V}O_2$ showed no significant difference between the groups throughout the investigation (Fig 5).

Discussion

It has been recognized that the sympathetic nervous system and the parasympathetic nervous system contend with each other and that a balance between them may be an important factor in the onset of ischemic heart disease and arrhythmia. Within the cardiac autonomic nervous system, the parasympathetic nervous system has been paid less attention compared with the sympathetic nervous system in relation to ischemic heart disease because the difficulty of its evaluation. Since a technique for evaluating HR variability and baroreflex sensitivity was established in the 1980s, the role of the parasympathetic nervous system in association with coronary artery disease has been investigated.[16,17] The prognostic value of HR variability was first reported in a cohort of patients with MI.[18] In that study, the relative risk for mortality was 5.3 times higher in patients with lower HR variability assessed in time domain measures from measurements taken over a 31-month follow- up. Wolf et al reported that patients with HR variability less than 32 ms had a significantly higher hospital mortality rate than those with a variability higher than 32 ms.[19] In their report of 176 patients with AMI, HR variability measured on the day of admission to the coronary care unit was a useful index as for predicting their mortality. Reportedly accelerated sympathetic nervous activity leads to a cardiac electrophysiological imbalance and facilitates the occurrence of fatal arrhythmia.[20] However, the parasympathetic nervous system may protect against this cardiac electrophysiological imbalance and against sudden cardiac death or fatal arrhythmia.[21,22] Despite the well known benefits of exercise training on exercise capacity after MI, little data are available on the effects of exercise training on the sympathetic nervous system/parasympathetic nervous system balance.

Recovery of the Autonomic Nervous System, Exercise Capacity and Cardiac Function

The present study was conducted during the early phase of MI to investigate the effects of supervised exercise training upon autonomic nervous activity and cardiac function. In the present study, although both sympathetic nervous activity and parasympathetic nervous activity improved during the investigation, the rate of recovery for each was different. The sympathetic nervous system improved during the first 3 weeks after the onset of MI, whereas the parasympathetic nervous system improved gradually during the 3-month study. Cardiac function during exercise also improved during the initial 3 weeks, whereas exercise capacity improved gradually throughout the observation period, similar to the recovery process of the parasympathetic nervous system. Both the training and control groups showed similar time courses regarding the recovery of both the sympathetic and parasympathetic nervous systems.

The parasympathetic nervous system is known to be predominant during the resting state in the healthy human. In heart failure patients, it is suspected that the parasympathetic nervous system is initially suppressed to preserve cardiac function, and the sympathetic nervous system is activated as the degree of heart failure worsens. In the present study, the sympathetic nervous system was activated and the parasympathetic nervous system was suppressed during the acute phase of MI, consistent with heart failure patients in previous reports. Bigger et al reported that from 1 week to 2 months after the onset of MI, all spectral components (LF and HF) of the HR variability of patients decreased one-third to one-half compared with healthy subjects.[23] All components also improved remarkably during the first 3 months after the onset of MI and then increased slightly from 3 to 12 months. However, even at 1 year after the onset, all components were about one-half to one-third that of healthy subjects. In another study, exercise training improved parasympathetic nervous activity along with increasing exercise capacity in healthy men.[6] In the present study, the sympathetic nervous activity improved soon after the onset of MI in conjunction with the improvement in cardiac function, whereas improvement in the parasympathetic nervous activity required a longer time during which exercise capacity also increased. This observation is consistent with the reversed image in the changes in autonomic nervous activities that occur with worsening of heart failure.

Effects of Physical Training on Cardiac Function and the Autonomic Nervous System

Currently, physical training is recommended for patients after AMI, as well as for patients with other cardiac diseases. Some reports[12,24] have shown beneficial effects of exercise training in the chronic phase of MI. These beneficial effects have been demonstrated even in patients with severely depressed ventricular function and chronic heart failure[25–27] and have been attributed to peripheral adaptations that result in greater oxygen utilization in the skeletal muscles. Several reports have shown that exercise training increased maximal exercise capacity and endurance capacity in patients with MI.[9–11,28] In the present study, peak $\dot{V}O_2$ increased significantly in the training group. The CI during exercise also increased significantly in the training group during the early phase after the occurrence of AMI. Coats et al reported that exercise training increases cardiac output during exercise in patients with stable, moderate-to-severe chronic heart failure caused by ischemic heart disease.[12] Our present findings would support the hypothesis that exercise training during the early phase following AMI can be effective in increasing exercise tolerance by improving the cardiac output response during exercise. In addition, the favorable effects were maintained at 3 months after the onset of MI, although no special program was prepared for either group after discharge.

A few studies have addressed the issue of the relation between exercise training and autonomic nervous activity

during the chronic phase of MI. Hull et al reported that exercise training increased the sensitivity of baroreceptor reflexes and suppressed the occurrence of ventricular fibrillation induced by exercise in the high-risk dog with ischemic heart disease?[29] This suggests that exercise training may not only increase the reflex of the parasympathetic nervous system, but also suppress the sympathetic nervous system in ischemic heart disease. Several reports have noted that many secondary abnormalities associated with chronic heart failure may reflect physical deconditioning;[12,13,24] which itself may be partly responsible for some of the associated abnormalities and exercise limitation's of chronic heart failure, including abnormalities in autonomic balance. Other reports have described increases in parasympathetic nervous activity as a result of exercise training, even in healthy men[6,7] In the present study, the parasympathetic nervous system and sympathetic nervous system of the training group were both improved significantly compared with the control group, and the anaerobic threshold level training had no adverse effects in the recovery process of cardiac function or autonomic nervous activity. As a result, improving the HR variability imbalance by aerobic exercise training during the early phase after MI may contribute to a decrease in mortality. These results indicate that anaerobic threshold level exercise training can be useful for increasing the exercise capacity in patients in the early phase of MI. Consequently, these results support the hypothesis that anaerobic threshold level exercise training can decrease the mortality rate by improving the autonomic nervous activity imbalance in patients with ischemic heart disease.

Regarding the serial changes in the measured parameters, both cardiac function and sympathetic nervous activity improved soon after the onset of AMI, and this improvement was not affected by exercise training. In contrast, the recovery of parasympathetic nervous activity requires a longer period, along with the recovery of exercise capacity, which is facilitated by even short-term aerobic exercise training. In conclusion, aerobic exercise training results in improvement of cardiac reserve and autonomic nervous imbalance during the early phase of AMI.

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