Predictors of Left Ventricular Remodeling in Patients With Acute Myocardial Infarction Participating in Cardiac Rehabilitation

Brain Natriuretic Peptide and Anterior Infarction

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Background This study was designed to determine the factors influencing the development of left ventricular (LV) remodeling in patients participating in a comprehensive cardiac rehabilitation (CR) program after acute myocardial infarction (AMI), with special reference to exercise intensity and frequency.

Methods and Results A total of 72 patients with AMI participated in CR consisting of exercise training of moderate intensity (heart rate reserve 40–60%) and education for 12 weeks. Plasma concentration of brain natriuretic peptide (BNP) was measured at the beginning and the end of CR. Echocardiography was performed before and 1 year after CR. An increase in LV end-diastolic dimension (delta-LVDD) from baseline was used as an index of remodeling. Delta-LVDD was significantly greater in patients with an anterior AMI than with other infarct locations (p<0.05) and correlated significantly with baseline BNP concentration (p<0.05). Delta-LVDD >5 mm occurred exclusively in patients with baseline BNP >150 pg/ml. Variables representing the intensity and frequency of exercise training did not correlate with delta-LVDD.

Conclusion In patients with AMI participating in CR, those having both anterior infarction and baseline BNP concentration >150 pg/ml are at high risk for subsequent LV remodeling, whereas neither exercise intensity nor participation frequency in CR appears to be associated with LV remodeling. (Circ J 2004; 68: 214–219)

Key Words: Acute myocardial infarction; Brain natriuretic peptide; Cardiopulmonary exercise test; Exercise training; Ventricular remodeling

Comprehensive cardiac rehabilitation (CR) has been shown to improve exercise capacity in patients with acute myocardial infarction (AMI), even in patients with moderate or severe left ventricular (LV) dysfunction. However, Jugdutt et al reported possible detrimental effects of exercise training on LV function and remodeling among patients with anterior Q-wave infarction. In contrast, the EAMI trial reported that patients with a baseline left ventricular ejection fraction (LVEF) <40% were prone to LV dilatation, and that physical training did not appear to worsen this anticipated effect. Moreover, the ELVD study reported attenuation of unfavorable remodeling by exercise training in postinfarction patients with LV dysfunction. In all those studies, however, exercise training was started late (3–8 weeks) after the onset of AMI, which may differ from the current clinical practice of early (2 weeks after onset) start of exercise training. In addition, those studies did not comprehensively analyze the predictive factors of LV remodeling in their study patients.

LV remodeling is a complex pathologic process of progressive dilatation, leading to dysfunction and heart failure in patients after myocardial infarction. Many factors have been reported to be related to LV remodeling in patients with AMI, and we have previously reported that the plasma brain natriuretic peptide (BNP) concentration is a predictor of progressive ventricular remodeling after AMI. However, the predictive factors of LV remodeling in patients participating in exercise CR have not been fully studied and this issue is important because exercise prescription with an appropriate exercise intensity should be given to all patients after AMI. Accordingly, the purpose of the present study was to clarify the predictive factors of LV remodeling in patients after AMI participating in CR with exercise training starting early (10–20 days) after onset. Our hypotheses were that the baseline plasma BNP concentration would be a predictive factor of LV remodeling in postinfarction patients participating in exercise CR and that variables representing exercise intensity or frequency may not unfavorably affect LV remodeling in these patients.

Methods

Patients The study group included 72 patients with an AMI who completed the recovery phase CR program with exercise training. The diagnosis of AMI was confirmed by typical chest pain, electrocardiographic (ECG) findings and subsequent elevation of cardiac enzymes. Patients with the usual contraindications for exercise training were excluded. Written informed consent was obtained from all enrolled
patients. Baseline clinical characteristics and medications are shown in Table 1. All patients underwent coronary arteriography and left ventriculography 3–4 weeks after the onset of infarction. The LVEF averaged 44±10% (range, 19–67%).

Exercise Training
The CR program consisted of exercise training of moderate intensity and education for 12 weeks. Patients who did not have angina or ischemic changes on the ECG at a low level of exercise intensity (500 m walking) were enrolled in the exercise training approximately 10–20 days (median 15 days) after AMI. The exercise program consisted of walking, bicycling on ergometer, and aerobic dance with a duration of 50–90 min per session and a frequency of 3–5 sessions per week for 3 months. Exercise intensity was determined individually at 50–60% of heart rate reserve (Karvonen’s equation, k=0.5–0.6) obtained in maximal symptom-limited cardiopulmonary exercise testing (CPX) or at level 13 (‘a little hard’) of the 6–20 scale perceived rating of exercise (original Borg’s score). Care was taken to prescribe a slightly lower level of exercise intensity (40–50% of heart rate reserve) to patients with low LVEF (<40%). The exercise program was started with supervised sessions for 2 weeks, followed by home exercise combined with once or twice-a-week supervised sessions for the remaining 10 weeks. Home exercise consisted mainly of brisk walking at a prescribed heart rate for 30–60 min 3–5 times a week. At the end of the 3-month program, patients were encouraged to continue exercise training at home by giving them an individual exercise prescription. Although exercise intensity during home exercise was not investigated in the present study, the average adherence rate to home exercise was 84% at 6 months and 64% at 1 year after the completion of the 3-month CR in our program.

Cardiopulmonary Exercise Testing (CPX)
A maximal symptom-limited cardiopulmonary exercise test (CPX) was performed at the beginning and the end of the 12-week CR program. In the CPX, after a 2-min rest on the bicycle ergometer (Examiner, Lode B.V. Groningen-Holland), patients started pedaling at an intensity of 0 W for 1 min (warm-up), then performed an incremental (15 W/min) exercise test until exhaustion. During exercise testing, breathed gas was continuously collected, and the respiration rate, tidal volume, oxygen consumption (VO₂), carbon dioxide production (VCO₂) and minute ventilation (VE) were measured breath by breath. A face mask was used to collect gas samples, which were analyzed using a gas analyzer AE280 (Minato Medical Electronics, Osaka, Japan) connected to a personal computer equipped with analyzing software. Blood pressure was measured every minute by a manual method. A 12-lead ECG was also continuously monitored during exercise. Only 2 patients showed definite ischemic ECG changes in the initial exercise test; one underwent percutaneous coronary intervention therapy 2 days after the CPX, and the other patient refused coronary intervention therapy, although no ischemic change on the ECG was noted during subsequent exercise training.

Plasma BNP Concentration
Plasma BNP concentration was measured at the beginning and the end of the 12-week CR program, using a specific immunoradiometric assay kit from Shionoria BNP (Shionogi Co, Ltd, Japan) for human BNP in the SRL Inc (Tokyo, Japan).

Echocardiography
All patients underwent a complete Doppler echocardiographic examination at the beginning and 1 year after the end of the CR program. Standard views, including the parasternal long-axis, short-axis at the papillary muscle level, and apical 4- and 2-chamber views were recorded. An increase in LV end-diastolic dimension (delta-LVDd) from the baseline to follow-up was used as an index of LV remodeling.

Statistical Analysis
Values are expressed as mean ±SD. Univariate analysis was performed using paired or unpaired Student’s t-tests. Categorical data were compared against a chi-square distribution. Linear regression analysis was used to determine the correlation between continuous variables. Multivariate analyses were performed using the StatView statistical software packages (SAS Institute Inc, Cary, NC, USA). A p-value less than 0.05 was considered statistically significant.

Results
Changes in Clinical Variables After Cardiac Rehabilitation
All patients safely completed the 12-week CR program. Peak VO₂ increased significantly from 1,283±409 ml/min to 1,457±470 ml/min (p<0.05) at the end of the 12-week program. Plasma BNP concentrations decreased significantly from 232±211 pg/ml to 146±239 pg/ml (p<0.05). However, LVDd did not significantly change from baseline to follow-up (52.0±5.7 mm to 51.5±6.5 mm, NS).

Relation Between Clinical Characteristics and Delta-LVDd
To assess determinants of LV remodeling, delta-LVDd was compared between subgroups of patients according to clinical characteristics and medications. There were no significant differences in delta-LVDd between subgroups
ences reached statistical significance (0.1 < p < 0.2).

groups without these factors, although none of these differ-

With diuretics was greater than the delta-LVDd in the sub-

With prior MI, Killip’s classification

There was a weak trend that delta-LVDd in the subgroups

with an anterior MI than in patients with other infarct loca-

ful coronary reperfusion, or medications (Table 2).

of patients divided by sex, age (≥70/<70 years), presence or absence of coronary risk factors, prior myocardial infarction (MI), Killip’s classification ≥ II, successful/unsuccessful coronary reperfusion, or medications (Table 2).

Of note, delta-LVDd was significantly greater in patients with an anterior MI than in patients with other infarct locations (0.7±5.1 vs –1.60±3.7 mm, p<0.05, unpaired t-test). There was a weak trend that delta-LVDd in the subgroups with prior MI, Killip’s classification ≥ II, with nitrates, and with diuretics was greater than the delta-LVDd in the subgroups without these factors, although none of these differences reached statistical significance (0.1 < p < 0.2).

Table 2 Comparison of Delta-LVDd According to the Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Delta-LVDd (mm)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>–0.8±4.2 / 1.1±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Age (≥70/&lt;70 years)</td>
<td>–0.7±4.6 / –0.3±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (with/none)</td>
<td>–0.1±5.0 / –0.8±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus (with/none)</td>
<td>–0.4±4.3 / –0.5±4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia (with/none)</td>
<td>–0.7±5.0 / –0.1±5.0</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (with/none)</td>
<td>–0.6±4.6 / 0.9±4.2</td>
<td>NS</td>
</tr>
<tr>
<td>Family history (with/none)</td>
<td>–0.1±4.0 / –0.7±4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Prior MI (with/none)</td>
<td>1.2±4.1 / –0.9±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>≥ Killip II (with/none)</td>
<td>1.4±4.7 / –0.8±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Anteroseptal MI (with/none)</td>
<td>0.7±4.6 / –1.6±4.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Successful coronary artery reperfusion (with/none)</td>
<td>–0.6±4.3 / –0.2±5.1</td>
<td>NS</td>
</tr>
<tr>
<td>ACEI (with/none)</td>
<td>–0.3±4.2 / –1.0±5.1</td>
<td>NS</td>
</tr>
<tr>
<td>ß-blocker (with/none)</td>
<td>–0.9±4.3 / –0.4±4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Ca antagonist (with/none)</td>
<td>–1.1±4.6 / 0.0±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Digitalis (with/none)</td>
<td>2.1±4.9 / –0.7±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrates (with/none)</td>
<td>–0.2±4.7 / –0.2±4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics (with/none)</td>
<td>2.3±3.0 / –0.7±4.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean value±SD. MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; Successful reperfusion, successful reperfusion of an infarct-related artery within 24 h of onset.

Relation Between Angiographic, Neurohumoral, and Exercise Variables and Delta-LVDd

Correlations between angiographic, neurohumoral, and exercise variables and delta-LVDd are summarized in Table 3. There was no significant correlation, except for baseline plasma BNP concentrations (r=0.30, p<0.05, Fig 1). In addition, none of the 29 patients with baseline plasma BNP concentration ≤ 150 pg/ml had an increase in delta-LVDd >5 mm, whereas 8 of 43 patients (18.6%) with plasma BNP concentration >150 pg/ml had increases in delta-LVDd >5 mm (p<0.05) (Fig 2).

With regard to infarct location, there was a tendency that patients with an anterior infarction had a higher incidence of delta-LVDd >5 mm than patients with other infarct locations (16.7% vs 5.6%, p=0.14), although the difference did not reach statistical significance. Of note, 3 of 8 patients (37.5%) with both an anterior MI and a baseline BNP con-
concentration >500 pg/ml had delta-LVDd >5 mm at follow-up, suggesting that patients with both of these factors may be at high risk of LV remodeling.

The 2 patients who showed definite ischemic ECG changes in the initial exercise test had delta-LVDd <5 mm.

Relation Between Exercise Variables and Delta-LVDd
To examine a possibility that excessive exercise intensity or frequency might be associated with LV remodeling, correlations between exercise variables (ie, prescribed training heart rate, frequency of participation in exercise training sessions, and the increase and percentage increase in peak VO₂ at the end of the 12-week program) and delta-LVDd were assessed (Table 4). The ranges of distribution of these variables were 75–140 beats/min for prescribed training heart rate, 2–76 attendances at exercise sessions, −348–692 ml/min for the increase in peak VO₂, and −32–64% for percentage increase in peak VO₂ for all patients. These variables were considered to reflect the intensity, frequency and overall amount of exercise training that could potentially affect the development of LV remodeling. However, none of these variables significantly correlated with delta-LVDd (Table 4), suggesting that exercise training with appropriate intensity and frequency is not associated with LV remodeling.

Multivariate Analysis
Multiple linear regression analysis using 2 variables (the baseline plasma BNP concentration and infarct location, which affected the development of LV remodeling in the univariate analysis) indicated that only the baseline plasma BNP concentration significantly affected the development of LV remodeling (p=0.046), whereas the infarct location (anterior) had a tendency to affect the development of LV remodeling (p=0.18).

The combination of the baseline plasma BNP concentration and infarct location (anterior) improved the specificity and positive predictive value for delta-LVDd >5 mm better than the individual variables (Table 5).

Discussion
The major findings of the present study of patients with AMI participating in a 12-week exercise CR program are that (1) delta-LVDd at 1 year after the end of the program was significantly greater in patients with an anterior MI than with other infarct locations (p<0.05), (2) delta-LVDd correlated significantly with the baseline BNP concentration (p<0.05) and delta-LVDd >5 mm occurred exclusively in patients with a baseline BNP concentration higher than 150 pg/ml, and (3) variables representing the intensity and frequency of exercise training did not significantly correlate with delta-LVDd. These findings suggest that in patients with AMI participating in exercise CR, the baseline plasma BNP concentration and infarct location, but not exercise intensity or frequency, are factors influencing the development of LV remodeling.

Previous Studies
The EAMI study⁹ and Dubach et al²³ have demonstrated that exercise training does not aggravate LV remodeling, and the ELVD study¹⁰ has shown that exercise training instead attenuates LV remodeling. However, these studies did not analyze the predictive factors of LV remodeling in
the patients participating in exercise training. In addition, in those studies, exercise training was started relatively late (3–8 weeks) after the onset of infarction, which is not recent trend of early discharge and early return to work after AMI.24 Thus, factors predicting subsequent LV remodeling in patients participating in exercise CR, starting early (approximately 2 weeks) after the onset of the AMI remain unknown. Recently, we demonstrated that patients with a low LVEF do not have aggravated LV remodeling after moderate intensity exercise training starting 2 weeks after the onset of AMI.25 However, neurohumoral or exercise variables were not analyzed in that study.

**Present Study**

Compared with previous studies, the present study is unique because it comprehensively analyzed the predictive factors of LV remodeling using clinical, angiographic, neurohumoral, and exercise variables at baseline in postinfarction patients participating in exercise CR. As far as we know, no previous study has performed such a comprehensive analysis to identify determinants of postinfarction LV remodeling.

In addition, the present study is unique because our exercise rehabilitation program starts relatively early (approximately 2 weeks) after the onset of AMI. Although this timing may not be very early when compared with the recent trend of early discharge (3–5 days) after AMI, it is much earlier than the timing (3–8 weeks after the onset) in the previous EAMI and the ELVD studies.

**Plasma BNP Concentration and Ventricular Remodeling**

The present findings that anterior infarct location and baseline plasma BNP concentration are major influencing factors of LV remodeling are in accordance with previous reports.12–14 We have shown in our previous studies that an initial elevation (>100 pg/ml on the 7th day after onset) and a subsequent sustained elevation (percentage decrease <25% from 30th to 90th day) of plasma BNP are reliable predictors of progressive LV remodeling after acute MI.13,14 The present result indicates that our previous findings also hold true in patients participating in exercise CR after AMI. In addition, the present results suggest that patients with both anterior infarct location and an elevated BNP concentration (>500 pg/ml) at baseline are at high risk of subsequent LV remodeling.

Hama et al reported that the expression of the rat ventricular BNP gene after MI mainly occurred at the border of the infarcted region, where mechanical wall stress may be maximal.26,27 Cerisano et al reported that LV dilatation occurring early after infarction is predictable from the Doppler-derived mitral deceleration time indicating an elevated LV filling pressure.28 These findings suggest that a high plasma BNP concentration may reflect elevated LV wall stress, which is likely to accelerate LV remodeling and may explain why a high plasma BNP concentration is predictive of LV remodeling. Although the determination coefficient ($r^2=0.09$) of plasma BNP concentration for LV remodeling was not remarkably high in the present study, the results suggest that plasma BNP concentration is one of many determinants of the complex process of LV remodeling.

**Exercise Intensity and Ventricular Remodeling**

The present study found that exercise variables representing intensity, frequency, and total amount of exercise in CR do not affect LV remodeling, even when the exercise training is started relatively early (approximately 2 weeks) after the onset of AMI. The reasons for this result may be two-fold. First, the impact of the plasma BNP concentration is so powerful that the influence of exercise intensity or frequency on ventricular remodeling is masked. In other words, a transient increase in LV wall stress by exercise training may have no or only a small impact on the development of LV remodeling compared with the impact of baseline wall stress determined by infarct size. This possibility is supported by the result of the EAMI study showing that LV remodeling developed in patients with low LVEF regardless of exercise training.24 A second potential explanation is that the prescribed exercise intensity (40–60% of heart rate reserve) and frequency were at appropriate levels for not aggravating LV remodeling. In fact, a slightly lower exercise intensity (40–50% of heart rate reserve) was prescribed for patients with low LVEF (<40%) in the present study. This suggests that exercise intensity or frequency is not associated with LV remodeling, as long as they are within an appropriate range in the CR program. If more vigorous and excessive exercise had been imposed, LV remodeling might have occurred, a possibility that is supported by previous experimental results showing that vigorous swimming exercise in rats after a large MI aggravated LV remodeling,29,30 whereas a moderate level of exercise either did not adversely affect31 or even favorably attenuated LV remodeling in the same rat model.32

**Clinical Implications**

On the basis of the present results, plasma BNP concentration and infarct location are useful tools for predicting the likelihood of LV remodeling before beginning an exercise CR program after AMI. The present results also suggest that a moderate exercise intensity (50–60% heart rate reserve) for patients with LVEF >40% and a slightly lower intensity (40–50% heart rate reserve) for those with LVEF <40% may be safe and appropriate for average patients participating in exercise CR after AMI. Because patients with an anterior infarction and BNP concentration >150 pg/ml at approximately 2 weeks after the onset (especially, >500 pg/ml) are at high risk for subsequent LV remodeling and these patients often overlap with those with LVEF <40%, a relatively low level of exercise intensity (40–50% of heart rate reserve) is recommended for these patients. A low to moderate level (50% of peak VO2) of exercise has been reported to increase exercise capacity while minimizing ventricular wall stress in patients with LV dysfunction.33 To determine whether a higher level of exercise intensity (50–70% heart rate reserve) aggravates LV remodeling, further studies are needed.

**Study Limitations**

The present study was a prospective observational study, and did not have a sedentary control group. Although this might have affected the association between exercise intensity and LV remodeling, the wide variation of exercise intensity and frequency does allow us to analyze correlations between exercise variables and delta-LVDd.

A one-dimensional measure, such as delta-LVDd, has a certain limitation in the assessment of 3-dimensional LV remodeling. We intentionally avoided LV end-systolic dimension (LVDs) as an index of LV remodeling, because LVDs suffers from a greater error than LVDd when local
asynergy of LV wall motion exists. The presence of myocardial ischemia may have affected both delta-LVdPd and peak VO\textsubscript{2}; however, we excluded patients presenting with myocardial ischemia in the initial exercise test.

**Conclusion**

In patients with AMI participating in exercise CR, baseline plasma BNP concentration and anterior infarct location, but not exercise intensity or frequency, are predictive factors of the development of LV remodeling. Patients with both anterior infarction and a BNP concentration >150pg/ml at approximately 2 weeks after onset are at high risk for subsequent LV remodeling.

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**References**


