Effects of Exercise Training in Patients With Chronic Heart Failure and Advanced Left Ventricular Systolic Dysfunction Receiving β-Blockers

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Background: It remains unclear whether patients with chronic heart failure (CHF) and advanced left ventricular (LV) dysfunction on β-blocker therapy benefit from exercise training (ET).

Methods and Results: We studied 45 CHF patients with advanced LV dysfunction [ejection fraction (LVEF) <25%] and impaired exercise tolerance [normalized peak oxygen uptake (PVO2) <70%] receiving a β-blocker: 33 patients participated in a cardiac rehabilitation program with ET (ET group) and 12 did not (inactive control group). Exercise capacity, LV dimension and plasma B-type natriuretic peptide (BNP) were assessed before and after a 3-month study period. At baseline, both groups had markedly reduced LVEF (ET group 18±4% vs. Control group 18±5%, NS) and impaired exercise capacity (normalized PVO2 51±10% vs. 55±9%, NS). Although one patient in the ET group withdrew from the program due to worsening CHF, no serious cardiac events occurred during the ET sessions. After 3 months, the ET group (n=24) had significantly improved PVO2 by 16±15% (1,005±295 to 1,167±397 ml/min, P<0.001), while the PVO2 of the control group was unchanged. LV end-diastolic dimension decreased in both groups to a similar extent, but plasma BNP was significantly decreased only in the ET group (432 to 214 pg/ml, P<0.05).

Conclusions: The data indicate that in CHF patients with advanced LV dysfunction on β-blocker therapy, ET successfully improves exercise capacity and BNP without adversely affecting LV remodeling or causing serious cardiac complications. (Circ J 2011; 75: 1649–1655)

Key Words: Advanced left ventricular dysfunction; Beta-blocker; Chronic heart failure; Exercise capacity; Exercise training
The Cardiac Rehabilitation Program

The cardiac rehabilitation program with ET for CHF at our institute has been previously described. Fourierteen patients were confirmed not to have evidence of ischemia or severe arrhythmia during a level walking test. All patients gave written informed consent before entering the program.

The exercise program consisted of walking, bicycling on an ergometer, and calisthenics of 40–60 min/session 3–5 sessions/week for 3 months. Exercise intensity was determined individually at 30–50% of heart rate (HR) reserve (Karvonen’s equation: \( k = 0.3–0.5 \))17, an anaerobic threshold (AT) level obtained in a maximal symptom-limited cardiopulmonary exercise test, or at levels 11–13 (“fairly light” to “somewhat hard”) of the 6–20 scale rating of perceived exertion (the original Borg’s score18,19). Care was taken to prescribe a slightly lower level of exercise intensity (30–40% of HR reserve or an AT level) and lower session frequency (3 sessions/week) to patients with very low LVEF (<20%). The exercise program usually began with supervised sessions for 2–4 weeks, followed by home exercise combined with once or twice weekly supervised sessions for the remaining 8–10 weeks. Home exercise consisted mainly of brisk walking at a prescribed HR for 30–50 min, 3–5 times a week.

Patients were encouraged to attend education classes, which were held 3 times each week with lectures given by physicians, nurses, dieticians, and pharmacists on coronary artery disease, secondary prevention, HF management, diet, smoking cessation, and medication. In addition, all ET group patients received individual counseling on exercise prescription, secondary prevention, and daily life activities by a physician and a nurse at the time of hospital discharge and at the end of the 3-month cardiac rehabilitation program.

The inactive control patients did not participate in any exercise program or perform regular home exercise.

Cardiopulmonary Exercise Testing

Patients were scheduled to undergo a symptom-limited cardiopulmonary exercise test at the beginning and end of the 3-month study period. After a 2-min rest period on the bicycle ergometer in an upright position, patients pedaled at an intensity of 0 W for 1 min (warm-up), and were then subjected to an incremental exercise test with a ramp protocol (10 or 15 W/min) until exhaustion. The 12-lead ECG was continuously monitored and blood pressure was measured every minute with a sphygmomanometer. Expired gases were collected and analyzed continuously with an AE-280S or AE-300S gas analyzer (Minato Co, Osaka, Japan). Peak oxygen uptake (peak VO\(_2\)) was measured at peak exercise. Ventilation (VE) and carbon dioxide output (VCO\(_2\)) were measured and the gradient of the VE–VCO\(_2\) relationship (VE vs. VCO\(_2\) slope) was determined.

Clinical Data

Patients were scheduled to undergo echocardiography and plasma B-type natriuretic peptide (BNP) measurements at the beginning and end of the 3-month study period. LV internal diameters were acquired from the parasternal short-axis view, at the approximate mitral chordae level, using direct 2-dimensional measurements or targeted M-mode echocardiography if the M-mode cursor could be positioned perpendicular to the septum and LV posterior wall. Plasma BNP levels were measured with a specific immunoradiometric assay for human BNP using a commercial kit (Shionoria). The upper limit of normal plasma BNP level was 18.4 pg/ml. The minimal and maximal detectable levels of BNP were 4 and 2,000 pg/ml, respectively.

Statistical Analysis

Data are presented as the means±standard deviations. Significant differences were determined with paired or unpaired t-tests.
Exercise for Advanced LV Dysfunction

t-tests as appropriate. Considering the small number of inactive control patients, we also analyzed the differences between groups using a non-parametric Mann-Whitney U test, and the differences before and after ET in each group using Wilcoxon test. Differences in frequencies were analyzed with the Fisher exact probability test or the chi-square test. Pearson’s correlation analysis was used to evaluate the correlation between the change in peak VO₂ and the change in BNP. Statistical calculations were performed using Statview software. A P value less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the clinical characteristics, baseline LV function and exercise tolerance in the ET and inactive control groups. There were no significant differences between the ET and control groups at baseline. The non-parametric Mann-Whitney U test yielded the same results (data not shown). All patients were already on β-blocker therapy at the time of study entry, but some patients were still being up-titrated. The proportion of patients taking β-blockers for more than 3 months was 24% (8/33 patients) in the ET group and 33% (4/12 patients) in the control group (NS). The doses of β-blockers were similar between the 2 groups at the time of

<table>
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<tr>
<th>Table 2. Results of ET in the Exercise and Control Groups</th>
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<td><strong>ET group (n=24)</strong></td>
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<tr>
<td>Plasma BNP (pg/ml)</td>
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<td>LVEDD (mm)</td>
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<td>LVFS (%)</td>
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<td>HR at rest (beats/min)</td>
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<td>Normalized peak VO₂ (%)</td>
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<td>Peak work rate (W)</td>
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<td>AT (ml/min)</td>
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<td>VE-VO₂ slope</td>
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Plasma BNP data were available for 21 patients in the ET group and 10 patients in the inactive control group. LVEDD data were available for 18 patients in the ET group and 11 patients in the inactive control group. LVFS data were available for 16 patients in the ET group and 11 patients in the inactive control group. AT data were available for 19 patients in the ET group and 11 patients in the inactive control group. LVFS, left ventricular fractional shortening; HR, heart rate; AT, anaerobic threshold. Other abbreviations as in Table 1.

Figure 1. (A) Peak oxygen uptake (peak VO₂) before and after the 3-month study period in the exercise training (ET) group (Left) and inactive control group (Right). (B) Peak workload before and after the 3-month study period in the ET group (Left) and inactive control group (Right). *P<0.001 compared with pretraining. Pre, pretraining; Post, posttraining; F/U, follow-up.
study entry (for carvedilol, 11.3 mg/day in the ET group and 13.2 mg/day in the control group, NS). The schedule of up-titration and the final dose of \(\beta\)-blockers were left to the attending physicians.

Of the 33 patients in the ET group, 24 (73%) completed the 3-month ET program, and among the 9 patients who did not complete the study, one had an exacerbation of HF (3%), one withdrew for a non-cardiac medical reason (claudication) (3%) and the remaining 7 withdrew for social reasons (the distance to the institute was too far, return to work, etc) (21%). These 9 patients were excluded from the statistical analysis of ET effects. There were no significant differences in the baseline plasma BNP levels, LV end-diastolic dimensions (LVEDD), LVEF, or exercise capacity between the 24 patients who completed the 3-month ET program and the 9 patients who withdrew. No serious cardiac events, including death or cardiopulmonary arrest, occurred during the ET sessions. No patients developed new atrial fibrillation during

**Figure 2.** (A) Left ventricular end-diastolic diameter (LVEDD) before and after the 3-month study period in the exercise training (ET) group (Left) and inactive control group (Right). (B) Plasma B-type natriuretic peptide (BNP) before and after the 3-month study period in the ET group (Left) and inactive control group (Right). \(\dagger\)P<0.005, \(\ddagger\)P<0.01, **P<0.05 compared with pretraining. Pre, pretraining; Post, posttraining; F/U, follow-up.

**Figure 3.** Significant inverse correlation between the relative change in peak oxygen uptake (peak \(\text{VO}_2\)) \(\left[\frac{(\text{peak }\text{VO}_2 \text{ after the 3-month—peak }\text{VO}_2 \text{ at baseline})}{\text{peak }\text{VO}_2 \text{ at baseline}}\right] \times 100\) and percentage change in plasma B-type natriuretic peptide (BNP) \(\left[\frac{(\text{plasma BNP after the 3-month—plasma BNP at baseline})}{\text{plasma BNP at baseline}}\right] \times 100\) in all study patients.
the rehabilitation program.

**Exercise Variables**

After the 3-month study period, resting HR was unchanged in the control group, but tended to decrease in the ET group (P=0.057, Table 2), and peak HR did not change in both groups (Table 2). The ET group showed significant improvements in peak VO₂ (1.005±295 to 1.167±397 ml/min, 16±15%; 16±3±43 to 18.7±5.1 ml·min⁻¹·kg⁻¹, 15±14%, both P<0.001) and its normalized value (P<0.001) after the study period, whereas the inactive control group did not (Table 2, Figure 1A). In addition, only the ET group achieved a significant increase in peak work rate after the 3-month ET (96±28 to 111±30 W, P<0.001) (Table 2, Figure 1B). VE vs. VCO₂ slope did not significantly change in either group after the 3-month study period (Table 2).

The non-parametric Wilcoxon test yielded the same results, except that VE vs. VCO₂ slope significantly decreased only in the ET group after the 3-month study period (median 31.1 to 29.4, P<0.05).

**LV Function and BNP**

LVEDD significantly decreased in both the ET group (P<0.005) and the inactive control group (P<0.01) (Table 2, Figure 2A), and the relative decrease in LVEDD was similar between the 2 groups (ET group –10±11% vs. inactive control group –10±10%, NS). LV fractional shortening (FS) increased in both groups, but the change reached a statistical significance only in the inactive control group (P<0.01) and not in the ET group (P=0.065) (Table 2). Compared to their baseline levels, plasma BNP concentrations significantly decreased (P<0.05) after the ET program, but did not change in the inactive control group (n=10) (Table 2, Figure 2B).

When the percentage change in BNP [(BNP after 3 months–BNP at baseline)/BNP at baseline]×100 was plotted against the relative change in peak VO₂ [(peak VO₂ after 3 months–peak VO₂ at baseline)/peak VO₂ at baseline]×100] in the entire patient population, there was a significant inverse correlation (r=0.625, P<0.001, n=31), indicating that a greater increase in peak VO₂ was associated with a greater decrease in plasma BNP (Figure 3).

**Discussion**

ET has been shown to favorably affect the outcomes and quality of life of many patients with CHF, but it has remained unclear whether ET is safe and beneficial for those CHF patients with advanced LV dysfunction and on β-blocker therapy. We set out to examine that question, and our data indicate that, in this subset of CHF patients, an appropriate ET program safely increased exercise capacity and decreased plasma BNP levels without promoting deleterious LV remodeling. Additionally, there was a significant inverse correlation between plasma BNP and peak VO₂ during the study period, suggesting that improvements in exercise capacity are associated with amelioration of elevated LV load. Finally, the prescribed ET program was very well tolerated; the withdrawal rate from the exercise program due to cardiac reasons was only 3%.

**Previous Studies**

Several other studies over the past 20 years have studied the role of ET in patients with advanced LV dysfunction (mean LVEF <20%) (Table 3), and demonstrated a significant improvement in peak VO₂ by 16–18% following ET.6,11,13,21 However, β-blockers were prescribed to only 0–25% of enrolled patients in most of those studies,6,11,13 and to 70% of the patients in one study.14 In contrast, in the present study, all patients were prescribed β-blockers. Thus, our results are more relevant in the current era when β-blocker therapy is the standard of care.

β-blocker therapy does not improve peak VO₂ in patients with CHF, despite the symptom amelioration, improvements in NYHA functional class, and increased LVEF associated with β-blocker therapy.22,23 In contrast, ET can increase peak VO₂ in patients with moderate to severe HF who are taking β-blockers.24,27 However, most of the previous studies examining ET in patients using β-blockers recruited only patients with LVEF in the range of 23–35%. The study population of the recent HF-ACTION trial, in which β-blockers were prescribed to 95% of patients, did not contain more than 50% of patients with an LVEF <25%.15 Thus, to our knowledge, the present study is the first to examine the effects of ET in CHF patients with advanced LV dysfunction (LVEF <25%) and concurrent β-blocker therapy.

**Exercise Capacity**

There was concern that β-blockers could abrogate the benefits of ET in patients with CHF, but one study reported that β-blocker therapy did not affect ET-associated increases in exercise capacity.24 Additionally, there were no differences in the effects of ET between patients receiving β-1 selective and non-selective α-β blockers.28 The increase in peak VO₂ in the ET group in the present study (15%) was less than that seen in the study of Demopoulos et al (24–27%),24 but was comparable to the increase reported by Forissier et al (14–17%).28

In the HF-ACTION trial,15 the ET group had a significant

<table>
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<th>First author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>NYHA (II/III)</th>
<th>LVEF (%)</th>
<th>ACEI/ARB (%)</th>
<th>BB (%)</th>
<th>Duration</th>
<th>Increments of peak VO₂ (ml·min⁻¹·kg⁻¹)</th>
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<td>14.3±16.7 (17%)</td>
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<td>61.8</td>
<td>10/7</td>
<td>19.6</td>
<td>88</td>
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<td>8 weeks</td>
<td>13.2±15.6 (18%)</td>
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<td>6/6</td>
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<td>57</td>
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<td>55</td>
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<td>15.9±18.5 (16%)</td>
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<td>46</td>
<td>57.5</td>
<td>34/12</td>
<td>17</td>
<td>100</td>
<td>70</td>
<td>4 months</td>
<td>19→21 (11%)</td>
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<td>51</td>
<td>11/13</td>
<td>17</td>
<td>88</td>
<td>100</td>
<td>3 months</td>
<td>16.3±18.7 (15%)</td>
</tr>
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Abbreviations as in Table 1.
improvement in peak VO$_2$ at 3 months compared to the usual care group (0.6 vs. 0.2 ml·min$^{-1}$·kg$^{-1}$; P<0.001), but this increase was relatively small (median 4%). The authors attributed the relatively small improvement to low adherence to the exercise protocol. Thus, baseline patient characteristics, the specific exercise program prescribed, and adherence to that program likely all contribute to the magnitude of change in exercise capacity observed in the different studies.

LV Remodeling

In the present study, both study groups showed a decrease in LVEDD (ie, there was reverse LV remodeling). This result differs from those of Giannuzzi et al who found that LV remodeling was reversed by ET, but worsened in a control non-ET group with moderate CHF (average LVEF 25%).$^{28}$ These conflicting results may be due to the low rate of prescription of β-blockers in the study by Giannuzzi et al (20%).

In addition, experimental studies using a rat model showed that excessive exercise after a large myocardial infarction aggravated LV remodeling.$^{30,31}$ but moderate exercise had either no effect$^{32}$ or attenuated adverse LV remodeling.$^{33}$ Although the myocardial infarction models in the rat differ from human CHF, these findings suggest that exercise intensity in an ET program can affect LV remodeling. Based on this, exercise intensity was adjusted according to the severity of LV dysfunction in each patient in the present study. In addition to β-blocker therapy, this appropriate adjustment of exercise prescription may also have contributed to reverse LV remodeling.

Plasma BNP

Passino et al reported that ET decreases plasma BNP levels in patients with moderate CHF.$^{34}$ The present results are consistent with that study, but we extended these findings to a patient population with more severe LV dysfunction (mean LVEF 18%) and higher baseline BNP (365 pg/ml) than Passino’s study (mean LVEF of 35% and baseline BNP of 187 pg/ml).

The significant inverse correlation that we found between changes in BNP and exercise capacity is also consistent with the previous report,$^{34}$ which is somewhat counterintuitive because one could hypothesize that a greater increase in exercise capacity requiring a greater amount of ET would result in sustained LV wall stress and an associated increase in plasma BNP. However, the available data suggests that ET of an appropriate intensity and duration ameliorates the increased LV wall stress that stimulates BNP production. This hypothesis is consistent with the observation in a canine model of HF that regular ET lowers LV end-diastolic pressure at rest through enhanced nitric oxide production.$^{35}$ One remaining question is whether the observed decrease in BNP is attributable to ET alone or to the combination of ET and β-blocker therapy.

Etiology of CHF

It is intriguing whether the response to ET differs between CHF due to ischemic and non-ischemic cardiomyopathies. Because the total number of patients was not sufficient, such subgroup analyses were beyond the scope of the present study. However, a tentative analysis of 26 patients with a non-ischemic etiology showed a consistent result with the study. However, a tentative analysis of 26 patients with a non-ischemic etiology showed a consistent result with the previous report, especially when the LVEF is markedly reduced. Our data suggest that, even in such patients with advanced LV dysfunction, ET may help to reverse adverse LV remodeling based on careful medical evaluation.

Study Limitations

Our data provide a good rationale for future studies of ET for patients with advanced LV dysfunction in CHF, but our study is limited because it is retrospective and from a single center with a relatively small number of patients. Therefore, a large controlled randomized study should be performed to confirm these results.

An additional confounding factor in our study is the exclusion from the analysis of the 9 patients who dropped out of the study. However, an additional comparison between the completion group (n=24) and dropout group (n=9) yielded similar results, and we expect little bias from the exclusion of these patients.

All the patients in the present study were clinically stable on β-blocker therapy or which β-blocker therapy was not considered to be the optimal therapy in patients with severe LV dysfunction at the start of ET. Additionally, β-blocker therapy was not standardized across the study participants. Therefore, we cannot draw any conclusions regarding the optimal time to initiate ET after the start of β-blocker therapy or which β-blocker is best combined with ET. Further studies are necessary to address these issues.

Conclusion

In patients with CHF, advanced LV dysfunction and on β-blockers, ET can safely increases exercise capacity with favorable effects on LV remodeling and plasma BNP with a low incidence of cardiac complications (3%).
Acknowledgments

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References


11. Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology: Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008; 29: 2388–2422.


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