Are Cardiac Events During Exercise Therapy for Heart Failure Predictable From the Baseline Variables?

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Background  Exercise training (ET) is an emerging therapy for chronic heart failure, but the baseline patient characteristics for predicting cardiac events (CEs) during the course of ET remain unknown.

Methods and Results  Of the 111 stable heart failure patients who participated in a 3-month ET program, 6 withdrew from the program for cardiac reasons and 9 had transient interruptions in the program because of CEs. The baseline clinical characteristics of these 15 patients (CE group) and the remaining 96 patients (No-CE group) were compared. Compared with the No-CE group, the CE group had a significantly higher prevalence of pacemaker/implantable cardioverter-defibrillators, larger left ventricular end-diastolic diameter (LVEDDs), lower peak oxygen uptake, greater ventilation drive, and higher plasma brain natriuretic peptide concentration at baseline. Multivariate logistic regression analysis showed that a larger LVEDD was a significant predictor of the occurrence of a transient interruption to or permanent withdrawal from the ET program because of CEs. Receiver operating characteristic curve analysis demonstrated that an LVEDD ≥65 mm had a sensitivity of 93% and specificity of 48% in predicting CEs.

Conclusions  Patients with a large LVEDD (≥65 mm) at baseline should be monitored carefully during the course of an ET program. (*Circ J 2007; 71: 1035–1039*)

Key Words: Cardiac events; Cardiac rehabilitation; Chronic heart failure; Exercise training; Predictors

Recent clinical studies have demonstrated that exercise training (ET) improves functional status, quality of life, and prognosis of patients with chronic heart failure. Because restricted physical activity promotes physical deconditioning, which may adversely affect the clinical status of a patient and exacerbate the exercise intolerance of patients with chronic heart failure, ET is recommended as an adjunct to improving the clinical status of ambulatory patients with current or prior symptoms of heart failure and a reduced left ventricular ejection fraction (LVEF). As might be expected, there are populations of patients with chronic heart failure who transiently interrupt or permanently withdraw from ET programs because of cardiac events (CE). Although we have reported that the rate of permanent withdrawal from such programs because of cardiac problems is approximately 5%, other patients may have a transient interruption to their ET for reasons such as a transient worsening of the heart failure or arrhythmias. Only a few reports, however, have investigated the characteristics of patients with chronic heart failure who are likely to transiently interrupt or permanently withdraw from an exercise program. Thus, it remains unclear which subgroup of patients with chronic heart failure is likely to experience these problems and if the predictors of these problems could be identified, ET for patients with heart failure would be safer and more effective.

Accordingly, the purpose of the present study was to identify such predictors. To this end, we used multivariate analysis to compare the baseline clinical characteristics of patients who did or did not transiently interrupt or permanently withdraw from an exercise program.

Methods

Patients  The entry criteria for our exercise cardiac rehabilitation program for heart failure were: aged 15–80 years, left ventricular (LV) systolic dysfunction with an LVEF ≤40%, reduced exercise tolerance, a well-controlled body fluid level (euvolemic), and no signs of worsening of heart failure during the past fortnight. LVEF was determined from left ventriculography using contrast medium or radioisotope. A total of 111 patients with heart failure participated in the program and all gave informed consent to the protocol. The clinical characteristics of the patients were as follows: 85% male, between 19 and 72 years old, 98% began as inpatients, and New York Heart Association classes I–III.

The Cardiac Rehabilitation Program  The cardiac rehabilitation program for chronic heart failure was developed by modifying a previously reported program for acute myocardial infarction. Patients were enrolled in the ET program when they did not have ischemic changes on electrocardiography (ECG) or severe arrhythmia during an initial submaximal exercise test (a 6-min walking test or a treadmill walking test with 0% slope to 75% of the predicted maximal heart rate) or to level 15 (“hard”) of the 6–20 scale rating of perceived exertion.
The exercise program consisted of walking, bicycling on an ergometer, and calisthenics for 40–60 min/session and 3–5 sessions/week for 3 months. Exercise intensity was determined individually at 30–50% of HR reserve (Karvonen’s equation: $k=0.3–0.5$)\(^{13}\) 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 score\(^{14}\)). 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 a 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 per 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 diseases, secondary prevention, heart failure management, diet, smoking cessation, and medication. In addition, all 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.

Cardiopulmonary Exercise Testing

Patients were scheduled to undergo a symptom-limited cardiopulmonary exercise test at the beginning and at the end of the 3-month cardiac rehabilitation program. After a 2-min rest on the bicycle ergometer in the upright position, the patient started pedaling at an intensity of 0 W for 1 min (warm-up), and then performed an incremental exercise test with a ramp protocol (10 or 15 W/min) until exhaustion. Twelve-lead ECG was continuously monitored and blood pressure was measured every minute with a sphygmomanometer. Expired gas was collected and analyzed continuously with an AE-280S or AE-300S gas analyzer (Minato Co, Osaka, Japan). Peak oxygen uptake (peak $\text{VO}_2$) was defined as the highest $\text{VO}_2$ value achieved at peak exercise. Ventilation (VE) and carbon dioxide output ($\text{VCO}_2$) were measured and the gradient of the VE-$\text{VCO}_2$ relationship ($\text{VE}/\text{VCO}_2$ slope) was determined.

Echocardiography

All 111 patients underwent echocardiography before the entry into the ET program. LV internal diameters were acquired from the parasternal short-axis view, approximately at the mitral chordae level, using direct 2-dimensional measurements or targeted M-mode echocardiography provided that the M-mode cursor can be positioned perpendicular to the septum and LV posterior wall.

Clinical Course and Patient Categories

Of the 111 patients, 73 patients completed the 3-month cardiac rehabilitation program and 38 did not (ie, permanent withdrawal). Of these 38 patients, 24 gave social reasons (the distance to the institute was too far, return to work etc), 7 had non-cardiac medical reasons (lumbago, claudication etc), 6 experienced cardiac problems, and 1 left for an unknown reason (Fig 1). The cardiac reasons provided by the 6 patients were exacerbation of the heart failure (n=4), ventricular tachycardia (n=1), and atrial fibrillation (n=1). Of the 73 patients who completed the program, 9 transiently interrupted the ET for cardiac reasons, including exacerbation of heart failure (n=2), implantation of an implantable cardioverter-defibrillator (ICD) to address ventricular fibrillation (n=1), discharges of ICD shocks for ventricular tachycardia (n=1), occurrence of ventricular tachycardia (n=2), implantation of a pacemaker (n=1), more coronary artery bypass surgery (n=1), and hypotension (n=1).

The patients who transiently interrupted their ET (n=9) and those who permanently withdrew from the program (n=6) for cardiac reasons were categorized together as the CE group (n=15), and the remaining patients were categorized as the no-CE group (n=96). We categorized the 24 patients who permanently withdrew for social reasons into the no-CE group because our previous study\(^{6}\) indicated that there were no differences in baseline clinical data, includ-
Table 1 Clinical Characteristics and Baseline Data of the 2 Groups

<table>
<thead>
<tr>
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<th>Cardiac event (n=15)</th>
<th>No cardiac event (n=96)</th>
<th>p value</th>
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<tr>
<td>Age (years)</td>
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<td>50±13</td>
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</tr>
<tr>
<td>Male (%)</td>
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<td>84</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class (I/II/III) (%)</td>
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<td>84/15/51</td>
<td>NS</td>
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<tr>
<td>DCM/IsCM/Other (%)</td>
<td>47/40/14</td>
<td>60/20/20</td>
<td>NS</td>
</tr>
<tr>
<td>Pacemaker/ICD (%)</td>
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<td>7</td>
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<td>HT (%)</td>
<td>20</td>
<td>35</td>
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</tr>
<tr>
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<td>NS</td>
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<tr>
<td>IGT/DM (%)</td>
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<td>31</td>
<td>NS</td>
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<tr>
<td>Body mass index</td>
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<td>22.7±4.6</td>
<td>NS</td>
</tr>
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</table>

Statistical Analysis

Data are presented as the mean±standard deviation. Significant differences were determined by paired or unpaired t-tests where appropriate. Differences in frequencies were analyzed with the Fisher exact probability test or the chi-squared test. Multivariate logistic regression analysis was performed to determine the significant predictors of transient interruption in or permanent withdrawal from the ET program because of CEs. Significant variables detected using an unpaired t-test, the Fisher exact probability test, or chi-squared test were included in the multivariate analysis. Then, receiver operating characteristic (ROC) curve analysis was performed to determine the best cutoff value that predicted the CE with the largest sum of sensitivity and specificity. Statistical calculations were performed using Statview or SPSS software (Chicago, IL, USA). A p-value less than 0.05 was considered statistically significant.

Results

Ninety patients (10 of the 15 patients in the CE group and 80 of the 96 patients in the no-CE group) completed a symptom-limited cardiopulmonary exercise test at the beginning and end of the program. In these patients, peak VO2 increased significantly from 1,227±452 to 1,372±527 ml/min (p<0.001), and the VE/VO2 slope marginally decreased (29.8±8.0 to 28.8±7.7, p=0.058) after ET.

Table 1 summarizes the clinical characteristics of the patients and the baseline data for LV function and exercise tolerance in both groups. Compared with the no-CE group, the CE group had a significantly higher prevalence of pacemakers/ICDs (27 vs 7%, p<0.05), larger LV end-diastolic diameter (LVEDD) (75±9 vs 66±8 mm, p<0.01), lower peak VO2 (899±407 vs 1,228±438 ml/min, p<0.05; 47±13 vs 60±14%, p<0.01), greater ventilation drive (VE/VO2 slope: 37.8±10.2 vs 29.8±7.5, p<0.001), and higher plasma BNP concentration (437±270 vs 216±266 pg/ml, p<0.01).

Multivariate logistic regression analysis, which incorporated pacemaker/ICD implantation, LVEDD, peak VO2, VE/VO2 slope, and plasma BNP concentration, demonstrated that a larger LVEDD (odds ratio: 1.085, confidence interval: 1.002–1.175) was a significant independent predictor of a transient interruption in or permanent withdrawal from the ET program for cardiac reasons (Table 2).

The ROC curve analysis indicated that a cutoff level of
LVEDD ≥65 mm best predicted CE, with a sensitivity of 93.3% and specificity of 47.9% (Fig 2). In addition, this criterion of LVEDD ≥65 mm had a positive predictive value of 21.9% and negative predictive value of 97.9% in the present patient population.

No serious CE, such as death or cardiopulmonary arrest, occurred during the ET sessions.

Discussion

Major Findings

The major finding of the present study was that the predictors of the occurrence of CE causing either a transient interruption or permanent withdrawal during the course of the 3-month ET program for chronic heart failure were: pacemaker/ICD implantation, larger LVEDD, lower exercise tolerance, greater ventilation drive, and higher plasma BNP concentration at baseline. In addition, multivariate analysis indicated that a large LVEDD was an independent predictor of CE during the ET program.

Previous Studies

Vanhees et al reported that 4 of 106 patients with an ICD decided to terminate rehabilitation after receiving shocks for ventricular tachycardia. In the present patients, all of whom had a poorly functioning LV, 3 of 7 patients with an ICD experienced shocks for ventricular tachycardia or refractory ventricular tachycardia. Therefore, chronic heart failure patients with implanted pacemakers/ICDs seem to be more likely to develop CE while participating in an ET program. However, ET with an appropriate prescription and careful supervision, rather than restriction of exercise, may be the recommended course of treatment for these patients, because cardiac rehabilitation with ET has been reported to improve exercise capacity and quality of life in patients with ICDs.

Webb-Peploe et al demonstrated that complications from ET were more common in patients with ischemic cardiomyopathy, larger LV diameters, reduced fractional shortening, earlier peak mitral flow, lower exercise tolerance, and greater ventilation drive at baseline? Although the present results, which show that a larger LV diameter, lower exercise tolerance, and greater ventilation drive were predictors of CE, agree with the results reported by Webb-Peploe et al, an ischemic origin and reduced LV contractile function were not identified by us as significant predictors of CE. This discrepancy may be explained by differences in the type of exercise program (home-based exercise in their study vs supervised exercise in the present study), the exercise intensity (70–80% of maximum HR vs 30–50% of HR reserve in the present study), and more importantly, the proportion of patients taking β-blockers (4% vs 92% in the present study). Thus, the present results may be more relevant for ET in patients with chronic heart failure in the current era of widely used β-blockers.

Present Study

Using multivariate analysis, we demonstrated that a larger LVEDD predicts that the patient is at high risk for transiently interrupting or permanently withdrawing from an ET for cardiac reasons. In addition, ROC curve analysis identified the best LVEDD cutoff level to be ≥65 mm. Although the specificity (47.9%) of the criterion of an LVEDD ≥65 mm was low, the sensitivity (93.3%) and negative predictive value (97.9%) were very high. This indicates that if a patient with heart failure has an LVEDD <65 mm, the risk is low that they will discontinue the ET program transiently or permanently for cardiac reasons. This criterion should help stratify heart failure patients before they start the ET program.

Why Does LVEDD Represent the Best Predictor?

In the present study, exacerbation of heart failure or hypotension (n=7) and arrhythmic events (n=7) were the main causative factors among the 15 patients who transiently interrupted or permanently withdrew because of CE. We consider that the reason why LVEDD represents the best predictor among the univariate predictors to be as follows. Compared with the 96 patients in the no-CE group, the 7 patients with heart failure exacerbation/hypotension had significantly higher plasma BNP levels at baseline (539±199 vs 216±266 pg/ml, p<0.05 by Scheffe’s method), whereas no significant difference was noted between the 7 patients with arrhythmic events and the no-CE group (360±325 vs 216±266 pg/ml, NS) (Fig 3). On the other hand, LVEDD at baseline in the 7 patients with heart failure exacerbation/hypotension was significantly greater than that in the no-CE group (66±8 mm). These findings suggest that the baseline plasma BNP concentration can predict exacerbation of heart failure, but not arrhythmic events, leaving the LVEDD as an independent index capable of predicting both events. Although this finding appears to disagree with the study of Berger R et al, who demon-
The present study included patients and social dropout patients into the same "no-CE group". However, an additional analysis of comparison between the uneventful completion group (n=64) and the CE group. Therefore, the inclusion of the social dropout patients into no-CE group would not compromise the present results.

Because we did not have a control heart failure group that did not undergo ET, we could not determine whether or not the CE were precipitated by the ET. This, however, is not a major concern because the main scope of the present study was to determine from the baseline data predictors of CE during the ET, regardless of the cause of the CE. With regard to whether or not ET precipitates CE, previous meta-analyses of prospective randomized studies have demonstrated that ET reduces the number of major CE in patients with heart failure.18

Conclusion

Patients who experience CE during ET programs characteristically have an implanted pacemaker/ICD, larger LV diameter, lower exercise tolerance, greater ventilation drive, and higher plasma BNP concentration. In particular, because LVEDD is an independent predictor of CE, patients with a large LVEDD (≥65 mm) should be monitored carefully during the course of an ET program.

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References