



Effect of Exercise Training in Heart Failure Patients Without Echocardiographic Response to Cardiac Resynchronization Therapy

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Background: Cardiac resynchronization therapy (CRT) is an effective treatment of heart failure (HF) with ventricular dyssynchrony, but not all patients respond to a similar extent. We investigated the efficacy and safety of exercise training (ET) in patients without response to CRT.

Methods and Results: Thirty-four patients who participated in a 3-month ET program and underwent cardiopulmonary exercise testing at baseline and after the program were divided into 17 responders and 17 non-responders based on echocardiographic response criteria: either an increase in ejection fraction (EF) $\geq 10\%$ or a reduction in left ventricular (LV) end-systolic volume $\geq 10\%$. Baseline characteristics including peak oxygen uptake ($\dot{V}O_2$) and isometric knee extensor muscle strength (IKEMS) were similar in both groups, but non-responders had lower EF and larger LV. During the ET program, neither group had exercise-related adverse event including life-threatening ventricular arrhythmia. Peak $\dot{V}O_2$ and IKEMS were significantly improved in both groups and there was no significant difference in change in peak $\dot{V}O_2$ or IKEMS between responders and non-responders. On multiple regression analysis, change in IKEMS was an independent predictor of change in peak $\dot{V}O_2$, whereas the response to CRT was not.

Conclusions: In HF patients undergoing CRT implantation, ET safely improved exercise capacity regardless of response to CRT, suggesting that even advanced HF patients without response to CRT can possibly benefit from ET.

Key Words: Cardiac resynchronization therapy; Exercise capacity; Exercise therapy; Heart failure; Peak oxygen uptake

Cardiac resynchronization therapy (CRT) is a highly effective treatment for drug-refractory systolic heart failure (HF) patients with a wide QRS complex. CRT implantation results in left ventricular (LV) reverse remodeling, as evidenced by a decrease in LV size and/or an increase in LV ejection fraction (LVEF), and reduces morbidity and mortality,^{1–3} but not all patients respond to a similar extent.^{4,5} According to Yu et al, patients who did not respond to CRT (non-responders) had a worse prognosis than those who did (responders) when echocardiographic response to CRT was defined as a relative reduction of LV end-systolic volume (LVESV) $\geq 9.5\%$ after CRT implantation.⁶ Similarly, Di Biase et al noted a significant reduction in ventricular tachyarrhythmia episodes in responders (defined as $>10\%$ improvement in LVESV), compared with non-responders.⁷ Furthermore, the improvement in LVESV after CRT as a continuous measure was also reported to be associated with a reduction in subsequent cardiac events⁸ and life-threatening ventricular tachycardia.⁹

In patients after CRT implantation, an exercise training (ET) program improves exercise capacity without adverse events.^{10,11} Patwala et al reported that after a waiting period of 3 months after CRT implantation, 3-month ET program led to further improvement in exercise capacity in addition to the improvement seen during the first 3 months, suggesting that the improvement in peak $\dot{V}O_2$ is due to a combined improvement in cardiac function and peripheral oxygen extraction.¹² Although echocardiographic non-responders, compared with responders, have poor improvement in exercise capacity after CRT implantation,^{13,14} whether echocardiographic non-responders safely benefit from an ET program remains unclear.

The purpose of this study was therefore to investigate the efficacy and safety of a 3-month ET program in echocardiographic non-responders compared with responders after CRT implantation.

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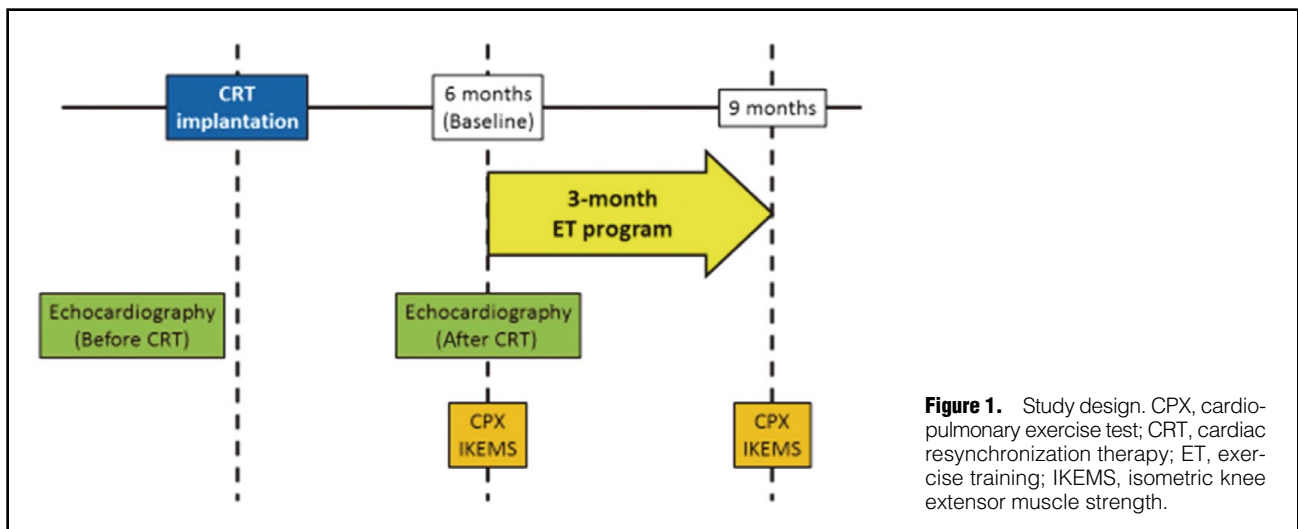


Figure 1. Study design. CPX, cardiopulmonary exercise test; CRT, cardiac resynchronization therapy; ET, exercise training; IKEMS, isometric knee extensor muscle strength.

Methods

Study Design and Participants

We retrospectively reviewed consecutive patients in whom a CRT device was implanted and who underwent echocardiography before and 6 months after CRT implantation at the National Cerebral and Cardiovascular Center, Osaka, Japan between March 2008 and July 2017. Of these, we studied patients who participated in a 3-month ET program at 6 months after CRT implantation, including at least 1 supervised in-hospital ET session and who underwent cardiopulmonary exercise test (CPX) at the beginning and end of the ET program (Figure 1). Patients were excluded from the study if they had a history of myocardial infarction (MI) in the previous 3 months or significant pulmonary, cerebrovascular, or orthopedic disease. Treatment for HF was tailored to all patients based on current guidelines,¹⁵ and was kept constant throughout the study period. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee. All patients gave written informed consent.

Echocardiographic Response to CRT

The LV end-diastolic diameter (LVDd) and LV end-systolic diameter (LVDs) were determined on 2-D echocardiography, and LVEF and LVESV were measured using the modified Simpson's method. The change in LVEF was determined as the absolute change during the period, and the change in LVESV was determined as the percent relative change. We defined echocardiographic response to CRT as either an absolute increase in LVEF $\geq 10\%$ or a relative reduction in LVESV $\geq 10\%$ during 6 months after CRT implantation, based on previous criteria.^{5-7,13,14}

Exercise Program

At 6 months after CRT implantation, the 3-month ET program was started with supervised in-hospital sessions consisting of walking, bicycle ergometer and low-intensity resistance training for 20–40 min per session 3–5 times per week, followed by home ET combined with once- or twice-per-week supervised in-hospital ET sessions. The duration of the exercise was increased to 30–60 min, and the intensity of the endurance exercise was determined individually at a

heart rate corresponding to 40–60% of heart rate reserve (maximum heart rate minus resting heart rate) or anaerobic threshold level obtained in baseline CPX, or at level 12–13 (“a little hard”) of the 6–20 scale perceived rating of exercise (original Borg scale).

CPX and B-Type Natriuretic Peptide

Symptom-limited CPX was performed using a cycle ergometer with respiratory gas exchange analysis at the beginning and end of the 3-month ET program. The test consisted of an initial 2 min of rest, 1 min of warm-up (0-W load), and full exercise using an individualized ramp protocol with increments of 10–20 W/min. Expired gas analysis was performed throughout CPX on a breath-by-breath basis, and the minute ventilation (\dot{V}_E), oxygen uptake ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$) data were stored in a computer hard disk every 6 s for off-line analysis (AE-300S; Minato Medical Science, Osaka, Japan). Based on the previous findings,¹⁶ all subjects undergoing CPX had been strongly encouraged to exercise towards exhaustion, with a target peak respiratory exchange ratio (RER; an objective index of effort adequacy) >1.20 . Peak $\dot{V}O_2$ was determined as the higher value of either the greatest $\dot{V}O_2$ during exercise (smoothed after a 5-point moving average) or the average $\dot{V}O_2$ of the last 3 data points (18 s) before termination of exercise and was expressed as adjusted to body weight (mL/kg/min). The percent-predicted peak $\dot{V}O_2$ (%) was calculated as peak $\dot{V}O_2$ (mL/kg/min) divided by the predicted value using the following equations: $52.1 - 0.38 \times \text{age}$ (years) for men; and $40.4 - 0.23 \times \text{age}$ (years) for women.¹⁷ The slope of the linear relationship between \dot{V}_E and $\dot{V}CO_2$ ($\dot{V}_E/\dot{V}CO_2$ slope), an index of ventilatory efficiency, was measured, excluding the part after the respiratory compensation point where the slope started to increase. The change in peak $\dot{V}O_2$ was determined as the percentage relative change during the 3-month ET program.

In all patients, blood samples were drawn for B-type natriuretic peptide (BNP) measurement at the beginning of the ET program (6 months after CRT), and plasma BNP concentration was measured on radioimmunoassay (Shionoria BNP kit; Shionogi & Co., Osaka, Japan).

Parameters	CRT non-responders (n=17)		CRT responders (n=17)	
	Before CRT	After CRT	Before CRT	After CRT
LVEF (%)	25.8±10.6	20.0±8.4*†	23.1±7.9	30.5±8.4*
ΔLVEF (%)		-5.8±7.1†		8.0±10.2
LVDd (mm)	69.5±9.8	72.3±7.8*†	66.8±6.7	63.1±8.0*
LVDs (mm)	60.8±11.4	65.7±8.9*†	58.7±6.4	54.0±7.5*
LVESV (mL)	193.9±77.3	228.9±68.1*†	173.3±60.2	130.0±40.9*
Change in LVESV (%)		24.9±29.2†		-23.4±13.0

Data given as mean±SD. *P<0.05 vs. before CRT, †P<0.05 vs. responders. CRT, cardiac resynchronization therapy; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

Characteristics	CRT non-responders (n=17)	CRT responders (n=17)	P-value
Age (years)	56.9±14.7	61.5±17.1	0.41
Male sex	15 (88)	13 (76)	0.66
Ischemic	11 (65)	10 (59)	0.72
BMI	21.0±3.6	21.0±2.2	0.99
BNP (pg/mL)	428.6±232.7	318.2±197.9	0.15
CVD	2 (12)	1 (6)	0.55
CRT-D	13 (76)	16 (94)	0.34
LVEF (%)	20.0±8.4	30.5±8.4	0.0009
LVDd (mm)	72.3±7.8	63.1±8.0	0.0018
LVDs (mm)	65.7±8.9	54.0±7.5	0.0002
LVESV (mL)	228.9±68.1	130.0±40.9	<0.0001
Medication			
Digitalis	5 (29)	2 (12)	0.20
Diuretic	16 (94)	16 (94)	1.00
ACEI/ARB	9 (56)	10 (59)	0.88
β-blocker	17 (100)	16 (94)	0.31
Inotropic drug	8 (47)	6 (35)	0.73

Data given as mean±SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CRT-D, CRT with a defibrillator; CVD, cerebrovascular disease; ET, exercise training. Other abbreviations as in Table 1.

Physical Performance

Isometric knee extensor muscle strength (IKEMS) was measured using the μ Tas MF-1 assembly (anima Co., Ltd., Tokyo, Japan).¹⁸ In the limb position, 1 end gripped the end of the examination table and the other hand was placed on the examination table. A sensor pad was placed on the distal anterior surface of the lower leg, the length of the belt was adjusted and the belt was fastened to the post of the examining table to keep the lower leg in a vertical position. The testers lightly held the sensor pad in place to prevent it from shifting during measurements. To avoid pain due to compression of the back of the knee, a towel was placed at the same region. The subjects were asked to extend the knee with maximum effort for 5 s while exhaling. Measurements were taken twice for each knee. The maximum for each knee was then averaged (kilogram-force [kgf]) and divided by body weight to derive the percentage/body weight (kgf/kg). IKEMS was measured at the beginning and the end of ET program, and the change in IKEMS was determined as the percentage relative change during the 3-month ET program.

Statistical Analysis

Continuous variables, presented as mean±SD, were compared using unpaired Student's t-test or Wilcoxon rank sum test, and categorical variables were compared using chi-squared test. The Spearman's rank correlation coefficient evaluated the relationship between change in peak $\dot{V}O_2$ and other variables of interest, and a correlation coefficient was expressed. A multiple regression analysis was performed based on variables that were significant on univariate analysis. P<0.05 was considered statistically significant.

Results

Baseline Characteristics

From March 2008 through July 2017, 34 patients met the inclusion criteria, of whom 17 responders (50%) and 17 non-responders (50%) were identified according to the definition of echocardiographic response as either an absolute increase in LVEF $\geq 10\%$ or a relative reduction in LVESV $\geq 10\%$ after CRT implantation. Serial echocardiog-

Parameters	CRT non-responders (n=17)		CRT responders (n=17)	
	Baseline	After ET	Baseline	After ET
ET session attendance (times)	19±10		21±9	
ΔBW (kg)	0.78±2.7		0.46±2.3	
Peak work rate (W)	77.8±31.2	85.5±28.0*	72.5±21.4	79.4±25.5
Peak RER	1.30±0.15	1.30±0.14	1.27±0.10	1.26±0.13
Peak $\dot{V}O_2$ (mL/min)	879.4±367.1	943.2±368.8*	739.2±196.8	813.1±264.2*
Peak $\dot{V}O_2$ (mL/min/kg)	15.0±5.9	15.8±5.3	13.1±2.4	14.1±3.2*
% Predicted peak $\dot{V}O_2$ (%)	49.9±15.9	53.2±16.2	48.3±12.5	52.2±14.4*
Change in peak $\dot{V}O_2$ (%)	9.1±16.4		9.1±15.0	
$\dot{V}E/\dot{V}CO_2$ slope	35.1±7.0	34.4±5.3	38.7±8.2	39.7±9.4
IKEMS (kgf)	28.7±11.7	33.2±12.1*	23.8±7.3	27.3±7.9*
IKEMS/BW (kgf/kg)	49.4±16.6	53.4±16.6	43.6±11.5	47.6±11.9*
Change in IKEMS (%)	18.9±24.2		11.9±12.9	

Data given as mean±SD. *P<0.05 vs. baseline. BW, body weight; CPX, cardiopulmonary exercise test; CRT, cardiac resynchronization therapy; ET, exercise training; IKEMS, isometric knee extensor muscle strength; RER, respiratory exchange ratio; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen uptake.

Variables	Correlation coefficient	P-value
Age (years)	-0.05	0.76
LVEF (%)	-0.21	0.24
LVESV (mL)	0.23	0.20
ΔLVEF (%)	0.02	0.91
ET session attendance (times)	0.59	0.0003
BMI	0.08	0.64
Peak $\dot{V}O_2$ (mL/min)	-0.11	0.52
$\dot{V}E/\dot{V}CO_2$ slope	0.09	0.63
BNP (pg/mL)	0.08	0.63
IKEMS (kgf)	-0.15	0.40
Change in IKEMS (%)	0.66	<0.0001

Abbreviations as in Tables 1–3.

raphy showed an improvement in LVEF and LVESV in responders, and a worsening in LVEF and LVESV in non-responders after CRT implantation (Table 1). Table 2 lists the baseline patient characteristics at the beginning of the ET program (6 months after CRT implantation). Mean patient age for the whole group was 59.2±15.6 years; 82% were men, and the mean LVEF was 25.3%±9.8%. There was no statistically significant difference in age, body mass index, or plasma BNP between the 2 groups, but non-responders had significantly lower LVEF and larger LVDD, LVDs and LVESV than responders. The use of cardioverter defibrillator capacity (CRT-D) was similar in the 2 groups (94% in responders and 76% in non-responders, P=0.34).

Change in Major Variables During the 3-Month ET Program

The number of attendances at the supervised in-hospital ET sessions during the 3-month ET program was similar in the 2 groups. At baseline, there was no difference in peak $\dot{V}O_2$ or IKEMS between the 2 groups. Table 3 lists the major variables before and after the 3-month ET program. Peak $\dot{V}O_2$ (mL/min) and IKEMS (kgf) had a significant

improvement during the ET program in both groups. Peak $\dot{V}O_2$ (mL/min/kg), % predicted peak $\dot{V}O_2$ (%) and IKEMS (kgf/kg) were significantly improved only in responders, but not in non-responders, because of the greater increase in body weight during the ET program in non-responders than responders (0.78 kg vs. 0.46 kg, respectively). There was no significant difference in change in peak $\dot{V}O_2$ between non-responders and responders (both 9.1%) or change in IKEMS (18.9% vs. 11.9%, respectively).

Predictors of Change in Peak $\dot{V}O_2$ During the ET Program

The association between the percentage change in peak $\dot{V}O_2$ and clinical variables in all patients is given in Table 4. The percentage change in peak $\dot{V}O_2$ was significantly related to the number of ET sessions (R=0.59; P=0.0003) and to the percentage change in IKEMS (R=0.66; P<0.0001). On multiple regression analysis (Table 5), the percentage change in IKEMS was an independent predictor of the percentage change in peak $\dot{V}O_2$, whereas the response to CRT was not. Even in non-responders alone, the association between change in peak $\dot{V}O_2$ and change in IKEMS was significant (R=0.82; P<0.0001; Figure 2).

Exercise-Related Adverse Events

During the 3-month ET program, there was no exercise-related adverse event, such as ventricular tachycardia, ventricular fibrillation, occurrence of cardioverter defibrillator therapy (antitachycardia pacing or shocks), lead dislocation, deterioration of surgical wound site, or malfunction of CRT in either the responder or the non-responder group.

Discussion

CRT confers a survival benefit and reduces HF hospitalizations in drug-refractory HF with reduced LVEF and ventricular dyssynchrony, but not all patients have a positive CRT response. In the present study, we divided patients who participated in 3-month ET program at 6 months after CRT implantation into 2 groups based on the echocardiographic response criteria and compared the effect of ET program in non-responders vs. responders. Although non-responders had significantly lower LVEF

Table 5. Multivariate Indicators of Change in Peak $\dot{V}O_2$ During ET in All Patients

Variables	β	t	P-value	95% CI
ET session attendance (times)	0.31	1.94	0.0638	-0.03 to 0.98
CRT response	-0.10	-0.68	0.50	-6.01 to 3.04
Change in IKEMS (%)	0.58	3.77	0.0009	0.19 to 0.66

Analysis of variance, $P < 0.0001$, $R^2 = 0.59$, adjusted $R^2 = 0.54$. β , standardized partial regression coefficient. Abbreviations as in Tables 1,3.

and larger LV size than responders at baseline, peak $\dot{V}O_2$ and IKEMS were significantly improved in both groups during the 3-month ET program, and there was no significant between-group difference in change in peak $\dot{V}O_2$ or change in IKEMS. Furthermore, no exercise-related adverse event such as life-threatening ventricular arrhythmia or cardioverter defibrillator therapy occurred in either group. To the best of our knowledge, this is the first study to show the efficacy and safety of an ET program in patients who did not respond to CRT implantation.

Patwala et al showed that CRT implantation improved exercise capacity during the first 3 months, accompanied by significant LV reverse remodeling such as a reduction in LV diameter and an increase in LVEF, but not by improvement of lower limb muscle strength.¹² During a subsequent 3-month period, they showed that the ET program led to further improvement in exercise capacity accompanied by improvement of skeletal muscle performance, but not by significant reduction in LV diameter.¹² This suggests that the improvement in peak $\dot{V}O_2$ is due to a combined improvement in cardiac function (central mechanism) and peripheral oxygen extraction (peripheral mechanism) and that a cumulative benefit can be derived from the combination of CRT implantation and ET.

Echocardiographic non-responders, compared with responders, have poor improvement in peak $\dot{V}O_2$ after CRT implantation,^{13,14} suggesting that non-responders have poor cardiac effects on exercise capacity. The present study has shown that echocardiographic non-responders had a significant improvement in peak $\dot{V}O_2$ during ET program and that changes in peak $\dot{V}O_2$ had a significant correlation with changes in IKEMS. Taken together, this suggests that even in non-responders with poor cardiac effects on exercise capacity, ET program improves exercise capacity, which is more likely due to a peripheral mechanism.

The proportion of CRT responders in this study (50%) was lower than that in some other studies (54–62%).^{6,7,13,14} LV reverse remodeling after CRT was reported to occur as early as 3 months, to be more pronounced at 6 months, and to continue by 12 months in some patients.^{19,20} In the present study, response to CRT was determined based on echocardiographic changes during 6 months after CRT (mean, 6.8 months). Therefore, the relatively short duration between paired echocardiograms in the present study may have resulted in the low proportion of CRT responders. Although a longer duration between paired echocardiograms would have allowed full LV reverse remodeling, it would have led to a decrease in the total number of study patients because most patients participated in the ET program early after CRT implantation based on current guidelines.

On multiple regression analysis, we observed no significant association between change in peak $\dot{V}O_2$ and the

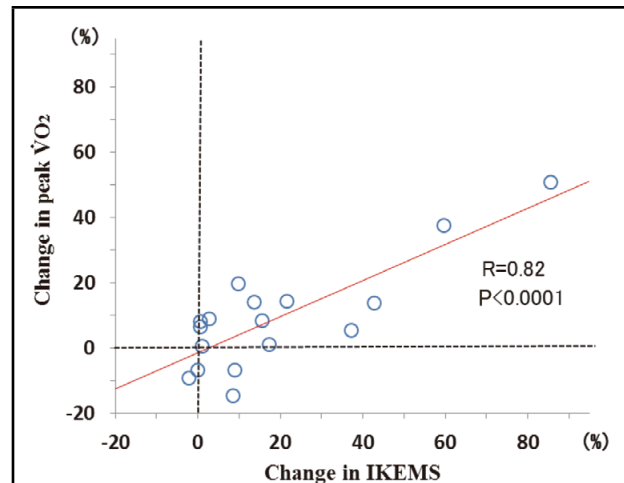


Figure 2. Change in peak oxygen uptake ($\dot{V}O_2$) vs change in isometric knee extensor muscle strength (IKEMS) during the exercise training program in non-responders.

number of attendances at supervised ET sessions. This is likely because the effect of the ET program is influenced by the total amount of ET including home ET, which was not assessed in this study. Further studies are needed to determine the most appropriate ET protocol regarding intensity, duration, frequency and modality for achieving the greatest improvement in exercise capacity in this cohort.

Study Limitations

This study has some limitations. First, it was a retrospective study involving a small number of patients without a control (non-exercise) group at a single institute. Second, a prospective randomized study is essential to clarify the effect of ET programs in HF patients, but it would not be ethical to assign HF patients to a non-ET group at present, when ET for HF patients is recommended in the guidelines. Finally, we studied only those patients who underwent echocardiogram before and after CRT implantation and underwent CPX before and after ET program, which might have resulted in some bias.

Conclusion

The ET program improved exercise capacity in HF patients undergoing CRT implantation without exercise-related adverse event regardless of echocardiographic response to CRT. Also, in non-responders, change in peak $\dot{V}O_2$ had a significant correlation with change in IKEMS, suggesting the important role of peripheral function in the

improvement in exercise capacity. This suggests that even advanced HF patients without echocardiographic response to CRT benefit from ET and should be referred to ET programs.

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Disclosures

The authors declare no conflicts of interest.

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