Depressive symptoms interfere with the improvement of exercise capacity by cardiac rehabilitation after left ventricular assist device implantation

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博士論文

Depressive symptoms interfere with the improvement of exercise capacity by cardiac rehabilitation after left ventricular assist device implantation

（左室補助人工心臓植込後の心臓リハビリテーションによる
運動耐容能向上に対する抑うつ症状の影響）

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Abstract

Background

Although depressive symptoms are associated with an increased risk of readmission after left ventricular assist device (LVAD) implantation, it is unclear whether they affect the efficacy of exercise-based cardiac rehabilitation (EBCR). This study aimed to investigate the effect of depressive symptoms on EBCR efficacy.

Methods

We analyzed 48 patients who participated in EBCR after LVAD implantation (mean age 45±12 years; 60% male). Patients were classified into two groups using the Zung Self-Rating Depression Scale (SDS): depressive group (SDS≥40, n=27) and non-depressive group (SDS<40, n=21). We examined changes in peak oxygen uptake (VO2), knee extensor muscular strength (KEMS), and quality of life (QOL) during EBCR using analysis of covariance.

Results

Although baseline characteristics were similar between the two groups, the non-depressive group was less likely to receive diuretics (22% vs. 52%, p=0.030). Peak VO_2, KEMS, and QOL significantly increased over time in both groups (all $p<0.05$). The depressive group had a significantly lower change in peak VO2 than the non-depressive group (2.7 vs. 1.6 mL/kg/min; mean difference: -1.1 mL/kg/min, 95% confidence interval [CI]: -0.045 – -2.17; p=0.041, d=0.59). There was no between-group difference regarding the change in KEMS or QOL. Adjusting for the baseline value, a significant difference between groups was observed only in peak VO_2 (p=0.045).

Conclusions

Although EBCR significantly improved exercise capacity after LVAD implantation, depressive symptoms interfered with this improvement. Further studies are needed to determine whether psychological interventions for depression, in addition to EBCR, would improve the response to EBCR after LVAD implantation.

Keywords: exercise capacity, depressive symptoms, exercise-based cardiac rehabilitation, left ventricular assist device, peak oxygen uptake

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1. Introduction

Approximately 5% of heart failure (HF) patients reach an end-stage status despite optimal medical and device therapy.[1,2] Left ventricular assist device (LVAD) implantation is an established life-saving therapy, which improves HF symptoms and quality of life (QOL) for end-stage HF patients.[3,4] However, patients often continue to have significant functional limitations even after LVAD implantation,[5,6] and exercise capacity after LVAD implantation has been shown to be associated with mortality.[7] As the waiting period for heart transplantation has been extended in recent years due to the shortage of donor hearts,[8] it is important to improve and maintain exercise capacity after LVAD implantation.

In end-stage HF patients, depressive symptoms are common and associated with poor physical functioning and worse outcomes.[9,10] Although LVAD implantation typically improves depression,[11] approximately 30–40% of patients remain depressive after 3 months of LVAD implantation.[12] Further, depression has been reported to be associated with an increased risk of readmission.[13]

Although exercise-based cardiac rehabilitation (EBCR) has been shown to improve exercise capacity and QOL in LVAD patients,[14-16] it is unclear whether depressive symptoms affect the efficacy of EBCR after LVAD implantation. This study aimed to examine the influence of depressive symptoms on the improvement in exercise capacity, muscle strength, and QOL by EBCR after LVAD implantation.

2. Methods

2.1 Study design and population

In this retrospective observational study, we retrospectively analyzed prospectively collected data (as a routine practice) of 87 consecutive patients ≥18 years of age who underwent continuous-flow LVAD implantation as a bridge to transplantation between March 2016 to February 2020 at our institution. Of these patients, those who participated in the EBCR program and underwent assessments, including cardiopulmonary exercise testing (CPET) at EBCR initiation (baseline) and at the 3-month follow-up, were included. Patients were excluded from the study if they could not perform CPET due to medical and/or physical limitations. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee of National Cerebral and Cardiovascular Center (M26-015-5). Written informed consent was obtained from all patients.

The flow chart for the study design is shown in Fig. 1. Of the 87 HF patients who underwent continuous-flow LVAD implantation as a bridge to transplantation, 69 HF patients met the inclusion criteria. Of these, 21 patients were excluded from the analysis due to loss to follow-up (n=15), complications of cerebrovascular disease (n=3), driveline exit-site infection (n=1), arrhythmia (n=1), and inappropriate measurement (n=1). The 48 remaining study patients were classified into either the depressive group, with Zung Self-Rating Depression Scale (SDS) ≥40 (n=27), or the non-depressive group, with SDS <40 (n=21).

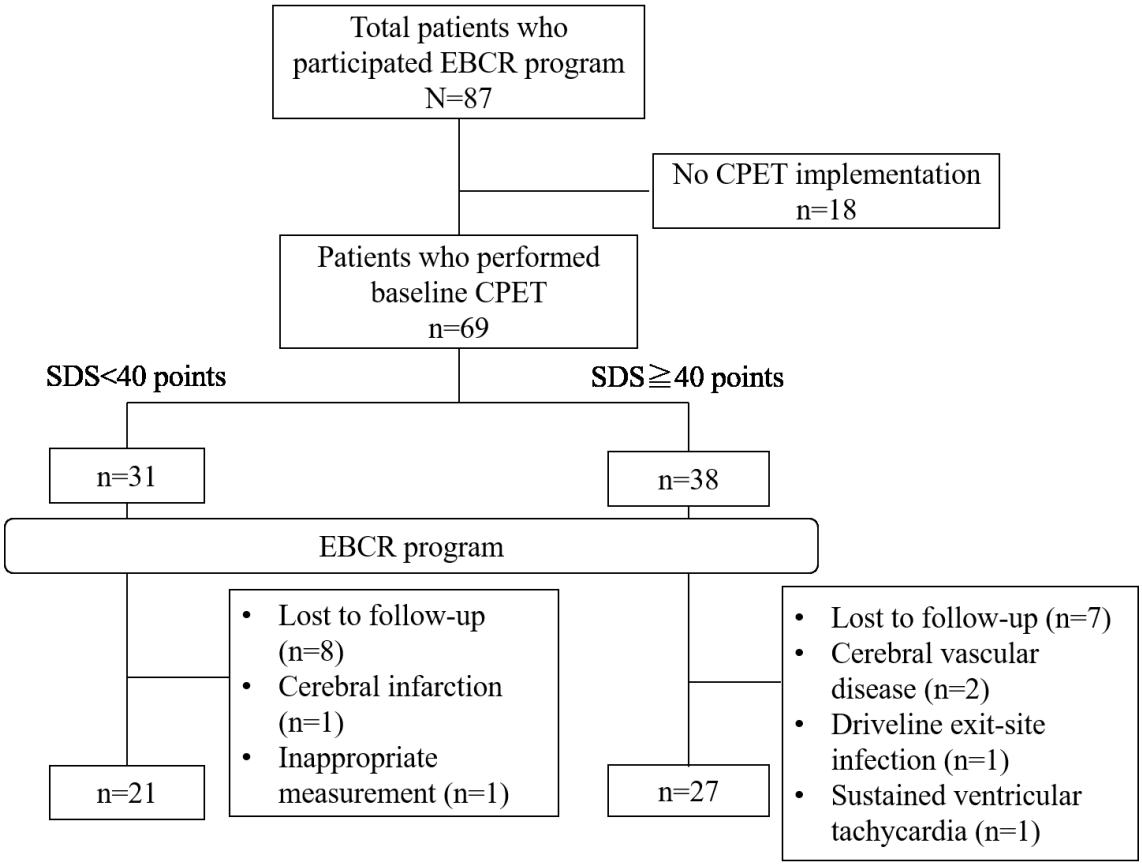

Fig. 1. Flow chart of patients through the study.

EBCR, exercise-based cardiac rehabilitation; CPET, cardiopulmonary exercise test; SDS, Self-Rating Depression Scale

2.2 Demographic and clinical variables

We obtained demographic and clinical variables from clinical records. Demographic variables of interest included age, sex, body mass index (BMI), and smoking history. Comorbidities included hypertension, dyslipidemia, and diabetes. Left ventricular ejection fraction (LVEF) was measured by echocardiography using the modified Simpson's method. We investigated cardiac index, pulmonary artery wedge pressure, mean pulmonary artery pressure, and right ventricular stroke work index[17] based on the results of right heart catheterization after LVAD implantation. Clinical variables of

interest included preoperative Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) profile,[18] preoperative number of admissions, type of cardiomyopathy (ischemic vs. nonischemic), LVAD device type (HeartMate II™ [Abbott Laboratories, Abbott Park, IL, USA], HeartMate 3™ [Abbott Laboratories], or HeartWare™ HVAD™ [Medtronic, Minneapolis, MN, USA]), medication, duration between LVAD surgery and the start of the EBCR program, and the number of attendances at EBCR sessions. Blood samples were collected to analyze serum creatinine, hemoglobin, and plasma B-type natriuretic peptide (BNP). We calculated the Controlling Nutritional Status (CONUT) score using serum albumin, lymphocyte count, and total cholesterol to assess nutritional status.[19]

2.3 Depressive symptoms

Depressive symptoms were assessed using SDS, which was designed to provide a quantitative assessment of the subjective experience of depression. The SDS contains 20 items covering affective, psychological, and somatic features of depression. Non-depressed individuals typically score less than 40, while a score of 40 to 80 covers various grades of depressive symptoms.[20] In this study, the standard cut-off points of SDS ≥40 at EBCR initiation (baseline) were used to classify patients as having depressive symptoms.

2.4 Cardiopulmonary exercise test (CPET)

A symptom-limited CPET was performed using a cycle ergometer with respiratory gas exchange monitoring (AE-300S; Minato Medical Science, Osaka, Japan). The CPET involved an initial 2 minutes of rest, 1 minute of warm-up (0-W load), and full

exercise using an individualized ramp protocol, with increments of 10–20 W/min until symptoms limited patient performance. Expired air sampled on a breath-by-breath basis and minute ventilation (VE), oxygen uptake (VO_2), and carbon dioxide production (VCO_2) data were obtained at 6-s intervals throughout the testing duration. Peak VO_2 was identified as the higher value of either the greatest VO_2 during exercise or the average VO_2 of the last three data points (18 s) before the termination of exercise. Percent of predicted peak VO_2 was calculated as peak VO_2 (mL/kg/min) divided by predicted value using the following equations: 52.1 – (0.38 × age [years]) for men; 40.4 – (0.23 × age [years]) for women.[21] The slope of the linear relationship between VE and VCO_2 (VE/VCO_2 slope), an index of ventilatory efficiency, was determined, excluding the part after the respiratory compensation point where the slope started to increase.

2.5 Lower limb muscular strength measurement

Isometric knee extensor muscular strength (KEMS) was determined using a hand-held dynamometer (μ-tas F1; ANIMA, Tokyo, Japan) as a measure of lower limb muscle strength.[22] The measurement was performed twice on both the left and right sides. The highest strength values on the right and left sides were averaged and expressed relative to body weight (kgf/kg).

2.6 Quality of life

QOL was assessed using the 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36). Similarly, we used the physical component summary (PCS) score and mental component summary (MCS) score from the SF-36. The scores were standardized based on the Japanese population to a mean of 50 and a standard deviation

of 10; higher scores indicated a better QOL.[23,24] This questionnaire had been used in previous studies of LVAD patients.[25]

2.7 Exercise-based cardiac rehabilitation (EBCR)

The exercise training consisted of three sessions per week during the hospitalized period supervised by physical therapists. Discharged patients attended at their convenience until 3-months after the initiation of the EBCR program, and the supervised exercise training consisted of aerobic and resistance exercises. Aerobic training consisted of walking and pedaling on a cycle ergometer, and resistance training consisted of three types of exercises: calf raise, half squat, and leg extension. The training intensity was set individually at levels 12 or 13 ("somewhat hard") of the 6–20 scale perceived rating of exercise (original Borg scale).[26] Exercise time started from 30 minutes and gradually increased to 60 minutes according to the patients' conditions. The exercise time, workload on the cycle ergometer, and walking speed reached at the end of the EBCR program were investigated from the medical records.

2.8 Statistical analysis

The normality of continuous variables was evaluated using the Shapiro-Wilk test. Continuous variables are presented as mean and standard deviation or median and interquartile range, whereas categorical variables are expressed as numbers and percentages. We compared each variable according to depressive symptoms (i.e., depressive group and non-depressive group) using Student's t-test or the Wilcoxon rank-sum test for continuous variables as appropriate; the chi-square test was used for categorical variables. The effect size between the depressive and non-depressive groups

was calculated for peak VO_2 using Cohen's d. Analysis of covariance was performed, after controlling for baseline values of the dependent variables, to investigate the differences between baseline and follow-up.[27] A value of $p<0.05$ was considered statistically significant, and all statistical analyses were performed using JMP for Macintosh (Version 14.2; SAS Institute Inc., Cary, NC, USA).

3. Results

Baseline characteristics of the LVAD patients are shown in Table 1. The mean age was 45 ± 12 years, and 60.4% were male. There were no significant differences between the two groups in baseline characteristics, except for a lower proportion of patients receiving diuretics in the depressive group (22% vs. 52%, $p=0.030$).

Table 1. Demographic and clinical characteristics of the study population

	All(n=48)	Non-depressive (n=21)	Depressive (n=27)	*p*-value
Age (years) *	45±12	42±10	48±13	0.055
Sex (male) ‡	29 (60)	12 (57)	17 (63)	0.68
BMI (kg/m^2) *	19.2±3.0	19.9±3.0	18.7±3.1	0.16
Smoking history ‡	21 (44)	8 (38)	13 (48)	0.49
LVEF (%) †	15 [10, 19]	15 [10, 15]	15 [10, 20]	0.33
Cardiac Index (L/min/m^2)	2.8±0.6	2.8±0.6	2.8±0.6	0.86
PAWP (mmHg)	4 [3, 6.75]	4 [3.5, 7]	4 [2,7]	0.89
Mean PAP (mmHg)	14 [10, 16]	14 [11, 16]	12 [10, 17]	0.93
RVSWI (mmHg • mL/m^2)	256.7 [199.8,371.2]	284.6 [216.8, 401.8]	233.4 [152.2, 369.7]	0.12
INTERMACS profile ‡				0.82
1	12 (25)	5 (24)	7 (26)	
2	12 (25)	4 (19)	8 (30)	

3	20 (42)	10 (48)	10 (37)	
4	4 (8)	2 (9)	2 (7)	
LVAD type ‡				0.27
HeartMate II™	32 (68)	15 (71)	17 (65)	
HeartMate 3™	6 (13)	1 (5)	5 (19)	
HeartWare™ HVAD™	9 (19)	5 (24)	4 (15)	
Ischemic cardiomyopathy ‡	5 (11)	2 (10)	3 (11)	0.86
Preoperative number of admissions (times) †	2 [1, 4]	3 [1.5, 4.5]	2 [1, 4]	0.34
Duration from surgery to EBCR (days) †	31 [23, 48]	28 [23, 42]	33 [23, 52]	0.28
β-blocker ‡	47 (98)	21 (100)	25 (96)	0.28
ACE-I ‡	29 (60)	13 (62)	16 (59)	0.85
ARB ‡	12 (25)	4 (19)	8 (30)	0.40
MRA ‡	43 (90)	19 (91)	24 (89)	0.86
Diuretics ‡	17 (35)	11 (52)	6 (22)	0.030
PDE5-I ‡	8 (17)	3 (14)	5 (19)	0.69

CCB ‡	11 (23)	5 (24)	6 (22)	0.90
Antiarrhythmic drugs ‡	9 (19)	4 (19)	5 (19)	0.96
Hypertension ‡	5 (10)	2 (10)	3 (11)	0.86
Dyslipidemia ‡	14 (29)	4 (19)	10 (37)	0.17
Diabetes ‡	9 (19)	4 (19)	5 (19)	0.97
BNP (pg/mL) †	123 [64, 197]	138 [70, 231]	118 [60, 170]	0.25
Hemoglobin (g/dL) *	10.1±1.2	9.8±1.2	10.4±1.1	0.085
Creatinine (mg/dL) †	0.63 [0.55, 0.81]	0.59 [0.54, 0.85]	0.63 [0.55, 0.78]	0.51
Albumin (g/dL) *	3.5±0.4	3.4±0.4	3.5±0.4	0.26
Lymphocyte Count*	1172±452	1084±317	1239±530	0.24
Total cholesterol (mg/dL) *	160±30	158±27	162±33	0.64
CONUT score †	4 [2, 5]	5 [3, 6]	4 [2, 5]	0.24

* Independent t-test; † Wilcoxon rank-sum test; ‡ chi-square test

Variables are expressed as mean ± standard deviation, median [interquartile range] or number of patients (%)

BMI, body mass index; LVEF, left ventricular ejection fraction; PAWP, pulmonary artery wedge pressure; PAP, pulmonary artery pressure; RVSWI, right ventricular stroke work index; INTERMACS, Interagency Registry of Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; EBCR, exercise-based cardiac rehabilitation; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; PDE5-I, phosphodiesterase type 5 inhibitor; CCB, calcium channel blocker; BNP, B-type natriuretic peptide; CONUT, Controlling Nutritional Status

The EBCR program was initiated at a median period of 31 days after LVAD implantation. The numbers of attendances at EBCR sessions were similar between the two groups (depressive group, 23±11 vs. non-depressive group, 22±11; p=0.64). However, the depressive group had a significantly shorter exercise time (40 [40, 35] vs. 40 [40, 40] min, p=0.042), lower walking speed (65 [61, 71] vs. 75 [64, 82] m/min, p=0.0096), and lower workload on the cycle ergometer (28 [20, 37] vs. 36 [30, 47] W, p=0.014) than the non-depressive group.

Peak VO_2 was significantly improved in both groups; however, the depressive group had a significantly lower change in peak VO_2 than the non-depressive group (1.6 vs. 2.7 mL/kg/min, respectively) with a mean difference of -1.1 mL/kg/min (95% confidence interval [CI]: -0.045 – -2.17, p=0.041, d=0.59; Fig. 2).

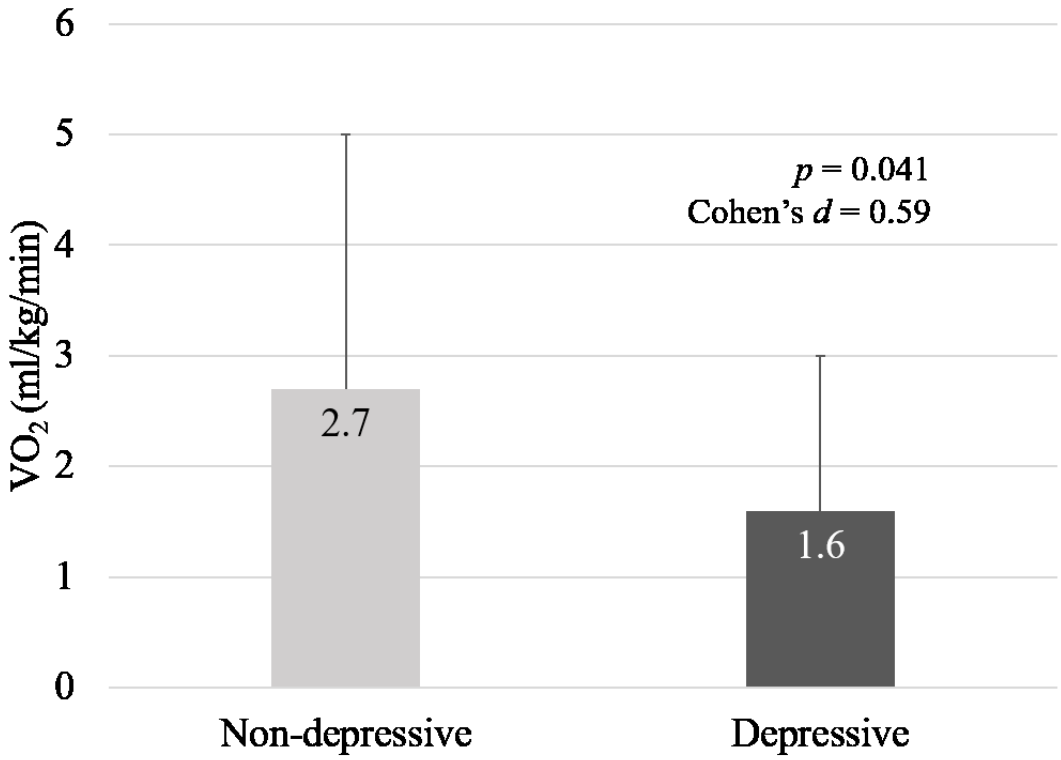

Fig. 2. Change in peak oxygen uptake (VO_2) during the EBCR program

EBCR, exercise-based cardiac rehabilitation

Additionally, VE/VCO_2 slope, KEMS, and PCS score were significantly improved in both groups, and there were no between-group differences with respect to changes in these variables.

In the depressive group, SDS was significantly decreased (Table 2), and as a result, 11 patients (41%) had SDS <40 at 3-month follow-up. According to the analysis of variance, a significant difference between the two groups was only detected for improvement in peak VO_2 (p=0.045; Table 2).

Table 2. Parameters at baseline and three months according to depression status

	Non-depressive (n=21)		Depressive (n=27)		
	baseline	3 months	baseline	3 months	*p*-value†
Peak RER	1.35±0.16	1.33±0.11	1.35±0.15	1.33±0.15	0.99
Peak VO_2 (mL/kg/min)	13.4±3.5	16.1±4.3*	12.6±2.8	14.2±3.0*	0.045
Peak VO_2 %predicted (%)	39.3±7.8	47.5±8.1*	40.2±9.8	46.5±10.2*	0.37
VE-VCO_2 slope	36.2±7.7	32.4±5.8*	37.3±8.6	33.6±8.7*	0.77
KEMS (kgf/kg)	0.43±0.17	0.60±0.17*	0.40±0.09	0.56±0.13*	0.71
SDS	33.2±4.0	35.2±7.6	47.5±5.2	42.4±8.0*	0.23
PCS score	28.6±11.4	42.1±10.7*	23.8±13.2	34.5±11.7*	0.074
MCS score	59.4±8.2	59.6±6.1	47.3±12.2	53.3±9.4	0.18

Variables are expressed as mean ± standard deviation

* $p<0.01$ for comparison of baseline vs. 3 months within groups using paired t-test

†*p*-value for comparison of non-depressive vs. depressive group using analysis of covariance adjusting for baseline peak VO_2

RER, respiratory exchange ratio; VO_2, oxygen uptake; VE, minute ventilation; VCO_2, carbon dioxide production; KEMS, knee extensor muscular strength; SDS, Self-Rating Depression Scale; PCS, physical component summary; MCS, mental component summary

4. Discussion

The present study demonstrated that although peak VO_2 was significantly improved via EBCR after LVAD implantation, LVAD patients with depressive symptoms had a significantly lower change in peak VO_2 than those without depressive symptoms. To the best of our knowledge, this is the first study to investigate the impact of depressive symptoms on EBCR efficacy after LVAD implantation.

This study found that 56% of patients had depressive symptoms after LVAD implantation, using the cut-off value of SDS ≥40. Therefore, the prevalence of depressive symptoms in this study was higher than that reported in previous studies (26–41%).[28,29] Additionally, contrary to the previous finding that women had a higher prevalence of depressive symptoms than men after LVAD implantation (41% vs. 32%, respectively),[13] no significant change in prevalence was observed between women and men in this study (53% vs. 59%, respectively). The reasons for these differences are unclear; however, possible explanations include differences in patient population, including race or the definition of depressive symptoms among assessment tools.

In this study, the extent of the increase in peak VO_2 was lower in the depressive group than in the non-depressive group. Previous studies observed that patients with severe symptoms of depression regularly exercised less frequently and were less likely to have an intention to exercise regularly.[30,31] Contrary to the previous studies, we observed that although the frequency of attendance at supervised EBCR sessions was similar in both groups, the depressive group had a lower amount and intensity of exercise training than the non-depressive group. These findings suggest that lack of motivation in the depressive group negatively influenced the amount and intensity of

supervised exercise training, which may have resulted in the poor improvement in exercise capacity.

The depressive group showed a significant improvement in SDS during EBCR; however, approximately 60% of patients remained depressive, suggesting that exercise training alone is insufficient to improve depressive symptoms for LVAD patients. A previous meta-analysis reported that psychological interventions in addition to EBCR had an additional impact on depressive symptoms for patients with coronary artery disease.[32] Furthermore, a multidisciplinary rehabilitation program for LVAD patients that included social workers and clinical psychologists was reported to improve depressive symptoms.[33] Nevertheless, further research is needed to evaluate whether improving depressive symptoms using additional treatment and counseling is helpful in enhancing EBCR efficacy after LVAD implantation.

This study has some limitations. First, we only included EBCR participants who could perform CPET, which might have introduced a selection bias. Second, the research was conducted using a small sample size at a single institute. Therefore, multiple comparison adjustments could not be performed. Nevertheless, since there was a difference in peak VO_2 between groups even after adjusting for baseline values, we believe that only minimal adjustments were made. Third, we did not have data on the amount and intensity of non-supervised home exercise performed during the EBCR program, which may have been affected by depressive symptoms. Forth, since this was a retrospective observational study, it might be insufficient to describe the causal relationship between depressive symptoms and peak VO_2. Therefore, it needs to be prospectively examined as a future study.

Finally, 21 patients (30%) eventually dropped out; however, we believe that this did not cause bias in the results, as attrition analysis of patients who dropped out and those who were traceable showed no difference in baseline depressive symptoms (SDS: 41.3 ± 8.5 vs. 41.2 ± 8.5, p=0.98) and peak VO_2 (13.0 ± 3.5 vs. 13.0 ± 3.1 mL/kg/min, p=0.98).

In conclusion, although the EBCR program significantly improved exercise capacity after LVAD implantation, depressive symptoms interfered with the ability of EBCR to improve exercise capacity. Therefore, further studies are needed to determine whether psychological interventions for depression, in addition to EBCR, would improve the response to EBCR after LVAD implantation.

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