Novel Scoring System Using Postoperative Cardiopulmonary Exercise Testing Predicts Future Explantation of Left Ventricular Assist Device

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Background: Although cardiopulmonary exercise (CPX) testing is an established tool for predicting survival in patients with heart failure (HF), its prognostic impact on explantation of left ventricular assist device (LVAD) was unknown.

Methods and Results: We enrolled 33 patients who had undergone implantation of extracorporeal pulsatile flow LVAD and symptom-limited CPX testing at 3 months after operation, and who were followed between 2005 and 2014. Patients who received conversion to continuous flow LVAD were excluded. On Cox regression analysis, E1 (maximum load ≥ 51 W; HR, 27.55), E2 (minute ventilation/carbon dioxide output [$\dot{V}E/\dot{V}CO_2$] slope ≤ 34 ; HR, 16.86), and E3 (peak oxygen consumption [$\dot{V}O_{2p}$] ≥ 12.8 ml $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$; HR, 18.35) significantly predicted explantation expectancy during 2 years after LVAD implantation ($P < 0.05$ for all). Explantation score, the sum of positive E1–3, significantly stratified 2-year cumulative explantation rate into low (0 points), intermediate (1–2 points), and high (3 points) expectancy groups (0%, 29%, and 86%, respectively, $P < 0.001$). When the scoring system was used for 45 patients with continuous flow LVAD, the 2 patients who had explantation were assigned to the high expectancy group.

Conclusions: Explantation score, calculated simply from 3 postoperative symptom-limited CPX testing parameters, is a novel tool to predict explantation expectancy of LVAD and to select good candidates for the weaning test. (*Circ J* 2015; **79**: 560–566)

Key Words: Oxygen consumption; Predictor; Reverse remodeling; Ventricular assist device

Left ventricular assist device (LVAD) treatment was initially used as a bridge to transplant (BTT) to maintain hemodynamics until heart transplantation.¹ Owing to innovations in device technology, improvement of perioperative management, and optimal patient selection,^{2–5} long-term continuous flow LVAD treatment as destination therapy has become increasingly popular.⁶

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In contrast, some patients experience myocardial recovery under LVAD support and achieve explantation of LVAD, that is, bridge to recovery (BTR).⁷ Some preoperative predictors for myocardial recovery have been reported,^{8–14} but none of them was definitive. Weaning test may be the best examination to see if recovery of native heart function is sufficient for explantation. The test, however, has a potential for adverse

events such as cardiogenic shock or thrombus complication, and therefore candidates for the weaning test must be chosen carefully. In this regard, there is an increasing need for non-invasive parameters during the postoperative period to predict the best candidates for the weaning test. Although cardiopulmonary exercise (CPX) testing is a useful tool to determine suitability for weaning, there is no established evidence. In this study, we examined postoperative parameters including CPX testing, and seek predictors of future explantation.

Methods

Patient Selection

A total of 83 consecutive patients with stage D heart failure (HF) had received extracorporeal pulsatile flow (E-PF) LVAD implantation for BTT strategy at University of Tokyo Hospital between March 2003 and August 2014. Of them, those who

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Preoperative parameters including laboratory, echocardiographic, and hemodynamic data were obtained <1 week before operation or initiation of any mechanical support. Demographic, laboratory, and echocardiographic data simultaneous with the first postoperative CPX testing (median, 87 days after operation) were obtained as baseline characteristics. Bisoprolol dose was normalized to approximate equivalent dose of carvedilol.¹⁵ To determine the frequency of native aortic valve (AV) opening, we counted the number of native AV openings per native heart rate (HR) for 1 min.¹⁶ We defined native AV opening per native HR $\geq 30\%$ as “opening”. The endpoint was explantation of LVAD within 2 years.

Symptom-limited CPX testing with a cycle ergometer was performed using a ventilator expired gas analyzer (AE-300S; Minato Igaku, Osaka, Japan). The result of the first CPX testing was used when patients underwent examination several times. All patients started at 20 W for a 4-min warm-up, followed by a 10-W/min ramp increment protocol. Data for oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$) were acquired continuously during the test on a breath-by-breath basis. Peak $\dot{V}O_2$ ($P\dot{V}O_2$) was defined

	n=33
Demographic parameters	
Age (years)	35±12
Male	26 (79)
BMI	18.6±3.1
Time from LVAD implantation (days)*	87 (34–352)
Ischemic etiology	7 (21)

Data given as n (%), mean $\pm$ SD or median (range). [†]At first CPX testing after LVAD implantation. [‡]From LVAD implantation to the first CPX testing. ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; CPX, cardiopulmonary exercise; HR, heart rate; HRR-2, HR recovery during 2-min recovery time; LVAD, left ventricular (LV) assist device; LVd, LV diastolic diameter; LVEF, LV ejection fraction; $\dot{V}O_2$, peak oxygen consumption; $\dot{V}CO_2$, carbon dioxide output; VE, minute ventilation.

Explantation Criteria

When patients were deemed to be potential candidates for LVAD weaning, the off test was performed with hemodynamic study for 10 min by stopping E-PF LVAD support, accompanied by successive volume challenge test with 10 ml/kg saline i.v. infusion for 15 min as reported previously.^{14,18} As for I-CF LVAD, the pump down test, in which rotation speed was reduced as low as possible, was carried out with hemodynamic and echocardiographic study followed by the same volume challenge test. When the results met all of the following conditions

Figure 2. Changes in hemodynamic and echocardiographic variables during weaning test. * $P<0.05$ (paired t-test) compared with VAD-OFF. CI, cardiac index; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; mRAP, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure; VAD, ventricular assist device.

Table 2. Change in CPX Variables in Explanation Patients (n=8)

	First CPX	Last CPX	P-value
Baseline HR (beats/min)	85±8	82±8	0.001*
Maximum HR (beats/min)	122±18	127±25	0.018*
Load (W)	77±24	107±22	<0.001*
$\dot{V}E/\dot{V}CO_2$ slope	31±9	26±3	<0.001*
$P\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	15.4±2.3	19.2±3.4	<0.001*
$\dot{V}O_2$ /load slope	7.5±2.4	8.2±1.2	0.068
HRR-2 (beats/min)	16±11	18±13	0.076

Data given as mean±SD. * $P<0.05$ (paired t-test). Abbreviations as in Table 1.

(or all except for one condition): pulmonary capillary wedge pressure (PCWP) <15 mmHg and mean right atrial pressure (mRAP) <10 mmHg, cardiac index $\geq 2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, and preservation of LV ejection fraction (LVEF) $\geq 30\%$ under reduced VAD flow, and increases in cardiac output $\geq 0.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ during saline infusion test, the patients were scheduled for explantation.^{11,14}

Statistical Analysis

All statistical analysis was performed using PASW Statistics 18 (SPSS, Chicago, IL, USA). Categorical variables are expressed as frequencies and percentages, and were compared using the chi-squared test or Fisher's exact test as appropriate. Continuous variables are summarized as mean±SD unless otherwise specified, and compared using unpaired t-test or Mann-Whitney U-test as appropriate. Each variable during the

weaning test was compared using paired t-test. Univariate analysis with Cox regression model was carried out for the baseline parameters to identify predictors of future explantation. Receiver operating characteristic (ROC) analysis was used to obtain cut-off points of each CPX parameter for achievement of the endpoint. Kaplan-Meier analysis of 2-year cumulative explantation rate was done for each group stratified by score. Multicollinearity for each variable that was significant on univariate analysis was analyzed by calculating variance inflation factors.

Results

Baseline Characteristics

In total, 33 patients (mean age, 35±12 years; 79% male) underwent CPX testing at a median of 87 days for the first time after

Table 3. Preoperative Predictors of Future LVAD Explantation

Preoperative parameters	Explantation (n=8)	Non-explantation (n=25)	P-value	Hazard ratio	95% CI
INTERMACS profile					
Profile 1	4 (50)	15 (60)	0.680	1.339	0.335–5.355
Profile 2	4 (50)	10 (40)	–	–	–
Laboratory parameters					
Hemoglobin (g/dl)	11.4±1.5	10.7±1.4	0.098	1.546	0.978–2.334
Platelets ($\times 10^3/\mu\text{l}$)	14±10	14±9	0.887	0.994	0.921–1.074
Serum albumin (g/dl)	3.1±0.5	3.3±0.5	0.102	0.217	0.050–1.024
Serum sodium (mEq/L)	136±6	132±6	0.149	1.082	0.972–1.205
Serum creatinine (mg/dl)	1.2±0.4	1.4±0.9	0.465	0.627	0.179–2.192
Serum total bilirubin (mg/dl)	3.7±4.2	2.9±3.0	0.837	1.020	0.845–1.232
Plasma BNP (pg/ml)	995±822	1240±1024	0.398	1.000	0.999–1.001
Echocardiographic parameters					
LVDd (mm)	69±10	67±12	0.645	1.014	0.957–1.074
LVEF (%)	19±5	19±12	0.952	0.998	0.937–1.063
Hemodynamic parameters					
mRAP (mmHg)	13±5	11±7	0.464	1.042	0.933–1.164
PCWP (mmHg)	28±7	24±9	0.490	1.031	0.945–1.124
Cardiac index ($\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)	2.0±0.5	1.9±0.4	0.791	1.335	0.157–11.33
RVSWI (g/m^2)	6.1±3.1	5.7±3.1	0.641	1.083	0.774–1.515

Data given as n (%) or mean±SD. * $P<0.05$ (Cox regression). INTERMACS, interagency registry for mechanical assisted circulatory support; mRAP, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure; RVSWI, right ventricular stroke work index. Other abbreviations as in Table 1.

LVAD implantation (Table 1). Achieved maximum load was 46 ± 25 W, and HR increased from 84 ± 14 to 114 ± 18 beats/min during the exercise. No patients experienced adverse events during CPX testing, and all patients accomplished symptom-limited exercise. Expiratory change ratio was 1.24 ± 0.17 (range, 1.12–1.42), and Borg scale, which indicates objective fatigue and can range from 0 to 20, was 18 ± 2 (range, 17–20).

Changes in Variables at Weaning Test

The LVAD was eventually explanted in 8 patients (24%), and among them 7 patients underwent weaning test (Figure 2). Duration between the first CPX testing and explantation averaged 216 ± 128 days. At weaning test, baseline LVEF and LV diastolic diameter during LVAD support was $36\pm 11\%$ and 59 ± 10 mm, respectively. PCWP and cardiac index were 7 ± 5 mmHg and $2.6\pm 0.3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, respectively. Major hemodynamic and echocardiographic parameters remained unchanged after stopping LVAD, whereas mRAP, PCWP, and cardiac index were increased significantly after saline infusion test ($P<0.01$ for all). CPX testing was also carried out immediately before explantation in the 8 explantation patients (Table 2). $\text{P}\dot{\text{V}}\text{O}_2$, $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope, maximum HR, and load improved significantly compared with that at baseline ($P<0.05$, paired t-test).

Predictors of Future Explantation: Explantation Score

Preoperative variables were not significant predictors of future explantation (Table 3). Among the CPX parameters, (1) higher maximum load; (2) lower $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope; and (3) higher $\text{P}\dot{\text{V}}\text{O}_2$ were significantly associated with future explantation of LVAD on Cox regression analysis ($P<0.05$ for all; Table 4). Among other baseline parameters, higher dose of β -blocker was also a significant predictor of future explantation (Table 4). ROC cut-off points of these conditions were as follows: (1) maximum load, 51 W (area under the curve [AUC], 0.955); (2) $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$

slope, 34 (AUC, 0.789); and (3) $\text{P}\dot{\text{V}}\text{O}_2$, $12.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (AUC, 0.918).

Explantation score (in which 1 point was allocated for each of the following: E1, load ≥ 51 W; E2, $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope ≤ 34 ; E3, $\text{P}\dot{\text{V}}\text{O}_2 \geq 12.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), significantly stratified cumulative explantation rate into 3 groups: low expectancy (0 points); intermediate expectancy (1–2 points), and high expectancy (3 points; $P<0.001$; Figure 3A).

Validation of Explantation Score in I-CF LVAD Patients

We used the scoring system in 45 patients who had undergone CPX testing after implantation of I-CF LVAD, for the validation study. Stratification by explantation score was not statistically significant among the 3 groups, but 2 patients who did have explantation were both assigned to the high expectancy group (Figure 3B).

Discussion

We constructed a novel scoring system, explantation score, to predict 2-year expectancy of explantation, calculated from 3 simple CPX variables obtained at 3 months after E-PF LVAD implantation. The score significantly stratified cumulative explantation rate into 3 groups. Among those with I-CF LVAD, both patients who achieved explantation were assigned to the high expectancy group, although overall stratification did not reach statistical significance.

Preoperative Predictors of Future Explantation

Considering the early studies, patients with non-ischemic etiology, less fibrosis in myocardium, less dilated LV cavity indicating less remodeling, or lower preoperative β -blocker treatment, can expect LV reverse remodeling under LVAD support.^{8–10,14} Definite prediction of explantation without postoperative information, however, is difficult. Preoperative vari-

Table 4. CPX and Other Baseline Predictors of Future LVAD Explantation

	Explantation (n=8)	Non-explantation (n=25)	P-value	Hazard ratio	95% CI
CPX parameters					
Continuous parameters					
Baseline HR (beats/min)	85±8	84±16	0.814	1.006	0.959–1.055
Max HR (beats/min)	122±18	111±20	0.229	1.026	0.984–1.072
Load (W)	77±24	35±17	<0.001*	1.056	1.027–1.085
$\dot{V}E/\dot{V}CO_2$ slope	31±9	45±13	0.023*	0.889	0.820–0.985
% $\dot{V}E/\dot{V}CO_2$ slope (%)	124±25	170±52	0.040*	0.967	0.940–0.999
$\dot{P}VO_2$ (ml·kg ⁻¹ ·min ⁻¹)	15.4±2.3	10.5±2.4	<0.001*	2.037	1.390–2.974
% $\dot{P}VO_2$ (%)	50±7	36±8	0.007*	1.175	1.073–1.285
$\dot{V}O_2$ /load slope	7.5±2.4	6.9±2.9	0.143	1.014	0.986–1.074
HRR-2 (beats/min)	16±11	14±9	0.152	1.012	0.982–1.071
Categorical parameters					
Load ≥51W	7 (88)	2 (8)	0.002*	27.55	3.356–226.1
$\dot{V}E/\dot{V}CO_2$ slope ≤34	7 (88)	5 (20)	0.007*	16.86	2.062–137.8
$\dot{P}VO_2$ ≥12.8 ml·kg ⁻¹ ·min ⁻¹	7 (88)	5 (20)	0.006*	18.35	2.227–151.0
Explantation score	2.6±0.7	0.5±0.7	0.001*	11.10	2.777–44.36
Other parameters					
Demographic parameters					
Age (years)	32±13	37±13	0.300	0.969	0.915–1.028
Male	7 (88)	19 (76)	0.410	1.193	0.782–1.823
BMI	20.8±2.7	18.5±3.2	0.410	1.194	0.786–1.824
Time from LVAD implantation (days)	81 (34–144)	99 (39–352)	0.285	0.991	0.976–1.008
Ischemic etiology	0 (0)	7 (28)	0.326	0.032	0.001–30.77
Medications					
β-blocker (mg)	48.4±23.9	28.8±17.2	0.028*	1.034	1.004–1.068
ACEI (mg)	3.1±2.2	2.7±1.5	0.376	1.200	0.805–1.794
Aldosterone antagonist (mg)	31±22	34±19	0.708	0.993	0.953–1.029
Laboratory parameters					
Hemoglobin (g/dl)	11.4±1.7	11.8±1.3	0.858	0.955	0.584–1.568
Platelets (×10 ³ /μl)	25±7	22±6	0.229	1.067	0.962–1.187
Serum sodium (mEq/L)	139±2	138±3	0.254	1.275	0.943–1.723
Serum creatinine (mg/dl)	0.8±0.3	0.8±0.3	0.829	0.757	0.065–9.225
Serum total bilirubin (mg/dl)	0.9±0.2	0.8±0.6	0.996	0.998	0.263–3.789
Plasma BNP (pg/ml)	84±44	136±98	0.187	0.993	0.982–1.004
Echocardiographic parameters					
LVDd (mm)	58±11	51±10	0.099	1.067	0.990–1.139
LVEF (%)	35±9	27±11	0.098	1.088	0.994–1.179
Opening of native aortic valve	8 (100)	6 (24)	0.124	131.8	0.291–596.4

Data given as n (%), mean±SD or median (range). *P<0.05 (Cox regression analysis). Abbreviations as in Table 1.

ables were consistently not significant predictors of future explantation, probably because these variables were improved by LVAD support at least in patients who could undergo CPX testing, irrespective of preoperative condition. Explantation of LVAD was limited among patients with non-ischemic cardiomyopathy, but ischemic etiology was not a significant predictor of explantation in this study, probably because of the small sample size.

Postoperative Predictors of Future Explantation

The best available examination to decide explantation is the weaning test thus far.¹¹ Because the test has a risk for hemodynamic deterioration or thrombus complication, optimal selection of candidates for the test is desired. Although early authors proposed several non-invasive parameters for LV reverse remodeling (ie, opening of native AV, decrease in B-type

natriuretic peptide, or increased LVEF^{11,14,16,19,20}), such parameters were not significant predictors of explantation in the present study. These variables seemed to be necessary, but not sufficient for future explantation.

Construction of Explantation Score

We constructed a novel scoring system, explantation score, consisting solely of 3 CPX predictors of future explantation among E-PF LVAD patients. This simple scoring system clearly stratified expectancy of future explantation. Assessing cardiac function during exercise would be more reasonable to understand native heart function than that at rest because LVAD flow does not increase sufficiently to support cardiac output during exercise.²¹ Patients assigned to the high expectancy group may be good candidates for the weaning test. In contrast, CPX testing during LVAD support would not be so risky for such patients,

Explanation Score

E1: LOAD ≥ 51 W : 1 point
 E2: $\text{PVO}_2 \geq 12.8$ mL/kg/min : 1 point
 E3: VE/VCO_2 Slope ≤ 34 : 1 point

Figure 3. Two-year cumulative explantation rate stratified by explanation score for (A) extracorporeal pulsatile flow (E-PF) and (B) implantable continuous flow (I-CF) left ventricular assist device (LVAD). CPX, cardiopulmonary exercise; PVO_2 , peak oxygen consumption; VCO_2 , carbon dioxide output; VE, minute ventilation.

because patients with relatively preserved exercise tolerability engage in cardiac rehabilitation with ergometer in general. Higher dose of β -blocker was also a significant variable in Cox regression analysis, probably because the attending physicians titrated β -blocker targeting LV reverse remodeling along with improved exercise tolerability.²²

The timing of the first CPX testing (approximately 3 months) had an advantage for considering conversion to I-CF LVAD. The conversion should be considered approximately by 3–6 months after E-PF LVAD implantation only in patients with low-intermediate expectancy of explantation. The longer waiting duration with E-PF LVAD has a higher risk of exit site infection,²³ and such patients may lose the chance of conversion. The present novel scoring system calculated at 3 months would indicate clearly which strategy to choose: BTB or BTR. Patients with high expectancy had better indications for the weaning test, whereas conversion to I-CF LVAD should be considered in those with low expectancy.

Although there were no studies demonstrating cut-offs for CPX parameters to predict explantation, at most $\text{PVO}_2 \geq 14$ mL $\cdot$ kg⁻¹ $\cdot$ min⁻¹ and VE/VCO_2 slope ≤ 34 were required, considering post-explantation prognosis.²⁴ The present cut-offs of E2 ($\text{PVO}_2 \geq 12.8$ mL $\cdot$ min⁻¹ $\cdot$ kg⁻¹) and E3 (VE/VCO_2 slope ≤ 34) are almost identical. Requirement of maximum load (E3: maximum load ≥ 51 W) for future explantation may result from improvement of skeletal muscle function and enhancement of oxidative muscle metabolism by sufficient systemic circulation.²⁵ These cut-offs were obtained from the first CPX testing after LVAD implantation, and duration between the first CPX testing and explantation averaged 216 ± 128 days. These CPX

parameters had increased consistently immediately before explantation.

Validation in Patients With I-CF LVAD

The score could not stratify cumulative explantation rate among patients with I-CF LVAD, probably because only 2 patients underwent explantation due to device-specific difficulty in explantation. Pump down test is insufficient to check native cardiac function compared with pump off test during E-PF LVAD, thereby also adding to the difficulty in explantation. Using the score, patients assigned to the high expectancy group may be identified as good candidates for explantation of I-CF LVAD.

Study Limitations

First, the present study was performed in a small sample at a single center. The 2-year duration of the study may be relatively long, but the longest duration between the first CPX testing and explantation was 428 days. Moreover, postoperative management or weaning protocol may vary in each institute. A definite protocol for weaning would be useful in future studies.

Second, we could not construct appropriate multivariate models, probably because of the small sample size and mild multicollinearity: the variance inflation factor for PVO_2 , VE/VCO_2 slope, and maximum load for explantation was 3.52, 2.30, and 2.84, respectively.

Third, we constructed the scoring system only from clinical data in patients with E-PF LVAD. We did not include I-CF LVAD patients because of device-related differences in mortality and explantation expectancy.²⁶

Fourth, the explantation score cannot be used in patients with lower exercise capacity who cannot undertake CPX testing. Such patients, however, would be too sick to be considered for explantation.

Fifth, we could not measure echocardiographic parameters indicating right ventricular function such as tricuspid annular plane systolic excursion or right ventricular fractional area change preoperatively because of the patients' severe systemic condition before the operation. We calculated instead right ventricular stroke work index to assess right ventricular function preoperatively.

Sixth, we did not perform the weaning test in all patients under LVAD support. Therefore, the non-explantation group may have included patients whose LVAD could be potentially explanted. The attending physicians, however, repeatedly considered and discussed the results of routine examinations including CPX testing, with regard to potential for explantation.

Seventh, we used the results of the first CPX testing to construct explantation score, and the score predicts expectancy of explantation. Each CPX parameter had consistently improved immediately before the explantation, therefore, each cut-off in the scoring system does not represent the threshold for explantation.

Conclusions

Explantation score, calculated using postoperative symptom-limited CPX testing parameters, is a novel tool to predict 2-year explantation expectancy after LVAD implantation. All patients should be considered for CPX testing after LVAD implantation if exercise tolerability permits it.

Disclosure

None.

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