Recovery From Exhaustion of the Frank-Starling Mechanism by Mechanical Unloading With a Continuous-Flow Ventricular Assist Device

Shunsuke Saito, MD, PhD; Koichi Toda, MD, PhD; Shigeru Miyagawa, MD, PhD; Yasushi Yoshikawa, MD; Hiroki Hata, MD, PhD; Daisuke Yoshioka, MD, PhD; Fusako Sera, MD; Kei Nakamoto, MD; Takashi Daimon, PhD; Yasushi Sakata, MD, PhD; Yoshiki Sawa, MD, PhD

Background: We describe our original left ventricular assist device (LVAD) speed ramp and volume loading test designed to evaluate native heart function under continuous-flow LVAD support.

Methods and Results: LVAD speed was decreased in 4 stages from the patient's optimal speed to the minimum setting for each device. Under minimal LVAD support, patients were subjected to saline loading (body weight [kg]×10 mL in 15 min). Echocardiographic and hemodynamic data were obtained at each stage of the LVAD speed ramp and every 3 min during saline loading. Patients were divided into Recovery (with successful LVAD removal; n=8) and Non-recovery (others; n=31) groups. During testing, increased pulmonary capillary wedge pressure caused by volume loading was milder in the Recovery than Non-recovery group (repeated measures analysis of variance; group effect, P=0.0069; time effect, P<0.0001; interaction effect, P=0.0173). Increased cardiac output from volume loading was significantly higher in the Recovery than Non-recovery group (group effect, P=0.0124; time effect, P<0.0001; interaction effect, P=0.0091). Therefore, the Frank-Starling curve of the Recovery group was located upward and to the left of that of the Non-recovery group.

Conclusions: The LVAD speed ramp and volume loading test facilitates the precise evaluation of native heart function during continuous-flow LVAD support.

Key Words: Bridge to recovery; Frank-Starling mechanism; Left ventricular assist device

Left ventricular assist devices (LVADs) have become a standard therapeutic option for patients with end-stage heart failure that is refractory to medical therapy.1 During a long period of LVAD support, the risks associated with LVAD therapy are far from negligible.2 Prolonged LVAD support is associated with an increased risk of infection, gastrointestinal bleeding, stroke, and device malfunction. Conversely, it has been well documented that mechanical unloading with an LVAD, along with aggressive medical treatment, can sometimes reverse the process of heart failure to an extent that permits removal of the device.3–10 Considering the risks associated with long-term LVAD support, lifelong immunosuppression, and limited lifespan after heart transplantation, it is obvious that device removal, if feasible, is the best outcome of device implantation.11 However, in the real world, only a small number of patients have an LVAD removed because of cardiac functional recovery.2,12 Obstacles to using an LVAD as a bridge to recovery include the low incidence of cardiac recovery and difficulty in evaluating native heart function under continuous-flow LVAD support.13 Herein we describe our original protocol designed to evaluate the native heart function of patients supported by a continuous-flow LVAD, as an alternative to the “LVAD-off test” in pulsatile LVADs,8,10 with the aim of investigating the predictors of successful LVAD removal.

Methods

Patients
The present retrospective study was approved by the Institutional Review Board of Osaka University, Japan. Written informed consent was obtained from each patient before LVAD implantation and before the LVAD speed ramp and volume loading tests were conducted.
From August 2010 to September 2017, continuous-flow LVADs were implanted in 154 patients at Osaka University Hospital 169 times. All patients underwent an echocardiographic study before hospital discharge, and the LVAD speed was set to allow intermittent aortic valve opening while maintaining a Doppler blood pressure >65 mmHg, middle interventricular septum position, and avoiding more than mild mitral valve regurgitation. After at least 3 months of medical treatment and unloading by the LVAD, the LVAD speed ramp and volume loading test was performed if a patient’s general condition was stable. Patients did not undergo the test and were excluded if they died within 3 months of LVAD implantation (n=10), required mechanical or continuous inotropic right heart support (n=12), were <16 years of age (n=11), underwent aortic valve closure due to significant aortic valve insufficiency (n=9), and had no possibility of LVAD removal (i.e., patients who did not exhibit any reverse remodeling of the heart under LVAD support and had no LVAD-related complications; n=73).

In all, 39 patients underwent the LVAD speed ramp and volume loading testing a total of 46 times and were included in the study (7 patients underwent the test twice). Of the 39 patients, 28 were male, 11 were female, and the mean (±SD) age was 37.2±11.7 years. Eighteen patients were implanted with the HeartMate II (Abbott Laboratories, Lake Bluff, IL, USA), 7 were implanted with the DuraHeart (Terumo Heart, Ann Arbor, MI, USA), 6 were implanted with the Jarvik2000 (Jarvik Heart, New York, NY, USA), another 6 were implanted with the EVAHEART (Sun Medical Technology Research, Nagano, Japan), and 2 were implanted with the HeartWare HVAD (Medtronic, Dublin, Ireland).

**Medication**

Medical treatment for heart failure was initiated as soon as the patient’s general condition was stabilized and organ dysfunction recovered after LVAD implantation. The medication regimen included angiotensin-converting enzyme inhibitors (enalapril, 10 mg/day as tolerated), spironolactone (50 mg/day), and a β-blocker (carvedilol or bisoprolol), which was initiated at a dose of 2.5 mg/day (carvedilol) or 0.625 mg/day (bisoprolol), with the dose doubled every week up to 20–40 mg/day (carvedilol) or 5–10 mg/day (bisoprolol).

**LVAD Speed Ramp and Volume Loading Test**

The protocol for the LVAD speed ramp and volume loading test is shown in Figure 1. Patients were brought to the catheterization laboratory, where an arterial pressure line and a right heart catheter were inserted. The speed of the LVAD pump was gradually decreased in 4 stages from the patient’s baseline setting (R1) down to the minimum setting for each device (R4). Under the lowest pump speed, patients were given a continuous saline injection (body weight [kg]×10 mL in 15 min) and changes in hemodynamic and echocardiographic parameters were recorded. BP, blood pressure; d, diastolic; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; m, mean; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; s, systolic.

![Figure 1. Protocol for the left ventricular assist device (LVAD) speed ramp and volume loading test. The speed of the LVAD pump was reduced from the patient’s baseline setting (R1) down to the minimum setting for each device (R4). Under the lowest pump speed, patients were given a continuous saline injection (body weight [kg]×10 mL in 15 min) and changes in hemodynamic and echocardiographic parameters were recorded. BP, blood pressure; d, diastolic; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; m, mean; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; s, systolic.](image-url)

| LVAD       | Rotational speed (r.p.m.) | R1* | R2  | R3  | R4  |
|------------|---------------------------|-----|-----|-----|-----|
| HeartMate II | 8,700±253                 | 8,000 | 7,000 | 6,000 | |
| Jarvik2000  | 9,571±535                 | 10,000 | 9,000 | 8,000 | |
| HVAD       | 2,570±240                 | 2,200 | 2,000 | 1,800 | |
| DuraHeart  | 1,657±53                 | 1,500 | 1,350 | 1,200 | |
| EVAHEART   | 1,731±75                 | 1,700 | 1,650 | 1,600 | |

*The mean ± SD baseline setting for patients. R2, R3, and R4 are sequentially reduced pump speeds for the ramp test. LVAD, left ventricular assist device.
Criteria for LVAD Removal

The decision to remove the LVAD was made according to a patient’s heart function and clinical indications, such as device infection, cerebrovascular complications, and other LVAD complications that make it difficult to continue LVAD support. The functional recovery criteria used are based on those proposed by the Berlin group, namely LVEDD <55 mm and LVEF >45%. The decision to remove the LVAD was prompted by LVAD-related complications, and some patients underwent LVAD removal even if they did not fulfill the Berlin criteria (Table 2). In contrast, the LVAD was not removed even if a patient

Table 2. List of Patients Who Underwent LVAD Removal and Those Who Did Not Even Though They Fulfilled the Berlin Criteria

| Patient no. | Age (years), sex | LVEDD (mm) | LVEF (%) | ΔSV/ΔPCWP | Clinical indications | LVAD removal | Reason for (not) removing LVAD | Recurrence of HF |
|-------------|-----------------|------------|----------|------------|---------------------|--------------|--------------------------------|-----------------|
| 1           | 33, M           | 50         | 47       | 7.1        | None                | Yes          | Berlin criteria                | No              |
| 2           | 33, M           | 42         | 46       | 8.7        | Cerebral bleeding   | Yes          | Berlin criteria + Clinical requirements | No |
| 3           | 28, M           | 53         | 36       | 4.1        | Driveline infection | Yes          | Clinical requirements          | No              |
| 4           | 39, M           | 47         | 46       | 3.8        | Driveline infection | Yes          | Berlin criteria + Clinical requirements | No |
| 5           | 50, M           | 52         | 45       | 4.1        | Driveline infection | Yes          | Clinical requirements          | No              |
| 6           | 41, M           | 52         | 59       | 7.2        | Pump pocket infection | Yes         | Berlin criteria + Clinical requirements | No |
| 7           | 50, M           | 55         | 70       | 8.7        | Lack of family support | Yes          | Clinical requirements          | No              |
| 8           | 27, M           | 50         | 59       | 8.7        | Pump pocket infection | Yes         | Berlin criteria + Clinical requirements | No |
| 9           | 55, M           | 47         | 49       | 4.0        | Pump pocket infection | Yes          | Berlin criteria + Clinical requirements | Yes |
| 10          | 63, F           | 40         | 61       | 1.4        | None                | No           | Patient’s preference           | –               |
| 11          | 43, M           | 45         | 78       | 2.6        | None                | No           | Patient’s preference           | –               |
| 12          | 36, F           | 32         | 68       | 4.9        | None                | No           | Arhythmia                      | –               |
| 13          | 18, M           | 50         | 55       | –1.9       | None                | No           | Arhythmia                      | –               |
| 14          | 26, M           | 46         | 51       | –1.0       | None                | No           | Patient’s preference           | –               |
| 15          | 44, F           | 48         | 60       | 0.4        | None                | No           | Patient’s preference           | –               |
| 16          | 35, F           | 42         | 53       | –3.4       | None                | No           | Arhythmia                      | –               |

F, female; HF, heart failure; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic dimension (at minimum pump speed); LVEF, left ventricular ejection fraction (at minimum pump speed); M, male; ΔSV/ΔPCWP, ratio of the increase in stroke volume to increase in pulmonary capillary wedge pressure during the LVAD speed ramp and volume loading test.

Table 3. Preoperative and Operative Characteristics of Patients

| Age at LVAD implantation (years) | Recovery group (n=8) | Non-recovery group (n=31) | P-value |
|----------------------------------|----------------------|---------------------------|---------|
| Male sex                         | 36.3±9.2             | 39.6±13.6                 | 0.5136  |
| Body surface area (m²)           | 1.76±0.21            | 1.62±0.21                 | 0.0995  |
| Etiology of heart failure, ischemic | 0 (0)               | 4 (12.9)                  | 0.5628  |
| Duration of heart failure (months) | 6.4±7.1             | 61.2±67.0                 | 0.0285  |
| INTERMACS Profile 1              | 4 (50.0)             | 3 (9.8)                   | 0.0222  |
| Device                           |                      |                           | 0.2697  |
| HeartMate II                    | 4                    | 15                        |         |
| Jarvik2000                      | 0                    | 5                         |         |
| HVAD                            | 0                    | 2                         |         |
| EVAHEART                        | 3                    | 3                         |         |
| DuraHeart                       | 1                    | 6                         |         |

Criteria for LVAD Removal

The decision to remove the LVAD was made according to a patient’s heart function and clinical indications, such as device infection, cerebrovascular complications, and other LVAD complications that make it difficult to continue LVAD support. The functional recovery criteria used are based on those proposed by the Berlin group, namely LVEDD <55 mm and LVEF >45%. The decision to remove the LVAD was prompted by LVAD-related complications, and some patients underwent LVAD removal even if they did not fulfill the Berlin criteria (Table 2). In contrast, the LVAD was not removed even if a patient

unless indicated otherwise, data are given as the mean±SD or n (%). INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device.
fulfilled the Berlin criteria if the indication for LVAD was uncontrollable arrhythmia or the patient had no LVAD-related complications and did not want to have the LVAD removed.

**Statistical Analysis**

Continuous variables are presented as the mean±SD, whereas categorical variables are presented as numbers and proportions. All continuous variables were checked for normal distribution using the Shapiro-Wilk test and a normal probability plot. For univariate analyses, normally distributed variables were compared using Student’s t-tests, whereas non-normally distributed variables were compared using the Mann-Whitney U-test. Categorical variables were compared using Chi-squared analysis or Fisher’s exact test, as appropriate. LVAD speed ramp and volume loading test parameters were analyzed using repeated-measures analysis of variance (ANOVA) with main effects for group and time and their interaction. The optimal cut-off value of the ratio of the increase in stroke volume (SV) to the increase in PCWP during the test (∆SV/∆PCWP) was derived from a receiver operating characteristic curve analysis using Youden’s index.

All P-values are 2-sided and P<0.05 was considered significant. Statistical analyses were performed using JMP Pro 13.0 (SAS Institute, Cary, NC, USA).

**Results**

**LVAD Removal**

Of the 39 patients in the study, the LVAD was removed from 9 patients (Table 2, Patients 1–9). All patients except 1 had a significant clinical indication for LVAD removal, such as device infection, cerebrovascular event, and lack of family support. One patient (Patient 1) underwent LVAD removal because of functional recovery and the patient’s desire to have the device removed even though the patient had no significant device-related complication. Three patients (Patients 3, 5, and 7) underwent LVAD removal for clinical indications even though they did not fulfill the Berlin criteria (LVEDD <55 mm and LVEF >45%). One patient (Patient 9) who had never been free from heart failure symptoms died 247 days after LVAD removal due to heart failure. The remaining 8 patients were free of heart failure recurrence for 38.6±25.7 months (maximum 80 months) after LVAD removal.

In contrast, the LVAD was not removed from 7 patients even though they fulfilled the Berlin criteria (Patients 10–16) because 3 had uncontrollable arrhythmia and the remaining 4 had no LVAD-related complications and did not want to take the risk of removing the LVAD (Table 2).

**Pre-LVAD Patient Characteristics and Operative Procedures**

Patients were divided into 2 groups based on whether the LVAD was removed successfully (Recovery group; n=8) or not (Non-recovery group; n=31), with the latter group including the 1 patient who had a recurrence of heart failure after LVAD removal. Table 3 summarizes patient characteristics before LVAD implantation and the surgical procedures in both groups. All patients in the Recovery group were male, and so tended to have a larger body size than the Non-recovery group, although the difference did not reach statistical significance. There were no patients with ischemic cardiomyopathy in the Recovery group. The duration of heart failure before LVAD implantation was

![Figure 2](image-url) Changes in hemodynamic and echocardiographic data during the left ventricular assist device (LVAD) speed ramp and volume loading test in the Recovery (n=8; red symbols) Non-recovery (n=31; blue symbols) groups: (A) heart rate (HR), (B) pulse pressure (PP), (C) mean pulmonary artery pressure (mPAP), (D) pulmonary capillary wedge pressure (PCWP), (E) right atrial pressure (RAP), (F) cardiac output (CO), (G) left ventricular end-diastolic dimension (LVEDD), (H) left ventricular ejection fraction (LVEF). Data are presented as the mean±SEM, ANOVA, analysis of variance.
Saito S et al.

Non-recovery group. RAP (Figure 2E) increased significantly with time (time effect, $P<0.0001$), but there was no significant difference between the 2 groups. CO (Figure 2F) was significantly higher in the Recovery than Non-recovery group (group effect, $P=0.0124$), and the increase in CO with volume loading was also significantly higher in the Recovery than Non-recovery group (interaction effect, $P=0.0091$). LVEDD (Figure 2G) increased significantly with decreasing LVAD speed and volume loading (time effect, $P<0.0001$), but there was no significant difference between the 2 groups. LVEF (Figure 2H) also increased significantly with time (time effect, $P=0.0229$), and was significantly higher in the Recovery than Non-recovery group (group effect, $P=0.0471$).

LVAD Speed Ramp and Volume Loading Test

Figure 2 shows changes in hemodynamic and echocardiographic data during the LVAD speed ramp and volume loading test. HR (Figure 2A) remained stable during the test, and there was no difference between the 2 groups. Pulse pressure (calculated as systolic arterial pressure minus diastolic arterial pressure; Figure 2B) increased significantly with decreasing LVAD pump speed and volume loading (time effect, $P<0.0001$), and was significantly higher in the Recovery than Non-recovery group (group effect, $P=0.0005$). Mean PAP (Figure 2C) increased significantly with decreasing LVAD pump speed and volume loading (time effect, $P<0.0001$), and was significantly higher in the Non-recovery than Recovery group (group effect, $P=0.0295$). The change in PCWP (Figure 2D) was similar to that in the mean PAP, but the interaction effect was also significant ($P=0.0173$), indicating that the increase in the PCWP with decreasing LVAD pump speed and volume loading was significantly milder in the Recovery group compared with the sharp increase in PCWP in the Non-recovery group. RAP (Figure 2E) increased significantly with time (time effect, $P<0.0001$), but there was no significant difference between the 2 groups. CO (Figure 2F) was significantly higher in the Recovery than Non-recovery group (group effect, $P=0.0124$), and the increase in CO with volume loading was also significantly higher in the Recovery than Non-recovery group (interaction effect, $P=0.0091$). LVEDD (Figure 2G) increased significantly with decreasing LVAD speed and volume loading (time effect, $P<0.0001$), but there was no significant difference between the 2 groups. LVEF (Figure 2H) also increased significantly with time (time effect, $P=0.0229$), and was significantly higher in the Recovery than Non-recovery group (group effect, $P=0.0471$).

Frank-Starling Curves

Based on the results of the LVAD speed ramp and volume loading test, each patient's PCWP and SV (CO/HR) was plotted from the minimum LVAD speed (R4 in Figure 1) to the completion of the volume loading (S15 in Figure 1). As shown in Figure 3, the Frank-Starling curves for the Recovery group were located higher up and to the left of those of the Non-recovery group, with steeper slopes for curves in the Recovery group.

Cut-Off Values for LVAD Removal

To represent the characteristics of the Frank-Starling curve in each patient, the $\Delta$SV/APCWP ratio was calculated. The mean $\Delta$SV/APCWP ratio was significantly higher in the Recovery than Non-recovery group (6.54±2.20 vs. 1.51±2.38 mL/mmHg; $P<0.001$). Receiver operating characteristic curve analysis (Supplementary Figure) revealed that the cut-off value of $\Delta$SV/APCWP for successful LVAD removal was 3.78 mL/mmHg (area under curve 0.94; sensitivity 1.00; specificity 0.81).
Frank-Starling Mechanism in LVAD-Supported Heart

In the present study we describe our original LVAD speed ramp and volume loading test protocol. The purpose of this test is to examine the reaction of the native heart to volume loading under a “near pump-off” status. Because pump stoppage results in backward flow through the pump, we tried to create a “zero-flow” status by minimizing the rotational speed of the pump. Prior studies suggest that a reduction in speed of the HeartMate II device to 6,000 r.p.m. effectively provides an “off-pump” state. Ando et al. studied the characteristics of pump flow through the EVAHEART in a mock circulation and demonstrated that mean pump flow became 0 L/min at a rotational speed between 1,500 and 2,000 r.p.m. under various conditions. The amount of forward flow and backward flow became similar around 1,500 r.p.m. To incorporate a safety margin, we set the lowest pump speed of the EVAHEART at 1,600 r.p.m., which is also the speed recommended by the manufacturer when initiating pump support at the time of LVAD implantation. We could not find similar studies with the other devices, so the minimum pump speed was set to the lowest speed possible for each device (DuraHeart: 1,200 r.p.m.; Jarvik2000: 8,000 r.p.m.; HeartWare HVAD: 1,800 r.p.m.).

The major finding of the present study is that the Frank-Starling mechanism of the heart is significantly exhausted in patients who require LVAD support. An increase in PCWP induced by volume loading under the minimum LVAD pump speed resulted in a blunted increase in SV. Therefore, we further confirmed previous findings suggesting that LVAD therapy improves cardiac function in some patients who had been diagnosed with end-stage heart failure to a level that meant that the patients could live a healthy normal life without LVAD support. In this group of patients, significant recovery of the Frank-Starling mechanism from exhaustion was observed. SV increased sharply in response to the increase in preload, resulting in an upward and leftward shift of the Frank-Starling curve. The frequency of cardiac functional recovery and LVAD removal in the present study was equivalent to reports in previous studies. In the present study, 8 patients were weaned off the LVAD and were free of heart failure recurrence. During the same period, 154 patients underwent LVAD implantation, resulting in a recovery rate of 5.2%. Recently, Wever-Pinzon et al published an analysis of INTERMACS data, including 15,138 patients and confirming the low rate of myocardial recovery for the overall LVAD population (1.3%). Because of the lack of an established bridge-to-recovery program in most LVAD centers, it is likely that the occurrence of cardiac recovery is underestimated. The difficulty in assessing native heart function under continuous-flow LVAD support and the uncertainty of a long-term prognosis after removing the device may also deter an LVAD team from proceeding with device removal. Another important finding in the study of Wever-Pinzon et al was that once a patient was identified as a potential candidate for cardiac recovery by an LVAD team, the incidence of cardiac recovery increased 9-fold. More sophisticated LVAD programs aiming at a bridge-to-recovery strategy are expected to increase the number of candidates for LVAD removal, and newly emerging technologies, such as regenerative medicine, may further increase cardiac recovery. However, before applying such new technologies, a method to precisely evaluate native heart function under continuous LVAD support is needed.
and criteria for safe LVAD removal need to be established.

The Frank-Starling mechanism represents the ability of the heart to adjust its SV in response to preload conditions. This ability is significantly impaired in the failing heart, and is usually represented by the Frank-Starling curve, which represents left ventricular systolic function, arterial elastance, and diastolic function. Gill et al used a canine ischemic heart failure model to examine differences in the Frank-Starling curve between the normal heart and failing heart. These authors created a heart failure model using intracoronary injections of microspheres. Saline was rapidly infused to load the heart with volume. The increases in stroke work and cardiac work in response to the volume loading were plotted, and Gill et al showed that the augmentation of stroke work and cardiac work was significantly more blunted in failing than normal hearts, and called this phenomenon “exhaustion of the Frank-Starling mechanism.”

In the present study, we demonstrated that the Frank-Starling mechanism was “exhausted” in the hearts of the patients who required continued LVAD support. In response to the acute volume challenge, the increase in myocardial contraction and augmentation of left ventricular SV were completely blunted, and the increase in CO was much less than in patients who underwent LVAD removal. In some patients in the Non-recovery group, the SV decreased in reaction to increased PCWP and criteria for safe LVAD removal need to be established. LVAD removal was successful even though they did not fulfill the Berlin criteria (Patients 9–15, Table 2). We believe that removal would not have been successful in those patients, although we cannot prove this without removing the LVAD from the patients. Conversely, in all 3 patients in whom LVAD removal was successful even though they did not fulfill the Berlin criteria, the ΔSV/ΔPCWP was >3.78 (Patients 3, 5, and 7, Table 2).

From the different Frank-Starling curves of the patients in the Recovery and Non-Recovery groups, we can predict the outcome of future LVAD removals (Figure 4). In the LVAD speed ramp and volume loading test, if the PCWP-SV line is located upward and to the left of the Frank Starling curve of the Recovery group and the slope (ΔSV/ΔPCWP) is >3.78 (Case A), native heart function can be considered well recovered. LVAD removal is highly likely to be successful, and aggressive LVAD removal is recommended. If the PCWP-SV line is located downward and to the right of the Frank Starling curve of the Non-recovery group and the slope (ΔSV/ΔPCWP) is <3.78 (Case B), the Frank-Starling mechanism is severely exhausted, the possibility of successful LVAD removal is very low, and LVAD removal is not recommended in such patients. If the slope of the PCWP-SV line is located between the 2 curves (Case C), the decision regarding LVAD removal is difficult. The nearer the line is to the curve of the Recovery group, the higher the possibility of successful removal; further, we found a cut-off value of 3.78 for the slope (ΔSV/ΔPCWP) in the present cohort. The patient in the present study who experienced heart failure recurrence after LVAD removal was in this between-curve, Case C, category. Further data need to be accumulated for clearer criteria regarding eligibility for LVAD removal, and to predict more long-term outcomes following LVAD removal. In this group of patients, we recommend removing the LVAD if the patient has a significant clinical indication for device removal, such as cerebrovascular events or device-related infections, and we recommend against removal if the patient has no device-related complications. The evidence of recovered SV in the Recovery group can also be seen in another finding in the LVAD speed ramp and volume loading test: the higher pulse pressure in the Recovery than Non-recovery group (Figure 2B). Pulse pressure (systolic arterial pressure minus diastolic arterial pressure) represents the ability of the heart to create positive pressure within the left ventricle (i.e., the ability to push open the aortic valve) and is significantly correlated with SV. Frazier et al reported using the aortic valve opening time at 6,000 r.p.m. in patients with the HeartMate II as a surrogate for assessing improvement in native ventricular function. It has also been noted that the ability of the left ventricle to generate sufficient force to open the aortic valve at high LVAD speeds (>10,000 r.p.m. in the HeartMate II) in the setting of clinical stability and the absence of LVAD malfunction may indicate myocardial recovery.

Study Limitations

The present study has several limitations, including those related to it being a single-center retrospective analysis of prospectively gathered information. The number of patients included in the study was relatively low, limiting statistical power. Because of the small number of patients, patients supported by different types of LVADs (i.e., centrifugal and axial flow pumps) were analyzed in the same cohort. Ideally, the Frank-Starling curve should be determined for each device, and the ΔSV/ΔPCWP cut-off value for successful LVAD removal also determined for each device. Another study limitation is the problem of patient selection bias. Patients in whom signs of myocardial recovery during LVAD support were not observed did not undergo the LVAD speed ramp and volume loading test and were excluded. LVAD explantation may have been possible in some patients who were not tested. Patients with severe right heart failure were also considered not to be candidates for LVAD explantation and were excluded. Therefore, changes in RAP by volume loading did not differ between the groups, although right heart function is generally known to be an important factor in evaluating native heart function. Moreover, the criteria for LVAD removal were based not only on a patient’s heart function, but also on clinical conditions. The LVAD was not removed in some patients even though they had adequate functional recovery.

Conclusions

We have demonstrated that our original LVAD ramp and volume loading test protocol is useful in estimating the characteristics of the Frank-Starling curve in each patient supported by continuous-flow LVAD. The Frank-Starling mechanism is exhausted in patients who require LVAD support. We also demonstrated that the Frank-Starling mechanism recovers from exhaustion by unloading with...
LVAD in some patients, and this recovery may be a predictor of successful LVAD removal. These findings may contribute to the establishment of LVAD as part of a bridge-to-recovery strategy, and may increase the number of patients who undergo LVAD removal, which we consider to be the best outcome of LVAD implantation.

Acknowledgments
The authors thank Editage (www.editage.com) for English language editing.

Sources of Funding
This paper did not receive any specific funding.

Disclosures
Y. Sakata and Y. Sawa are members of the Editorial Team of Circulation Journal.

IRB Information
This study was approved by the Institutional Review Board of Osaka University (Approval no. 16158-2).

References
1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62: e147–e239.
2. Kirklan JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplant 2017; 36: 1080–1086.
3. Frazier OH, Myers TJ. Left ventricular assist system as a bridge to myocardial recovery. Ann Thorac Surg 1999; 68: 734–741.
4. Dandel M, Weng Y, Siniawski H, Potapov E, Lehmkuhl HB, Hetzer R. Long-term results in patients with idiopathic dilated cardiomyopathy after weaning from left ventricular assist devices. Circulation 2005; 112(Suppl): 137–145.
5. Dandel M, Weng Y, Siniawski H, Potapov E, Drews T, Lehmkuhl HB, et al. Prediction of cardiac stability after weaning from left ventricular assist devices in patients with idiopathic dilated cardiomyopathy. Circulation 2008; 118(Suppl); S94–S105.
6. Birks EJ, Tansley PD, Hardy J, George RS, Bowles CT, Burke M, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med 2006; 355: 1873–1884.
7. Birks EJ, George RS, Hedger M, Bahrami T, Wilton P, Bowles CT, et al. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological treatment: A prospective study. Circulation 2011; 123: 381–390.
8. Matsumiya G, Monta O, Fukushima N, Sawa Y, Funatsu T, Toda K, et al. Who would be a candidate for bridge to recovery during prolonged mechanical left ventricular support in idiopathic dilated cardiomyopathy? J Thorac Cardiovasc Surg 2005; 130: 699–704.
9. Saito S, Matsumiya G, Sakaguchi T, Miyagawa S, Yamauchi T, Kuratani T, et al. Cardiac fibrosis and cellular hypertrophy decrease the degree of reverse remodeling and improvement in cardiac function during left ventricular assist. J Heart Lung Transplant 2010; 29: 672–679.
10. Saito S, Toda K, Miyagawa S, Yoshikawa Y, Fukushima S, Sakata Y, et al. Hemodynamic changes during left ventricular assist device-off test correlate with the degree of cardiac fibrosis and predict the outcome after device explantation. J Artif Organs 2015; 18: 27–34.
11. Frazier OH, Baldwin AC, Demirozu ZT, Segura AM, Hernandez R, Taugmeyer H, et al. Ventricular reconditioning and pump explantation in patients supported by continuous-flow left ventricular assist devices. J Heart Transplant 2015; 34: 766–772.
12. Weger-Pincon O, Drakos SG, McKellar SH, Horne BD, Caine WT, Kfoury AG, et al. Cardiac recovery during long-term left ventricular assist device support. J Am Coll Cardiol 2016; 68: 1540–1553.
13. Ando M, Nishimura T, Takeya K, Kyo S, Ono M, Taenaka Y, et al. Creating an ideal “off-test mode” for rotary left ventricular assist devices: Establishing a safe and appropriate weaning protocol after myocardial recovery. J Thorac Cardiovasc Surg 2012; 143: 1176–1182.
14. Park SJ, Milano CA, Tatooles AJ, Rogers JG, Adamson RM, Steidley DE, et al. Outcomes in advanced heart failure patients with left ventricular assist devices for destination therapy. Circ Heart Fail 2012; 5: 241–248.
15. George RS, Sabharwal NK, Webb C, Yacoub MH, Bowles CT, Hedger M, et al. Echocardiographic assessment of flow across continuous-flow ventricular assist devices at low speeds. J Heart Lung Transplant 2010; 29: 1245–1252.
16. Ando M, Nishimura T, Takeya K, Ogawa D, Yamazaki K, Kashiwa K, et al. Intracircuit back-flow analysis in a mock circulation model. J Artif Organs 2011; 14: 70–73.
17. Jakovlevic DG, Yacoub MH, Schueler S, MacGowan GA, Velicki I, Seferovic PM, et al. Left ventricular assist device as a bridge to recovery for patients with advanced heart failure. J Am Coll Cardiol 2017; 69: 1924–1933.
18. Adler E, Silva Enciso J. Functional improvement after ventricular assist device implantation: Is ventricular recovery more common than we thought? J Am Coll Cardiol 2013; 61: 1995–1997.
19. Birks EJ, Drakos S, Selzman C, Starling R, Cunningham C, Slaughter M, et al. Remission from Stage D Heart Failure (RESTAGE-HF): Early results from a prospective multi-center study of myocardial recovery. J Heart Lung Transplant 2015; 34(Suppl); S40–S41.
20. Yoshikawa Y, Miyagawa S, Toda K, Saito A, Sakata Y, Sawa Y. Myocardial regenerative therapy using a scaffold-free skeletal-muscle-derived cell sheet in patients with dilated cardiomyopathy even under a left ventricular assist device: A safety and feasibility study. Surg Today 2018; 48: 200–210.
21. Sequeira V, van der Velden J. Historical perspective on heart function: The Frank-Starling Law. Biophys Rev 2015; 7: 421–447.
22. Schwinger RH, Böhm M, Koch A, Schmidt U, Morano I, Eissner HJ, et al. The failing human heart is unable to use the Frank-Starling mechanism. Circ Res 1994; 74: 959–969.
23. Sunagawa K, Sagawa K, Maughan WL. Ventricular interaction with the loading system. Am J Physiol 1984; 20: 163–189.
24. Gill RM, Jones BD, Corbly AK, Ohad, DG, Smith GD, Sandusky GE, et al. Exhaustion of the Frank-Starling mechanism in conscious dogs with heart failure induced by chronic coronary microembolization. Life Sci 2006; 79: 536–544.
25. Sarnoff SJ, Berglund E. Ventricular function. I. Starling’s law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation 1954; 7: 200–210.
26. Estep JD, Stainback RF, Little SH, Torre G, Zoghbi WA. The role of echocardiography and other imaging modalities in patients with left ventricular assist devices. JACC Cardiovasc Imaging 2010; 3: 1049–1064.

Supplementary Files
Please find supplementary file(s) at http://dx.doi.org/10.1253/circj.CJ-20-0070