Myocardial Recovery in Patients Receiving Contemporary Left Ventricular Assist Devices

Results From the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)

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Background—Time course and predictors of myocardial recovery on contemporary left ventricular assist device support are poorly defined because of limited number of recovery patients at any implanting center. This study sought to investigate myocardial recovery using multicenter data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).

Methods and Results—Thirteen thousand four hundred fifty-four adult patients were studied. Device explant rates for myocardial recovery were 0.9% at 1-year, 1.9% at 2-year, and 3.1% at 3-year follow-up. Independent predictors of device explantation for myocardial recovery were age <50 years (odds ratio [OR] 2.5), nonischemic etiopathology (OR 5.4), time since initial diagnosis <2 years (OR 3.4), suboptimal heart failure therapy before implant (OR 2.2), left ventricular end-diastolic diameter <6.5 cm (OR 1.7), pulmonary systolic artery pressure <50 mm Hg (OR 2.0), blood urea nitrogen <30 mg/dL (OR 3.3), and axial-flow device (OR 7.6). Patients with myocarditis (7.7%), postpartum cardiomyopathy (4.4%), and adriamycin-induced cardiomyopathy (4.1%) had highest rates of device explantation for recovery. Use of neurohormonal blockers on left ventricular assist device support was significantly higher in patients who were explanted for recovery. Importantly, 9% of all left ventricular assist device patients who were not explanted for recovery have demonstrated substantial improvement in left ventricular ejection fraction (partial recovery) and had remarkable overlap in clinical characteristic profile compared with patients who were explanted for recovery (complete recovery). Complete and partial recovery rates have declined in parallel with recent changes observed in device indications and technology.

Conclusions—Myocardial recovery is a spectrum of improvement rather than a binary clinical end point. One in every 10 left ventricular assist device patients demonstrates partial or complete myocardial recovery and should be targeted for functional assessment and optimization. (Circ Heart Fail. 2016;9:e003157. DOI: 10.1161/CIRCHEARTFAILURE.116.003157.)

Key Words: cardiomyopathy ■ heart failure ■ left ventricular assist device ■ myocardium ■ reverse remodeling

Left ventricular assist device (LVAD) therapy has become standard of care in patients with end-stage heart failure (HF) and increasingly being used worldwide with excellent long-term outcomes.1,2 Although originally intended as a bridge-to-transplant device, it became evident early in the 1990s that mechanical unloading with LVAD may facilitate recovery of the failing ventricle, allowing for device explant in select patients, also termed as bridge-to-recovery.3,4 These clinical observations were supported by molecular studies of human myocardial samples obtained before and after LVAD support, which showed reversal normalization of several components of the left ventricular (LV) remodeling phenotype, including cardiomyocyte hypertrophy, β-receptor desensitization, cytokine activation, cytoskeletal protein disarray, and deranged collagen turnover.5–9 Despite favorable changes observed in the myocardial structure and function with mechanical unloading, sustained recovery leading to device explantation occurs rarely and is reported in <5% of LVAD-supported patients in the current era of mechanical circulatory support therapy.10

See Clinical Perspective


Circ Heart Fail is available at http://circheartfailure.ahajournals.org DOI: 10.1161/CIRCHEARTFAILURE.116.003157
Although the precise mechanisms for the disconnect between molecular and structural recovery are largely unknown, growing lines of evidence suggest that a systematic, program-based approach incorporating use of guideline-directed pharmacological therapy, serial assessment of native cardiac function by turnbuckled echocardiograms, and individualized LVAD weaning strategies may promote myocardial recovery and lead to higher rates of clinically successful device explants. Because recovery optimization requires an active effort and resource utilization by LVAD programs, improved understanding of the time course and clinical predictors of myocardial recovery is critically important to develop appropriate patient selection and management strategies. Several studies have suggested young age, nonischemic etiology, and short duration of heart failure as potential predictors of myocardial recovery on LVAD support. However, the majority of the available data are derived from single-center studies and patients supported with pulsatile-flow LVADs, which are no longer in clinical use. Moreover, previous studies have consistently used device explantation end point as a binary definition for recovery. This approach fails to consider the possibility that myocardial recovery may rather represent a spectrum of structural and functional improvement.

Given the limited number of recovery patients at any implanting center and significant gap in knowledge, we sought to investigate time course and predictors of myocardial recovery on continuous-flow LVAD (CF-LVAD) support using the multicenter Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).

Methods

Data Source and Study Population

The INTERMACS is a prospective registry of durable mechanical circulatory support devices implanted in the United States. In-depth description of the registry has been published and is available at http://www.INTERMACS.org. The INTERMACS protocol was approved by the National Institutes of Health, the Institutional Review Board at the Data Coordinating Center at the University of Alabama at Birmingham, and at the institutional review board of each participating hospital. All prospective implants between June 2006 and June 2015 were included in this study (Figure 1 in the Data Supplement). Fourteen thousand seven hundred forty-six adult LVAD patients (age ≥19 years at implant) were identified. Patients who underwent total artificial heart placement (n=325), who underwent pulsatile-flow LVAD placement (n=962), or those with prior history of heart transplantation (n=16) were excluded from the analysis. The remaining 13,454 CF-LVAD patients were included in the study. Patients who received an LVAD and a right ventricular assist device in the same operating room visit were included (n=427). Comprehensive clinical data were collected at the time of device implantation and at serial follow-up time points after CF-LVAD implantation, as previously defined.

Myocardial recovery on LVAD support was defined using 2 separate but interrelated criteria: (1) complete myocardial recovery: defined as device explantation for myocardial recovery, similar to what has been traditionally used in previous studies of myocardial recovery on CF-LVAD support. Patients who had their devices removed or turned off for other reasons, such as infection, device malfunction, or thrombosis, were excluded from this category. This definition is based on ultimate clinical outcome of the patient irrespective of the number of device implants required (per patient analysis). (2) Partial myocardial recovery: defined as demonstration of substantial improvement of the LV function on CF-LVAD support (LV ejection fraction [LVEF] >40% at any follow-up), yet not achieving the device explantation clinical end point. Of the 13,291 patients not reaching the device explantation end point, 9238 (69.5%) had reported LVEF data before and after CF-LVAD implantation. Patients with LVEF >30% before CF-LVAD implantation (n=433) were excluded from this analysis. Remaining patients (n=8805) were categorized into partial myocardial recovery versus no myocardial recovery cohorts based on their highest LVEF achieved on CF-LVAD support during follow-up.

Statistical Analysis

Continuous variables were defined as mean and standard deviations, and categorical variables were summarized as percentages. Baseline characteristics were compared using independent t test for continuous variables and χ² test for categorical variables. Cumulative incidence of complete myocardial recovery was calculated and plotted using Kaplan-Meier estimates. Patients who were transplanted off device support were censored from the analysis at the time of these events. Nonparametric estimate of the hazard function for complete myocardial recovery was performed using a Kernel-based approach. INTERMACS registry provided echocardiographic data, laboratory results, and medications used at predefined time points on pump support. Serial changes in these parameters were plotted for myocardial recovery cohorts. Groups were then compared cross-sectionally using analysis of variance with Tukey’s post hoc test for continuous variables and χ² test for categorical variables. To account for potential within subject correlations, groups were also compared using mixed models for continuous variables and generalized linear models for categorical variables by adjusting time variable into ordinal. A negative binomial regression method was used to model complete and partial recovery rates over time by using calendar year as a predictor of the number of recovery events. To account for biases because of varying lengths of observation time, the logarithm of events per person year was used as an offset in the negative binomial model. Univariable predictors of complete myocardial recovery on LVAD support were identified using logistic regression. Clinical factors with a P value <0.10 were entered into a multivariable logistic regression model (exit criteria P>0.05) to determine independent predictors of device explant for recovery after LVAD implantation. Correlated variables were not entered simultaneously into the multivariable model to avoid overfitting. Continuous variables were dichotomized at optimal cutoff points based on sensitivity and specificity values. A 2-tailed P value ≤0.05 were considered statistically significant for all comparisons. Data were analyzed with the use of IBM SPSS Statistics software, version 22.0 (IBM Corp, Armonk, NY), and R software, version 3.1.2.

Results

Incidence of the Complete and Partial Myocardial Recovery on CF-LVAD Support

Of the 13,454 LVAD patients studied, 163 (1.2%) underwent device explantation because of ultimate recovery of the LV function. Of those, 150 patients (92.0%) recovered after the initial LVAD implantation, 12 patients (7.4%) recovered after second LVAD implantation, and 1 patient (0.6%) recovered after third LVAD implantation. Median support time to complete myocardial recovery from initial device implantation was 11.4 months (interquartile range: 19.4 months). Cumulative incidence of complete myocardial recovery after initial LVAD implantation was 0.9% at 1-year, 1.9% at 2-year, and 3.1% at 3-year follow-up (Figure 1A). Hazard rate of recovery had a linear increment within the first 6 months of device support and remained relatively constant until 36 months of device support (Figure 1B). Of 8805 patients with LVEF <30% at the time of device implantation, 761 (8.6%) achieved partial myocardial recovery outcome defined as LVEF >40% on LVAD support during any follow-up time point. Three hundred fifty-five patients (4.0%) had LVEF improvement to >50%, and 406
patients (4.6%) had LVEF improvement to 40% to 50%. Of note, complete and partial recovery rates observed in patients supported by pulsatile-flow LVADs in the INTERMACS registry (excluded from this contemporary analysis) were 3.1% and 17.8%, respectively, which were significantly higher than in patients supported by CF-LVADs ($P<0.001$).

Clinical Characteristics of the Complete and Partial Myocardial Recovery Cohorts
Baseline characteristics of patients achieving complete and partial myocardial recovery were represented in Tables 1–4. Female sex, low body mass index, low body surface area, nonischemic etiology of HF, shorter duration of disease, CF-LVAD type (axial versus centrifugal flow), implant strategy, INTERMACS profile, preimplant extracorporeal membrane oxygenation use, and preimplant mechanical ventilation were significantly associated with both complete and partial recovery (Table 1). Of note, complete myocardial recovery cohort patients were more likely to be young, use tobacco on presentation, work for income, and have a lower incidence of previous cardiac surgery, peripheral vascular disease, and chronic kidney disease.

When hemodynamic parameters were analyzed, complete and partial recovery cohort patients had significantly lower pulmonary artery systolic, diastolic, and capillary wedge pressures before device implantation compared with nonrecovery cohorts (Table 2). Preimplant LV end-diastolic diameter (LVEDD) was significantly lower in both complete and partial myocardial recovery cohorts. Partial recovery cohort patients had a significantly higher baseline LVEF and lower incidence of severe mitral insufficiency; however, these factors were not significant for the complete myocardial recovery cohort patients.

Common preimplant laboratory abnormalities for the complete and partial recovery cohorts included lower blood urea nitrogen and lower serum albumin, potentially reflecting superior renal function and acuity of presentation in these cohorts (Table 3). Complete myocardial recovery was associated with higher hemoglobin, elevated platelet counts, lower serum creatinine, and a decreased B-type natriuretic peptide (BNP) levels. On the contrary, partial recovery was associated with increased serum Na, lower prealbumin, lower hemoglobin, and higher pro-BNP levels.

Utilization of HF therapies before CF-LVAD implantation is summarized in Table 4. As shown, both complete and partial myocardial recovery patients were less likely to be on a $\beta$-blocker, angiotensin receptor blocker, and aldosterone blocker compared with no-recovery cohorts. In addition, utilization of intracardiac defibrillator and cardiac resynchronization therapy devices was significantly lower in both partial and complete myocardial recovery cohorts. Interestingly, only 32.5% of complete-recovery patients were on optimal HF therapy—defined as use of at least 2 neurohormonal blockers in combination with an intracardiac defibrillator and/or cardiac resynchronization therapy device—as compared with 47.5% of partial-recovery patients and 62.0% of no-recovery patients ($P<0.001$).

When specific HF etiologies were investigated, the highest rates of myocardial recovery leading to device explantation were observed in patients with myocarditis (7.7%), followed by those with postpartum cardiomyopathy (4.4%) and adriamycin-induced dilated cardiomyopathy (4.1%; Figure II in the Data Supplement). Similarly, the highest rates of partial recovery were observed in patients with adriamycin-induced dilated cardiomyopathy (22.1%), followed by postpartum cardiomyopathy (17.3%) and valvular heart disease (12.8%).

Time Course of Reverse Remodeling on LVAD Support
Time-dependent changes in mean LVEDD, mean LVEF (%), mitral regurgitation, and serum BNP levels in complete and partial myocardial recovery patients are summarized in Figure 2. As shown, both cohorts demonstrated an early reduction in LVEDD **Figure 1. Complete myocardial recovery leading to continuous-flow left ventricular assist device explantation in the INTERMACS registry. A, Cumulative incidence of complete myocardial recovery. B, Hazard risk of complete myocardial recovery. INTERMACS indicates Interagency Registry for Mechanically Assisted Circulatory Support; and VAD, ventricular assist device.**
Table 1. Clinical Characteristics of Complete and Partial Myocardial Recovery Cohorts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete Recovery</th>
<th>Partial Recovery</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Explant (n=163, 1.2%)</td>
<td>No Explant (n=13291, 98.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVEF (≥40%) (n=761, 8.6%)</td>
<td>LVEF (&lt;40%) (n=8044, 91.4%)</td>
<td></td>
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<tr>
<td>Age, y</td>
<td>45.9±13.8</td>
<td>57.0±13.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>63 (38.7%)</td>
<td>2824 (21.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ethnicity (Hispanic)</td>
<td>8 (4.9%)</td>
<td>819 (6.2%)</td>
<td>0.498</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27±6.9</td>
<td>28.7±6.9</td>
<td>0.017</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.97±0.28</td>
<td>2.06±0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure etiology</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Ischemic</td>
<td>23 (14.1%)</td>
<td>6218 (46.8%)</td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>140 (85.9%)</td>
<td>7073 (53.2%)</td>
<td></td>
</tr>
<tr>
<td>Time since first cardiac diag</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;1 mo</td>
<td>44 (28.8%)</td>
<td>644 (5.0%)</td>
<td>74 (10.2%)</td>
</tr>
<tr>
<td>1 mo to 1 y</td>
<td>38 (24.8%)</td>
<td>1249 (9.8%)</td>
<td>106 (14.6%)</td>
</tr>
<tr>
<td>1–2 y</td>
<td>16 (10.5%)</td>
<td>820 (6.4%)</td>
<td>58 (8.0%)</td>
</tr>
<tr>
<td>&gt;2 y</td>
<td>55 (35.9%)</td>
<td>1070 (78.8%)</td>
<td>487 (7.2%)</td>
</tr>
<tr>
<td>CF-LVAD type</td>
<td></td>
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</tr>
<tr>
<td>Axial-flow</td>
<td>156 (95.7%)</td>
<td>11516 (86.6%)</td>
<td>721 (94.7%)</td>
</tr>
<tr>
<td>Centrifugal flow</td>
<td>7 (4.3%)</td>
<td>1775 (13.4%)</td>
<td>40 (5.3%)</td>
</tr>
<tr>
<td>Preimplant strategy</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bridge to recovery</td>
<td>5 (3.1%)</td>
<td>50 (0.4%)</td>
<td>8 (1.1%)</td>
</tr>
<tr>
<td>Bridge to transplant</td>
<td>32 (19.6%)</td>
<td>3682 (27.7%)</td>
<td>158 (20.8%)</td>
</tr>
<tr>
<td>Bridge to candidacy</td>
<td>79 (48.5%)</td>
<td>4294 (32.3%)</td>
<td>241 (31.7%)</td>
</tr>
<tr>
<td>Destination therapy</td>
<td>46 (28.2%)</td>
<td>5211 (39.2%)</td>
<td>351 (46.1%)</td>
</tr>
<tr>
<td>Other/rescue</td>
<td>1 (0.6%)</td>
<td>54 (0.4%)</td>
<td>3 (0.4%)</td>
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<tr>
<td>INTERMACS profile</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermacs 1</td>
<td>38 (23.5%)</td>
<td>1968 (14.9%)</td>
<td>136 (17.9%)</td>
</tr>
<tr>
<td>Intermacs 2</td>
<td>48 (29.6%)</td>
<td>4922 (37.2%)</td>
<td>259 (34.1%)</td>
</tr>
<tr>
<td>Intermacs 3</td>
<td>56 (34.6%)</td>
<td>3949 (29.8%)</td>
<td>223 (29.4%)</td>
</tr>
<tr>
<td>Intermacs 4–7</td>
<td>20 (12.3%)</td>
<td>2391 (18.1%)</td>
<td>141 (18.6%)</td>
</tr>
<tr>
<td>Severity of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>9 (5.5%)</td>
<td>316 (2.4%)</td>
<td>0.009</td>
</tr>
<tr>
<td>IABP</td>
<td>20 (12.3%)</td>
<td>2225 (16.7%)</td>
<td>0.128</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>13 (8.0%)</td>
<td>504 (3.8%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Dialysis</td>
<td>7 (4.3%)</td>
<td>331 (2.5%)</td>
<td>0.144</td>
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<tr>
<td>Comorbid conditions</td>
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</tr>
<tr>
<td>Previous cardiac operation</td>
<td>27 (16.6%)</td>
<td>4558 (34.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tobacco use, history</td>
<td>24 (33.3%)</td>
<td>2343 (30.1%)</td>
<td>0.552</td>
</tr>
<tr>
<td>Tobacco use, current</td>
<td>9 (12.5%)</td>
<td>337 (4.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe diabetes mellitus</td>
<td>6 (8.3%)</td>
<td>771 (9.9%)</td>
<td>0.656</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0 (0.0%)</td>
<td>380 (4.9%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>4 (5.6%)</td>
<td>1727 (22.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major stroke</td>
<td>0 (0.0%)</td>
<td>297 (3.8%)</td>
<td>0.116</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>7 (9.7%)</td>
<td>734 (9.4%)</td>
<td>0.933</td>
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(Continued)
Predictors of Myocardial Recovery in INTERMACS

after CF-LVAD insertion, which remained stable throughout the follow-up period. Prevalence of moderate-to-severe mitral insufficiency and serum BNP levels decreased in all patients; however, the reduction was more significant in complete and partial myocardial recovery patients at multiple time points. Mixed model analysis confirmed significant reduction in LVEDD and improvement in LVEF in myocardial recovery groups, accounting for potential within subject correlations ($P<0.001$).

Utilization of neurohormonal blocking agents, including $\beta$-blocker, angiotensin-converting enzyme inhibitors, and aldosterone antagonists, was significantly higher in the complete-recovery cohort compared with no-recovery cohort (Figure 3). The partial-recovery cohort also had increased use of $\beta$-blockers and angiotensin-converting enzyme inhibitors, primarily limited to the first 6 months of CF-LVAD support and to a much lower extent as compared with the complete-recovery cohort, suggesting underutilization of reverse remodeling therapies in this cohort. Generalized linear model analysis confirmed higher $\beta$-blocker and angiotensin-converting enzyme inhibitor use in myocardial recovery cohorts, accounting for potential within subject correlations ($P<0.001$).

### Changing Trends in Myocardial Recovery

Because the analysis extends over a lengthy period in which device indications and utilization patterns were rapidly changing, we analyzed myocardial recovery trends in the INTERMACS registry from 2007 to 2014 (Figure 4). Complete and partial myocardial recovery rates were significantly decreased in this time period in a time-dependent manner. This was accompanied by a significant change in device technology, with early predominance of pulsatile-flow pumps and more recent introduction of centrifugal-flow CF-LVADs. Although

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete Recovery</th>
<th>Partial Recovery</th>
<th>$P$ Value</th>
<th>$P$ Value</th>
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<td>Social risk factors</td>
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<td>0.683</td>
</tr>
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<td>21 (0.2%)</td>
<td></td>
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<tr>
<td>Grade school</td>
<td>1 (0.9%)</td>
<td>336 (3.4%)</td>
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</tr>
<tr>
<td>High school</td>
<td>55 (48.7%)</td>
<td>4451 (45.0%)</td>
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<td></td>
</tr>
<tr>
<td>College and tech school</td>
<td>36 (31.9%)</td>
<td>2690 (27.2%)</td>
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</tr>
<tr>
<td>Associate/bachelor</td>
<td>13 (11.5%)</td>
<td>1645 (16.6%)</td>
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<tr>
<td>Post-grad degree</td>
<td>8 (7.1%)</td>
<td>752 (7.6%)</td>
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<tr>
<td>Working for income</td>
<td>51 (34.2%)</td>
<td>2058 (16.9%)</td>
<td>&lt;0.001</td>
<td>0.475</td>
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<tr>
<td>Center volume</td>
<td>0.196</td>
<td>0.158</td>
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<tr>
<td>1–10 implants</td>
<td>11 (6.7%)</td>
<td>1210 (9.2%)</td>
<td>73 (9.7%)</td>
<td>710 (8.9%)</td>
</tr>
<tr>
<td>11–20 implants</td>
<td>34 (20.9%)</td>
<td>1996 (15.2%)</td>
<td>120 (16.9%)</td>
<td>1200 (15.0%)</td>
</tr>
<tr>
<td>21–30 implants</td>
<td>26 (16.0%)</td>
<td>2659 (20.2%)</td>
<td>167 (22.1%)</td>
<td>1538 (19.3%)</td>
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<tr>
<td>31–50 implants</td>
<td>51 (31.3%)</td>
<td>3917 (29.8%)</td>
<td>226 (30.0%)</td>
<td>2526 (31.7%)</td>
</tr>
<tr>
<td>&gt;50 implants</td>
<td>41 (25.2%)</td>
<td>3350 (25.5%)</td>
<td>168 (22.3%)</td>
<td>2006 (25.1%)</td>
</tr>
<tr>
<td>Concomitant surgery</td>
<td>96 (58.9%)</td>
<td>7927 (59.7%)</td>
<td>413 (54.3%)</td>
<td>4813 (59.8%)</td>
</tr>
<tr>
<td>Duration on device support, mo</td>
<td>16.6±12.2</td>
<td>16.5±15.5</td>
<td>0.892</td>
<td>24.1±17.5</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BSA, body surface area; CF-LVAD, continuous-flow left ventricular assist device; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; and LVEF, left ventricular ejection fraction.

### Predicting Complete and Partial Myocardial Recovery: INTERMACS Recovery Risk Model

Two independent risk prediction models were developed to predict complete myocardial recovery and partial myocardial recovery (Table 5). Preimplant clinical factors independently associated with complete myocardial recovery (device explantation) were young age, nonischemic etiology, shorter duration of cardiac disease, suboptimal HF therapy, small LV size, absence of pulmonary hypertension, low blood urea nitrogen, and use of axial-flow device. Preimplant clinical factors independently associated with partial myocardial recovery included female sex, low body surface area, nonischemic etiology, short duration of cardiac disease, suboptimal HF therapy, small LV size, higher baseline LVEF, absence of pulmonary hypertension, absence of hyponatremia, low serum blood urea nitrogen, and use of axial-flow pump. Because CF-LVAD device design was a significant factor for both complete and partial myocardial recovery with highest odds ratios, we further investigated reverse remodeling patterns between the 2 device types, which demonstrated a significantly lower LVEDD, higher LVEF, lower incidence of moderate-to-severe mitral regurgitation, and lower BNP in patients supported with axial-flow devices (Figure III in the Data Supplement).
the percentage of patients with nonischemic etiology remained relatively stable, prevalence of patients with acute presentation have declined significantly. In 2010, there was a steep increase in the prevalence of destination therapy patients coinciding with the FDA approval of CF-LVAD technology for this indication and a parallel increase in mean age at device implantation.

Discussion
This study evaluated the time course and clinical risk factors associated with complete and partial myocardial recovery in patients supported with contemporary LVADs in an era in which application of this technology is rapidly expanding to broader HF populations. Our principal findings are as follows: (1) complete myocardial recovery leading to device explantation is rare (1.2%) in the current mechanical circulatory support device era but not uncommon even beyond the first year of device support; (2) 8.6% of patients exhibit substantial improvement of LV function (partial myocardial recovery) on long-term CF-LVAD support; (3) patients achieving complete versus partial myocardial recovery on device support have a remarkable overlap in clinical characteristics, suggesting that myocardial recovery represents a spectrum of improvement rather than a binary phenomenon; (4) patient-related (age, etiology of HF, duration of disease, LV size, renal function) and treatment-related (device type, use of neurohormonal blockade) factors seem to be associated with recovery on CF-LVAD support; (5) recent changes in device indications and technology have contributed to the lower rates of myocardial recovery observed. Taken together, these findings suggest that substantially higher number of LVAD patients than previously reported improve their myocardial function while on device support. Such patients might be most likely to benefit from targeted approaches and treatment strategies to enhance myocardial recovery.

Single-center studies using a combinatorial approach to promote recovery through prospective assessment of native

### Table 2. Hemodynamic and Echocardiographic Parameters at the Time of LVAD Implantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete Recovery</th>
<th>Partial Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>Expant (n=163, 1.2%)</td>
<td>No Expant (n=13,291, 98.8%)</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, per min</td>
<td>96.4±19.0</td>
<td>88.3±17.6</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>101.9±15.5</td>
<td>104.4±16.1</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>65.9±12.4</td>
<td>64.2±11.5</td>
</tr>
<tr>
<td>RA mean, mm Hg</td>
<td>11.6±7.7</td>
<td>13.5±8.4</td>
</tr>
<tr>
<td>PA systolic, mm Hg</td>
<td>40.9±13.2</td>
<td>50.4±14.7</td>
</tr>
<tr>
<td>PA diastolic, mm Hg</td>
<td>21.4±8.7</td>
<td>25.2±8.8</td>
</tr>
<tr>
<td>PCWP mean, mm Hg</td>
<td>22.2±8.5</td>
<td>24.7±9.0</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.07±1.40</td>
<td>4.19±1.44</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>6.3±1.05</td>
<td>6.8±1.12</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>18.6±7.1</td>
<td>18.6±6.1</td>
</tr>
<tr>
<td>RV Function</td>
<td>0.371</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>28 (31.8%)</td>
<td>1995 (25.3%)</td>
</tr>
<tr>
<td>Mild</td>
<td>17 (19.3%)</td>
<td>2046 (25.9%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>29 (33.0%)</td>
<td>2476 (31.3%)</td>
</tr>
<tr>
<td>Severe</td>
<td>14 (15.9%)</td>
<td>1382 (17.5%)</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>0.249</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12 (8.2%)</td>
<td>886 (7.5%)</td>
</tr>
<tr>
<td>Mild</td>
<td>60 (41.1%)</td>
<td>4053 (34.4%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>39 (26.7%)</td>
<td>3984 (33.9%)</td>
</tr>
<tr>
<td>Severe</td>
<td>35 (24.0%)</td>
<td>2842 (24.2%)</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>18 (12.4%)</td>
<td>1153 (9.9%)</td>
</tr>
<tr>
<td>Mild</td>
<td>67 (46.2%)</td>
<td>5340 (45.9%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>47 (32.4%)</td>
<td>3668 (31.5%)</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (9.0%)</td>
<td>1484 (12.7%)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrial; and RV, right ventricular.
cardiac function, use of guideline-directed medical therapy, and individualized device weaning strategies reported substantially higher rates of complete myocardial recovery than reported in this study, highlighting the importance and the proactive role of LVAD programs in achieving this favorable outcome.11–14,16,17

The most effective approach reported to date remains the Harefield protocol, which combines mechanical unloading with a novel 2-stage pharmacological strategy using neurohormonal blockers followed by addition of beta-2 agonist to prevent myocardial atrophy once the maximal regression in the LVEDD had been observed.11,12 Sixty percent (12 out of 20) of patients with chronic nonischemic cardiomyopathy supported with CF-LV AD (HARPS) were not replicated in the United States.12 Moreover, results from the multicenter Harefield Recovery Protocol Study (n=163, 1.2%) were successfully explanted using this protocol; however, patients reported in these cohorts were predominantly young (mean age range: 27–50) with nonischemic etiology (range, 60%–100%; mean, 94%), thus consistent with our findings. Only few studies to date investigated potential predictors of myocardial recovery in LVAD-supported patients.11–14,16,17

This study represents the largest myocardial recovery risk prediction analysis performed to date. Previous single-center and multi-center studies have also reported factors associated with LVAD-induced myocardial recovery (Table IA in the Data Supplement). It is important to note that the majority of these studies were conducted on patients with pulsatile-flow devices, were statistically underpowered, and were primarily focused on device explantation as the recovery end point. Yet, recovery patients reported in these cohorts were predominantly young (mean age range: 27–50) with nonischemic etiology (range, 60% to 100%; mean, 94%), thus consistent with our findings. Only few studies to date investigated potential predictors of recovery by comparing patients who recovered versus who did not. Risk predictors of myocardial recovery

### Table 3. Laboratory Values at the Time of LVAD Implantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete Recovery</th>
<th>Partial Recovery</th>
<th>P Value</th>
<th>Complete Recovery</th>
<th>Partial Recovery</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mEq/L</td>
<td>135.4±6.8</td>
<td>134.8±6.8</td>
<td>0.123</td>
<td>135.5±6.4</td>
<td>134.7±6.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>4.05±0.48</td>
<td>4.07±0.50</td>
<td>0.580</td>
<td>4.06±0.49</td>
<td>4.07±0.49</td>
<td>0.880</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>21.4±11.8</td>
<td>29.8±18.4</td>
<td>&lt;0.001</td>
<td>27.6±15.9</td>
<td>29.6±18.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.16±0.59</td>
<td>1.41±0.71</td>
<td>&lt;0.001</td>
<td>1.37±0.82</td>
<td>1.39±0.64</td>
<td>0.500</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.23±0.75</td>
<td>3.40±0.66</td>
<td>0.002</td>
<td>3.33±0.60</td>
<td>3.40±0.67</td>
<td>0.005</td>
</tr>
<tr>
<td>Pre-albumin, mg/dL</td>
<td>18.6±7.0</td>
<td>18.6±7.4</td>
<td>0.998</td>
<td>17.9±7.2</td>
<td>18.7±7.4</td>
<td>0.041</td>
</tr>
<tr>
<td>Bilirubin, tot, mg/dL</td>
<td>1.46±2.26</td>
<td>1.41±1.83</td>
<td>0.743</td>
<td>1.35±1.61</td>
<td>1.39±1.54</td>
<td>0.459</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>87.0±221.8</td>
<td>61.6±239.3</td>
<td>0.188</td>
<td>76.4±309.7</td>
<td>56.3±206.4</td>
<td>0.091</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>97.2±143.4</td>
<td>71.4±233.8</td>
<td>0.170</td>
<td>87.9±323.0</td>
<td>68.5±231.8</td>
<td>0.117</td>
</tr>
<tr>
<td>WBC count, ×1000/μL</td>
<td>9.45±3.8</td>
<td>8.58±4.1</td>
<td>0.006</td>
<td>8.38±4.0</td>
<td>8.52±3.9</td>
<td>0.336</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.8±2.0</td>
<td>11.3±2.1</td>
<td>0.007</td>
<td>11.1±2.0</td>
<td>11.4±2.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelets, ×1000/μL</td>
<td>198.9±85.1</td>
<td>197.5±80.8</td>
<td>0.824</td>
<td>196.3±88.4</td>
<td>198.5±79.3</td>
<td>0.502</td>
</tr>
<tr>
<td>INR</td>
<td>1.27±0.42</td>
<td>1.33±0.43</td>
<td>0.133</td>
<td>1.31±0.41</td>
<td>1.32±0.43</td>
<td>0.554</td>
</tr>
<tr>
<td>Pro-BNP, pg/mL</td>
<td>4642.4±7323.3</td>
<td>6787.2±7887.3</td>
<td>0.153</td>
<td>9880.8±11664.4</td>
<td>6617.3±7737.5</td>
<td>0.003</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>926.7±860.9</td>
<td>1169.9±1097.6</td>
<td>0.024</td>
<td>1240.9±1149.5</td>
<td>1157.4±1086.1</td>
<td>0.199</td>
</tr>
</tbody>
</table>

ALT indicates alanine transaminase; AST, aspartate transaminase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; INR, international normalized ratio; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; pro-BNP, pro B-type natriuretic peptide; and WBC, white blood cell.
factors identified in at least 2 independent studies were limited to young age, nonischemic etiology, and short duration of heart failure (Table IB in the Data Supplement).16–18 Our findings confirm and extend these original observations. Focusing on factors common to both complete and partial recovery, we identified suboptimal preimplant heart failure therapy, small LV, absence of pulmonary hypertension, preserved renal function, and use of axial-flow device as novel independent predictors of myocardial recovery. Patients who have not been exposed to neurohormonal blockade or cardiac resynchronization therapy before device implantation are potentially more likely to respond to these therapies after CF-LVAD implantation, which may explain the higher recovery rates observed in patients who are not on optimized HF therapy. Concomitant kidney disease may potentially interfere with the recovery process by reducing diuretic response, leading to incomplete unloading of the failing ventricle as well as creating challenges for use or titration of neurohormonal blocking agents, particularly angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists. LV chamber size at the time of LVAD implantation may indicate extent of LV remodeling and reflect chronicity of structural changes in the myocardium. Pulmonary hypertension may reflect presence of underlying pulmonary parenchymal disease and chronically remodeled pulmonary vasculature because of long-standing HF.

Interestingly, large clinical studies assessing predictors of cardiac resynchronization therapy response in less sick heart failure populations also demonstrated nonischemic etiology, recent onset of symptoms, small LV size/volume as significant predictors, suggesting presence of a common recovery pathway in heart failure, irrespective of the platform used.22 Specifically, patients with adriamycin-induced heart failure had the highest chances of partial myocardial recovery, with nearly 1 in every 4 patients exhibiting substantial improvement in LVEF during LVAD support. Interestingly, LVAD unloading leads to significant improvements in mitochondrial structure and function, which is the target organelle for adriamycin, a widely used chemotherapeutic agent associated with cardiotoxicity.23,24 Myocarditis and peripartum cardiomyopathy were among other specific heart failure etiologies that were associated with significantly higher rates of myocardial recovery. Finally, a much higher percentage of patients who achieved complete myocardial recovery received neurohormonal blockers on LVAD support as compared with those with partial or no recovery, highlighting importance of medical therapy in promoting recovery outcome. Future studies will be required to investigate whether patients who achieved only partial recovery on LVAD support could be further improved to complete recovery and device explantation with augmentation of neurohormonal blocker therapy.

### Table 4. Utilization of Heart Failure Therapies Before LVAD Implantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete Recovery</th>
<th>Partial Recovery</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Explant (n=163, 1.2%)</td>
<td>No Explant (n=13291, 98.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVEF (≥40%) (n=761, 8.6%)</td>
<td>LVEF (&lt;40%) (n=8044, 91.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td></td>
<td></td>
<td>0.008</td>
<td>0.038</td>
</tr>
<tr>
<td>Current use</td>
<td>72 (47.4%)</td>
<td>7148 (55.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior use</td>
<td>31 (20.4%)</td>
<td>2944 (22.8%)</td>
<td>153 (20.8%)</td>
<td>1906 (24.3%)</td>
</tr>
<tr>
<td>No</td>
<td>49 (32.2%)</td>
<td>2803 (21.7%)</td>
<td>177 (24.1%)</td>
<td>1642 (21.0%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
<td>0.197</td>
<td>0.369</td>
</tr>
<tr>
<td>Current use</td>
<td>55 (35.7%)</td>
<td>3783 (30.5%)</td>
<td>212 (29.4%)</td>
<td>2294 (30.5%)</td>
</tr>
<tr>
<td>Prior use</td>
<td>23 (14.9%)</td>
<td>2468 (19.9%)</td>
<td>142 (19.7%)</td>
<td>1601 (21.3%)</td>
</tr>
<tr>
<td>No</td>
<td>76 (49.4%)</td>
<td>6155 (49.6%)</td>
<td>366 (50.8%)</td>
<td>3620 (48.2%)</td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td></td>
<td>0.013</td>
<td>0.453</td>
</tr>
<tr>
<td>Current use</td>
<td>12 (7.8%)</td>
<td>1165 (9.6%)</td>
<td>59 (8.5%)</td>
<td>704 (9.6%)</td>
</tr>
<tr>
<td>Prior use</td>
<td>2 (1.3%)</td>
<td>851 (7.0%)</td>
<td>47 (6.8%)</td>
<td>544 (7.4%)</td>
</tr>
<tr>
<td>No</td>
<td>139 (90.8%)</td>
<td>10060 (83.3%)</td>
<td>590 (84.8%)</td>
<td>6055 (82.9%)</td>
</tr>
<tr>
<td>Aldosterone blocker</td>
<td></td>
<td></td>
<td>0.030</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current use</td>
<td>52 (34.2%)</td>
<td>5334 (42.5%)</td>
<td>266 (37.5%)</td>
<td>3343 (43.9%)</td>
</tr>
<tr>
<td>Prior use</td>
<td>17 (11.2%)</td>
<td>1704 (13.6%)</td>
<td>87 (12.3%)</td>
<td>1105 (14.5%)</td>
</tr>
<tr>
<td>No</td>
<td>83 (54.6%)</td>
<td>5501 (43.9%)</td>
<td>356 (50.2%)</td>
<td>3161 (41.5%)</td>
</tr>
<tr>
<td>Device therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>68 (37.4%)</td>
<td>10854 (79.7%)</td>
<td>&lt;0.001</td>
<td>503 (66.4%)</td>
</tr>
<tr>
<td>CRT</td>
<td>11 (14.1%)</td>
<td>2348 (29.6%)</td>
<td>0.003</td>
<td>100 (21.7%)</td>
</tr>
<tr>
<td>Optimal HF therapy*</td>
<td>51 (32.5%)</td>
<td>7789 (59.7%)</td>
<td>&lt;0.001</td>
<td>355 (47.5%)</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, intracardiac defibrillator; LVAD, left ventricular assist device; and LVEF, left ventricular ejection fraction.

*Defined as prior or current use of at least 2 neurohormonal blocking agents from 3 major drug classes (β-blockers, ACE inhibitors/ARB, and aldosterone antagonists) and in combination with ICD and/or CRT device.
A novel finding of this study was the significant association between device type and myocardial recovery outcomes. Compared with those supported with pulsatile-flow LVADs, patients supported with CF-LVADs had significantly lower rates of myocardial recovery, a finding consistent with a previous single-center report.25 Pulsatile-flow LVADs may unload the failing ventricle more effectively than CF-LVADs as evidenced by greater improvements in LV systolic and diastolic function and greater reduction in circulating levels of BNP, tissue inhibitor of metalloproteinase 4, and matrix metalloproteinase 9 in patients supported with these older-generation pumps.26 In addition, continuous-flow devices are typically operated on lower speed settings in an attempt to maintain aortic valve opening and pulsatility, and such low speed operation may lead to ineffective...
unloading of the failing heart. An observation, even more relevant in the current era of device support, is the higher incidence of complete (1.3% versus 0.4%) and partial (9.5% versus 3.3%) myocardial recovery in patients supported with axial compared with centrifugal continuous-flow pumps. Notable physiological differences exist between the 2 pump designs, including increased flow pulsatility and afterload sensitivity (flat pressure head versus flow curves) seen in centrifugal pumps, which may in turn lead to differential patterns of unloading and reduction in wall stress in the failing heart. A recent in vitro study suggested inadequate hemodynamic unloading of the centrifugal-flow pumps using an experimental, mock-circulatory loop model, which was further supported by the clinical observations from RAMP studies, demonstrating a relatively flat LVEDD slope in patients supported by a centrifugal-flow pump. These findings were challenged by a recent in vivo study of bovine model of ischemic HF, as well as a clinical hemodynamic RAMP study, both of which suggested comparable unloading between the 2 pump designs. Nevertheless, future prospective studies will be required to confirm association between different device physiologies with reverse remodeling, which may have strong clinical implications for device selection in patients who have higher likelihood of recovery. It will be interesting to see whether newer device designs that implement artificial pulse technology may lead to higher recovery rates in LVAD patients.

### Study Limitations

Although INTERMACS represents a high-quality registry data set, limitations inherent to retrospective data analysis apply to the current study. Because only FDA-approved devices are included in the INTERMACS, the selection of device type was potentially biased by approval status at the time of implantation. Proper assessment of native cardiac function on LVAD support requires speed adjustment to ensure minimal device support (ie, 6000 rpm in patients with Heartmate II LVAD); however, weaning echocardiogram data and device speed settings at the time of follow-up echocardiograms were not available in the INTERMACS registry. Paired echocardiogram data were unavailable in a significant number of patients, which could introduce potential bias because of missing data. Previous studies have shown a substantial risk of recurrent heart failure, cardiac transplantation, and mortality in patients after LVAD explantation for myocardial recovery. Unfortunately, postexplant data were not available in the INTERMACS registry. Our analysis identified device type as a potential predictor of myocardial recovery. This finding needs to be interpreted with caution because the primary intention of this study was not to compare differences in outcomes or unloading patterns between different device types. Moreover, device selection is nonrandomized in the INTERMACS registry, which may affect our findings.
regarding device type. Finally, we were unable to perform cellular, molecular, or genetic correlates of myocardial recovery because analysis of cardiac tissue was not available in the INTERMACS registry.

In conclusion, although myocardial recovery leading to device explantation is rare, in every 10 LVAD patients exhibit substantial improvement in LV function while on device support. Efforts should be maximized to properly identify individuals with high likelihood of recovery on LVAD support, systematically monitor native cardiac function, and optimize reverse remodeling therapy to achieve best possible outcomes.

Acknowledgments
We thank the INTERMACS investigators, coordinators, and participating institutions for the data they have provided for this registry. The content is solely the responsibility of the author(s) and does not necessarily represent the official views of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) or the National Institutes of Health. This study was supported by Lisa and Mark Schwartz and the Program to Reverse Heart Failure at New York Presbyterian Hospital/Columbia University.

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Disclosures
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References
Mechanical unloading with continuous-flow left ventricular assist device leads to favorable changes in the structure and function of the failing ventricle termed as reverse remodeling. Despite these improvements, complete myocardial recovery leading to device explantation occurs rarely in the current era of mechanical circulatory support. Using the multicenter Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data set, we investigated incidence and predictors of myocardial recovery on long-term left ventricular assist device support. Results from the United Network for Organ Sharing database. *J Heart Lung Transplant*. 2015;34:1624–1629. doi: 10.1016/j.healun.2015.08.004.


**CLINICAL PERSPECTIVE**

Mechanical unloading with continuous-flow left ventricular assist devices lead to favorable changes in the structure and function of the failing ventricle termed as reverse remodeling. Despite these improvements, complete myocardial recovery leading to device explantation occurs rarely in the current era of mechanical circulatory support. Using the multicenter Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data set, we investigated incidence and predictors of myocardial recovery in patients supported with durable contemporary continuous-flow left ventricular assist devices. We found that incidence of complete myocardial recovery was 1% at 1 year and 3% at 3 years, suggesting that myocardial recovery occurs beyond the first year of device support. More importantly, 9% of patients supported with continuous-flow left ventricular assist devices exhibited significant improvement in cardiac function (left ventricular ejection fraction >40%) on device support, termed as partial myocardial recovery. Clinical characteristics of patients with complete and partial myocardial recovery showed a remarkable overlap, suggesting that myocardial recovery represents a spectrum of improvement rather than a binary phenomenon. Clinical and molecular studies focusing on patients with partial myocardial recovery may provide insights into mechanisms of reverse remodeling, despite the low incidence of device explantation observed in the current era. Taken together, these findings suggest that a substantially higher number of continuous-flow left ventricular assist device patients than previously reported exhibit functional improvement on device support and can be targeted for myocardial recovery. Patients who are likely to recover based on their risk profile may benefit from prospective recovery assessment by serial echocardiograms, guideline-directed neurohormonal blockade, and individualized weaning strategies.
Myocardial Recovery in Patients Receiving Contemporary Left Ventricular Assist Devices: Results From the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)


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Supplementary Figure 1. Identification of study cohort from the INTERMACS Registry

- **Assessed for Eligibility**
  - 14,746 LVAD Patients

- **Assessed for Device Explantation for Myocardial Recovery**
  - (n=13,454 CF-LVAD Patients)
  - **Excluded patients (n=1,292)**
    - Pulsatile-flow LVAD Placement (n=962)
    - Total Artificial Heart Placement (n=325)
    - Previous Heart Transplantation (n=16)

- **Device Explantation for Myocardial Recovery**
  - (n=163, 1.2%)

- **Device NOT Explanted for Myocardial Recovery**
  - (n=13,291, 98.8%)
  - **Excluded patients (n=4,486)**
    - Missing LVEF data before or after LVAD implantation (n=4,053)
    - Patients with baseline LVEF >30% (n=433)

- **LVAD Patients with Baseline and Follow-Up LVEF Data**
  - (n=8,805)

- **LVEF Improvement to > 40% on LVAD Support**
  - (n=761, 8.6%)

- **No LVEF Improvement on LVAD Support**
  - (n=8,044, 91.4%)

**COMPLETE RECOVERY COHORT**

**PARTIAL RECOVERY COHORT**
Supplementary Figure 2. Specific HF Etiologies in Patients with Complete or Partial Myocardial Recovery on LVAD Support

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>Complete Recovery (LVAD Explant) (N=163 / 13,454, 1.2%)</th>
<th>Partial Recovery Cohort (Max LVEF &gt; 40%) (N= 761 / 8,805, 8.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated myopathy: Myocarditis</td>
<td>5 / 65 (7.7%)</td>
<td>4 / 42 (9.5%)</td>
</tr>
<tr>
<td>Dilated myopathy: Postpartum</td>
<td>9 / 203 (4.4%)</td>
<td>24 / 139 (17.3%)</td>
</tr>
<tr>
<td>Dilated myopathy: Adriamycin</td>
<td>8 /194 (4.1%)</td>
<td>29 / 131 (22.1%)</td>
</tr>
<tr>
<td>Dilated myopathy: Familial</td>
<td>12 / 312 (3.8%)</td>
<td>17 / 215 (7.9%)</td>
</tr>
<tr>
<td>Dilated myopathy: Other</td>
<td>30 / 1273 (2.4%)</td>
<td>85 / 842 (10.1%)</td>
</tr>
<tr>
<td>Dilated myopathy: Viral</td>
<td>6 / 273 (2.2%)</td>
<td>22 / 195 (11.3%)</td>
</tr>
<tr>
<td>Dilated myopathy: Idiopathic</td>
<td>64 / 4234 (1.5%)</td>
<td>225 / 2902 (7.8%)</td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>2 / 141 (1.4%)</td>
<td>12 / 94 (12.8%)</td>
</tr>
<tr>
<td>Dilated myopathy: Alcoholic</td>
<td>1 / 80 (1.3%)</td>
<td>4 / 49 (8.2%)</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>7 / 855 (0.8%)</td>
<td>56 / 482 (11.6%)</td>
</tr>
<tr>
<td>Dilated Myopathy: Ischemic</td>
<td>16 / 5386 (0.3%)</td>
<td>246 / 3460 (7.1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 / 100 (3.0%)</td>
<td>11 / 61 (18.0%)</td>
</tr>
</tbody>
</table>

Recovery rate for each specific diagnosis is represented in parentheses.
Supplementary Figure 3. Reverse remodeling based on CF-LVAD Type (Axial-flow device data represented in blue, Centrifugal-flow device data represented in red, * p<0.05)
<table>
<thead>
<tr>
<th>Author</th>
<th>Gender (F)</th>
<th>Mean Age</th>
<th>N</th>
<th>Duration of Support (days)</th>
<th>Specific Etiology</th>
<th>Device Type</th>
<th>Study Design</th>
<th>LVEDD (cm)</th>
<th>EF Time Course</th>
<th>LVAD Type</th>
<th>Other Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mancini et al. 1998</td>
<td>31</td>
<td>20% (1)</td>
<td>5</td>
<td>158 (68 - 380)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>80% (4)</td>
</tr>
<tr>
<td>Farar et al. 2002</td>
<td>32</td>
<td>25% (2)</td>
<td>22</td>
<td>57 (11-90)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>55%</td>
</tr>
<tr>
<td>Matsui et al. 2005</td>
<td>30</td>
<td>10% (0)</td>
<td>5</td>
<td>108 (23-602)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>10.2</td>
<td>7.1</td>
<td>Yes</td>
<td>10% (5)</td>
</tr>
<tr>
<td>Kik et al. 2007</td>
<td>31</td>
<td>27% (1)</td>
<td>11</td>
<td>318 (75 - 208)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>50% (4)</td>
</tr>
<tr>
<td>Simon et al. 2010</td>
<td>33</td>
<td>10% (0)</td>
<td>5</td>
<td>49 (11-263)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>36% (5)</td>
</tr>
<tr>
<td>Birks et al. 2011</td>
<td>32</td>
<td>33% (1)</td>
<td>14</td>
<td>16 (1.5 - 84)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>100%</td>
</tr>
<tr>
<td>Simon et al. 2012</td>
<td>31</td>
<td>10% (0)</td>
<td>4</td>
<td>16 (1.5 - 84)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>100%</td>
</tr>
<tr>
<td>Birks et al. 2011</td>
<td>32</td>
<td>33% (1)</td>
<td>14</td>
<td>16 (1.5 - 84)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>100%</td>
</tr>
<tr>
<td>Lamarche et al. 2013</td>
<td>30</td>
<td>10% (0)</td>
<td>5</td>
<td>60 (61%)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>25% (61)</td>
</tr>
<tr>
<td>Frazier et al. 2015</td>
<td>31</td>
<td>10% (0)</td>
<td>5</td>
<td>60 (61%)</td>
<td>Retrospective</td>
<td>PF (100%)</td>
<td>Single-center</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>30% (61)</td>
</tr>
</tbody>
</table>
**Supplementary Table 1b.** Clinical risk factors associated with myocardial recovery on LVAD Support based on previous publications represented in a heat-map format

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Matsumiya ³</th>
<th>Simon ⁷</th>
<th>Birks ⁹</th>
<th>Krabatsch ¹¹</th>
<th>Goldstein ¹²</th>
<th>Patel ¹³</th>
<th>Pan ¹⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Young)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Female)</td>
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<td></td>
<td></td>
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<tr>
<td>BMI (Low)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Ischemic Etiology</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Duration of HF (Short)</td>
<td>Red</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>LVEDD (Small)</td>
<td></td>
<td>Orange</td>
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<tr>
<td>Cardiac Index (Low)</td>
<td></td>
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<tr>
<td>Creatinine (Low)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Absence of ICD</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PF- vs. CF-LVAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVAD Speed (High)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Duration of LVAD support (Long)</td>
<td>White</td>
<td>Orange</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Red:** Significant positive association by multivariate analysis, **Orange:** Significant positive association by univariate analysis, **Black:** Significant negative association by multivariate analysis, **Green:** Significant negative association by univariate analysis, **White:** Either non-significant association or variable not reported in the respective study
References:


12. Goldstein DJ, Maybaum S, MacGillivray TE, Moore SA, Bogaev R, Farrar DJ, Frazier OH and HeartMate IICI. Young patients with nonischemic cardiomyopathy have higher likelihood of left ventricular recovery during left ventricular assist device support. *Journal of cardiac failure*. 2012;18:392-5.
