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EDITORIAL COMMENT

Another Grain in the Search for the True Rate of Myocardial Recovery*

Emma J. Birks, MD, PhD

Advanced heart failure (HF) is rarely thought of as a reversible process; however, mechanical unloading using a left ventricular assist device (LVAD) has been shown to promote reversal of the HF phenotype, with regression of pathologic myocardial hypertrophy and improvement in both left ventricular (LV) chamber size and LV function, a process called "reverse remodeling." This process can be significant and may result in myocardial recovery; that is, the normalization of functional, structural, and hemodynamic changes sufficient to allow sustained explantation of the LVAD. Improvements are seen at the clinical, molecular, and cellular levels (1).

It is a highly contentious topic because reported rates of myocardial recovery sufficient to allow device explantation have varied widely. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), the national LVAD database (2), and some specific centers that do not specifically look for recovery have reported low explantation rates (3); conversely, individual studies from centers that assess and promote recovery have reported much higher rates (3). The INTERMACS highly valuable dataset has transformed and advanced our field, but it has many shortcomings when analyzed for recovery. INTERMACS is not designed to optimally track rates of recovery; it does not record many pertinent pieces of information such as pump speed, echo data performed at reduced speed, or post-explantation information.

In this issue of the *Journal*, Wever-Pinzon et al. (4) studied the INTERMACS data to more thoroughly investigate what these findings tell us about rates of recovery. The authors analyzed 15,138 adult LVAD recipients in the INTERMACS database between March 2006 and June 2015. Overall, 192 (1.3%) of the total

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INTERMACS patient population experienced cardiac recovery resulting in LVAD explantation (n = 172) or device deactivation (n = 20) after a median of 323.3 days. The incidence of cardiac recovery varied widely depending on the implantation strategy. Only 125 patients (0.8%) had an a priori implantation strategy of bridge-to-recovery (BTR) but, in this group, cardiac recovery was observed in 11.2% (n = 14), compared with 1.2% (n = 178) in patients with a non-BTR strategy ($p < 0.0001$). Cardiac recovery using LVADs, or the ability to induce remission from HF using these devices, is increasingly recognized, yet likely remains underreported and diagnosed. The problem is that most centers implant the LVAD either as a bridge to transplantation or destination therapy, and they do not look for or promote recovery (ie, they do not monitor the patient for improved LV function nor test them with the pump reduced to a speed at which there is no net forward or backward flow to assess underlying myocardial function). Centers do not generally run the pump optimally for unloading to promote recovery, instead selecting a speed that minimizes patient symptoms (5) without really unloading the left ventricle. Furthermore, many clinicians purposely leave the aortic valve opening for some pulsatility, again without adjusting the pump for maximal unloading. In addition, many centers do not actually explant a pump, even if the ejection fraction is good; they are nervous to do so with limited confidence and experience in recovery, and they believe transplantation is the proven endpoint for these patients.

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From the Division of Cardiovascular Medicine, University of Louisville, Louisville, Kentucky. Dr. Birks has reported that she has no relationships relevant to the contents of this paper to disclose.

Hence, the true rate of myocardial recovery is likely underreported in registries such as INTERMACS.

This theory is supported in the current study (4) by the subgroup of 7,084 patients who had at least 1 follow-up echocardiogram after 3 months of LVAD support; of these, 892 (12.6%) achieved an LV ejection fraction ≥40%, with a relative increase in LV ejection fraction ≥50%. Hence, although device explantation due to cardiac recovery only occurred in 1.3% of the population overall, a favorable "cardiac response" occurred in an additional 12.6% of patients who ultimately did not undergo explantation (and might have done so after further testing in more aggressive centers that look for recovery). The higher explantation rate in those with an a priori BTR strategy (9-fold) may in part be explained by the group's patient characteristics but more likely suggests that these patients were in a center that planned to monitor for and/or promote recovery. This possibility is borne out by the fact that even in patients with a similar clinical cardiac recovery profile, the incidence of recovery was higher in the BTR group than in the non-BTR group.

Although the rate of spontaneous recovery might be low, it can be readily promoted by aggressively optimizing pharmacotherapy. LVAD support allows administration of neurohormonal and other HF medications at high doses that are often not tolerated before pump implantation due to hypotension and renal dysfunction. HF medications have been shown to promote reverse remodeling by reversing pathologic hypertrophy, reducing fibrosis, and normalizing cellular metabolic functions, leading to improved mortality and functional status (1). Once the LVAD restores good flow to patients with advanced HF, the patients can tolerate these medications at much higher doses. Interestingly, in the current analysis (4), patients with cardiac recovery were more frequently receiving HF therapies after LVAD implantation compared with those with no recovery; specifically, at 12 months, patients with cardiac recovery were more frequently taking a beta-blocker (95% vs. 77%; $p < 0.01$), an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (80% vs. 53%; $p < 0.01$), and an aldosterone receptor blocker (49% vs. 34%; $p = 0.05$). The probability of cardiac recovery was 55% higher with the use of mineralocorticoid receptor antagonists and approximately 250% higher with the use of beta-blockers and ACE inhibitors or angiotensin receptor blockers. Patients who experienced cardiac recovery were less frequently taking a beta-blocker, ACE inhibitor, or aldosterone receptor antagonist before LVAD implantation compared with patients without recovery, suggesting that after LVAD implantation, patients overcame a previous intolerance to these agents. Thus, an LVAD can be used as a platform for more aggressive use of these drugs. Furthermore, continuous-flow LVADs are afterload dependent; therefore, increased afterload will decrease pump flow and reduce LV unloading. Hence, the afterload (and blood pressure) reduction provided by these afterload-reducing HF medications will also increase pump flow and unload the heart further. Ascertaining the optimal unloading for each pump is an important step to pursue recovery.

Assessing the clinical characteristics of patients who experienced cardiac recovery in this study showed that, with few exceptions, this was a fairly homogeneous group independent of the LVAD implantation strategy (4). After multivariable adjustment, the authors identified 6 independent predictors of cardiac recovery (age <50 years, nonischemic cardiomyopathy, time from cardiac diagnosis <2 years, absence of an implantable cardioverter-defibrillator, serum creatinine level ≤1.2 mg/dl, and LV end-diastolic diameter <6.5 cm). They then assigned each of these variables a number of points proportional to its regression coefficient to derive a prognostic score they labeled the INTERMACS Cardiac Recovery Score with a range of 0 to 9. They defined 3 groups with significantly different prognoses: low probability (0 to 3 points), intermediate probability (4 to 6 points), and high probability (7 to 9 points). A weighted score was derived and externally validated in 190 recipients prospectively enrolled in the Utah Cardiac Recovery program with good performance. Such a score might help centers that do not want to apply an extensive recovery protocol to all patients yet still target individuals with a higher chance of success. In those implanted with a BTR strategy according to the INTERMACS database, those with an INTERMACS Cardiac Recovery Score >7 had an explanation rate of 24.5%. However, it must be noted that this analysis is slightly misleading because most INTERMACS centers will have only attempted to monitor/recover patients they believe are more likely to recover (e.g., younger patients, those with nonischemic cardiomyopathy). It is from these data that the score is derived, which might skew the score; for example, it might be that recovery has not really been tested in older patients with ischemia.

Cardiac recovery occurred infrequently early after LVAD implantation: only 2.1% ($n = 4$) in the first month, 14.6% of patients by 3 months, and 80% of all patients recovered by 2 years after LVAD implantation (4). Thus, at 319 days, the median follow-up in this study might have been too short, resulting in underreporting of recovery.

Although implant volume was not associated with explantation rate in this INTERMACS analysis, it is probably not the center's volume that is important but its interest and the presence of protocols such as those discussed earlier to monitor for and promote recovery combined with earlier experience and, hence, confidence in pump removal. A growing number of centers are now using such protocols, and it would be interesting to determine the rate of recovery in such centers compared with others.

INTERMACS contains little data regarding post-explantation outcomes. Survival after LVAD explantation was available for only 21 (11%) patients (4). However, encouragingly, 18 (86%) of these patients were alive 1 year post-explantation.

A rapidly increasing number of patients with advanced HF are now being implanted with LVADs (2), particularly since the introduction of continuous-flow pumps, which have generally replaced pulsatile pumps because they are associated with better survival, lower morbidity, and a much longer durability due to a very low rate of device failure. Increased pump durability, combined with the lengthening wait for a donor organ for transplantation, means that these patients experience long periods of stability before transplantation, during which time myocardial recovery can be attempted as a therapeutic target. The bridge-to-transplant clinical trials also show that even if the patient undergoes implantation as a bridge to transplantation, fewer and fewer of these patients are actually undergoing transplantation (6). Furthermore, a rapidly growing number of patients are now undergoing implantation as destination therapy (i.e., there is no intent of transplantation). Although pump durability has markedly improved, significant complications remain, including stroke, pump thrombosis, gastrointestinal bleeding, and infection. These complications limit long-term survival and quality of life. Consequently, it is also important to strongly consider these destination therapy patients for myocardial recovery to offer them a better therapeutic option.

Although this retrospective analysis by Wever-Pinzon et al. (4) of the INTERMACS database reported a low rate of recovery overall, given that monitoring for reverse remodeling is not routine practice, the true incidence of recovery remains unknown and underappreciated. Its incidence was 8.6-fold higher in patients implanted with an a priori BTR strategy, and this higher rate likely reflected the center's commitment to more careful evaluation of these patients over time. There were study limitations, too, such as the follow-up duration <1 year, which also contributed to underestimation of the recovery rate.

Combining mechanical unloading with LVADs, run at a pump speed optimized for unloading, with aggressive pharmacotherapy together with regular testing of underlying myocardial function (with the pump reduced to a speed at which it is not contributing), is likely to dramatically increase the frequency of sustained recovery from HF (7). Frequent echocardiographic and hemodynamic evaluation of underlying myocardial function should be performed, particularly in selected patients. LVADs provide a relatively safe platform to promote and monitor patients for myocardial recovery, hopefully avoiding the need for heart transplantation (along with preserving that much-needed donor heart for another individual) or long-term mechanical support with its associated complications.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Emma J. Birks, Heart Failure, Transplantation and Mechanical Support Program, University of Louisville, Advanced Heart Failure and Transplantation, 201 Abraham Flexner Way, 10th Floor, Suite 1001, Louisville, Kentucky 40202. E-mail: emma.birks@louisville.edu.

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