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EDITORIAL COMMENT

Recovering the Broken-Hearted

The Ultimate (and Uncertain) Goal of Mechanical Circulatory Support*

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Myocardial recovery induced by chronic unloading and reverse remodeling with durable left ventricular assist devices (LVAD) remains an elusive clinical prospect. Numerous studies describe evidence for structural and cellular improvements with chronic LVAD support, but most fail to include convincing functional and clinical outcomes data, and vice versa, leading to the often described "structure-function" disconnect in myocardial recovery research (1-4). Furthermore, clinicians lack a standard definition for recovery that is clinically meaningful and sustainable, with evidenced-based approaches that target this outcome after LVAD. For patients with advanced heart failure (HF), cardiac transplantation is epidemiologically insignificant at 2,200 patients per year in the United States, and the adverse event profile with long-term LVADs either as destination therapy or bridge to transplantation remains problematic. Thus, a recovery strategy with a goal toward device explantation and sustained restoration of cardiac function is desirable and should be aggressively pursued. By current estimates, a substantial population of patients with advanced HF may be suitable candidates for recovery (5), particularly younger, nonischemic patients with acute or short durations of HF (6-8). However, recovery rates among experienced LVAD centers are highly variable, with many centers reporting recovery rates of nearly 0%, perhaps because of limited clinical and research programs emphasizing recovery in otherwise stable LVAD patients (9). As a result, the field of mechanical circulatory support remains in a state of cognitive dissonance over this important concept.

LVAD therapy serves as a powerful mechanical vehicle by which to actively recover the failing heart when medical therapy alone becomes insufficient to reverse the disease course. Conceivably, most patients experience favorable myocardial structural and molecular changes after left ventricular pressure and volume unloading and improved neurohormonal activation. What remains to be explored is whether a unique phenotype exists for those who sufficiently recover to allow for device explantation. This requires deeper phenotyping using tissue and clinical characterizations to distinguish those who completely recover from those who simply improve ("partially recover") with myocardial rest. Describing recovery as a continuum with biological remodeling and disease regression, against the current staging of HF, can guide the understanding of mechanisms and treatment goals at various stages along this pathway (**Figure 1**).

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In this issue of the *Journal*, Wever-Pinzon et al. (10) expand the field of myocardial recovery by directly comparing rates of recovery in patients with nonischemic cardiomyopathy (NICM) versus patients with ischemic cardiomyopathy (ICM). To date, most recovery studies have focused on the nonischemic patient population, postulating that patients with ICM have lower likelihood of recovery because of irreversible myocardial scar. The authors' hypothesize that some patients with ICM progress to end-stage disease through adverse remodeling of noninfarcted myocardium long after the ischemic insult. Thus, the myocardial substrate for recovery in ICM and NICM may have considerable overlap,

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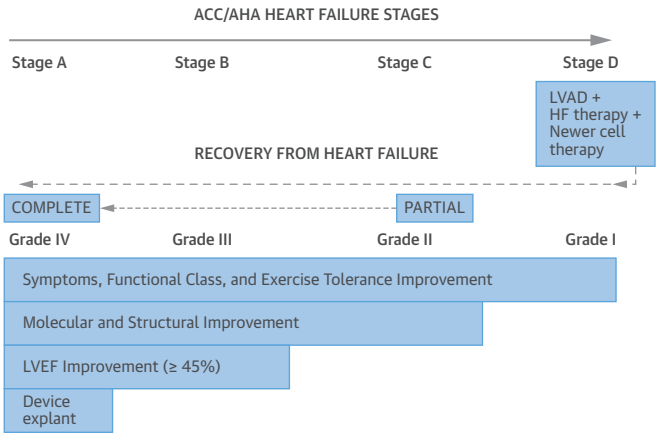
FIGURE 1 Proposed Framework for Recovery Juxtaposed With ACC/AHA Stages of Heart Failure



The ACC/AHA stages suggest an "inviolate" progression to advanced HF stages that is typically irreversible (13). In this hypothetical model, complete recovery and device explant could represent regression to stage A (normal structure, no symptoms), but these patients may remain "at high risk" for redeveloping heart failure. ACC = American College of Cardiology; AHA = American Heart Association; HF = heart failure; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction.

suggesting that a recovery strategy in patients with ICM is worthwhile. In this single-center, prospective study, 61 patients with ICM and 93 patients with NICM with long-standing chronic HF (excluding HF <3 months duration) on continuous-flow LVAD support were studied. The study's primary outcome was left ventricular ejection fraction (LVEF) at 6 months post-LVAD compared with baseline between the 2 groups. Sustained recovery was defined as 2 or more consecutive LVEF measurements ≥40% post-LVAD with no LVEF <40% at any time point thereafter. The device speed was tailored early to ensure adequate left ventricular decompression on echocardiography and confirmed by hemodynamic testing 2 months after LVAD showing an improvement in left-sided filling pressures. A similar proportion received axial versus centrifugal continuous-flow pumps. HF medications were not standardized or controlled for in this recovery effort, leading to variable usage per physician discretion. Patients with ICM had statistically significantly higher LVEF at baseline than the patients with NICM, and at 6 months, both patient cohorts saw significant improvements in LVEF (20% to 24% in ICM vs. 17% to 27% in NICM from baseline to 6 months). The authors found that 5% and 21% of the patients with ICM and patients with NICM, respectively, met the pre-specified definition of recovery with an LVEF ≥40% after 6 months, with slightly fewer patients having sustained recovery. Although turn-down studies (30 min of lowest LVAD support) were performed at each echocardiographic study time point per protocol, and left ventricular systolic function remained preserved under increased loading conditions, this was not a prospective bridge-to-recovery study and no patients with sustained recovery actually underwent device explant. Thus, post-explant clinical outcomes, arguably the most important piece of recovery investigations, are lacking from this study. We may draw some useful insights from knowing that peak LVEF improvement can occur by 6 months, but without the event of device explant itself to corroborate these findings, the authors leave us with the lingering question over what recovery truly means for any patient with HF, be they ischemic or nonischemic.

Because the number of patients with ICM who recovered according to the authors' study definition was low, it is difficult to make any conclusions about specific physiologic predictors of recovery in patients with ICM. The extent of myocardial infarction in the ICM subgroup was not elucidated, and perhaps viability testing or fibrosis quantification could further discriminate those who are likeliest to recover. The patients with NICM recovered at a rate of 21% similar to previously reported studies with phenotypic features typical of the recoverable: younger, shorter HF duration, and more prognostically favorable NICM etiologies. It should be acknowledged that a LVEF cutoff of 40% by Wever-Pizon et al. (10) for defining sustained recovery is lower than the threshold of other studies (i.e., ≥45%) and this may have impacted their reported recovery rate.

Nonetheless, the authors should be commended for their thought-provoking work, which asks us to confront our own bias and expand the candidate population for recovery beyond the patient with NICM. Very few prospective studies or multicenter registries have delved into subgroup analyses of patient cohorts with recovery potential. Yet the higher rates of recovery observed in patients with NICM from those studies and further confirmed by Wever-Pinzon et al. (10) argue for staying committed to this population and even ramping up efforts to maximize results, especially for younger patients who could be stabilized back to medical therapy. We eagerly await the results of the RESTAGE-HF (Remission from Stage D Heart Failure) trial, a multicenter, prospective study with promising early results of device explanation specifically in a NICM population treated with high-dose neurohormonal blockade therapy (11).

Prospective and well-controlled studies with structure-function concordance will continue to write the story for recovery. We look forward to future investigations that clarify the percentage of recovery that is defined by long-term clinical success, develop recovery prediction models (ideally to be used in every patient's risk assessment before device implant), and provide a practical framework for LVAD weaning and subsequent treatment for the recovered patient.

In its highest and rarest form, recovery might mean a cure from HF. Although purely aspirational, this is a worthwhile pursuit when one considers the enduring complications after LVAD or cardiac transplantation. LVADs may serve as a safe and novel platform from which to test regenerative and antiremodeling therapies because mechanically supported patients can better tolerate the adverse hemodynamic or arrhythmic effects of experimental agents (9). Thus, the synergistic combination of LVAD unloading plus traditional medical therapy and newer regenerative therapies may dramatically alter the HF pathway and change the natural history of the disease. Recovery should mean a return to native heart function with reversal of myocardial biology and dysfunction to the extent that one can live reasonably free from HF. Because recovery can occur to different degrees, it requires a classification that can be applied to clinical practice and investigation. Recently, a systematic review of recovery and device explantation from small, mostly observational studies, showed promising 1- and 10-year survival rates of 91% and 65.7%, respectively, with a 5-year freedom from HF of 81% (12). For those in the field of advanced HF, it is agreed that the human heart can recover from severe insult. LVAD technology has the potential to be the long-awaited restorative piece.

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REFERENCES

1. Hall JL, Fermin DR, Birks EJ, et al. Clinical, molecular, and genomic changes in response to a left ventricular assist device. J Am Coll Cardiol 2011;57:641–52.

2. Drakos SG, Kfoury AG, Hammond EH, et al. Impact of mechanical unloading on microvasculature and associated central remodeling features of the failing human heart. J Am Coll Cardiol 2010;56:382–91.

3. Birks EJ. Molecular changes after left ventricular assist device support for heart failure. Circ Res 2013;113:777–91.

4. Drakos SG, Kfoury AG, Stehlik J, et al. Bridge to recovery: understanding the disconnect between clinical and biological outcomes. Circulation 2012;126:230–41.

5. Birks EJ. The promise of recovery. J Am Coll Cardiol HF 2016;4:577–9.

6. Boehmer JP, Starling RC, Cooper LT, et al. Left ventricular assist device support and myocardial recovery in recent onset cardiomyopathy. J Card Fail 2012;18:755–61.

7. Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med 2006;355:1873–84.

8. Birks EJ, George RS, Hedger M, et al. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacologic therapy: a prospective study. Circulation 2011;123:381–90.

9. Drakos SG, Mehra MR. Clinical myocardial recovery during long-term mechanical support in advanced heart failure: insights into moving the field forward. J Heart Lung Transplant 2016;35:413–20.

10. Wever-Pinzon J, Selzman CH, Stoddard G, et al. Impact of ischemic heart failure etiology on cardiac recovery during mechanical unloading. J Am Coll Cardiol 2016;68:1741–52.

11. Birks EJ, Drakos SG, Selzman CH, et al. Remission from stage D heart failure (RESTAGE HF); early results from a prospective multicenter study of myocardial recovery (abstr). J Heart Lung Transplant 2015;34:S40–1.

12. Phan K, Huo YR, Zhao DF, Yan TD, Tchantchaleishvili V. Ventricular recovery and pump explantation in patients supported by left ventricular assist devices: a systematic review. ASAIO J 2016;62:219–31.

13. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;53:e1–90.

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