

EDITORIAL COMMENT

Functional Improvement After Ventricular Assist Device Implantation

Is Ventricular Recovery More Common Than We Thought?*

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*He who's down one day can be up the next,
unless he really wants to stay in bed, that is . . .*

—Miguel de Cervantes Saavedra, *Don Quixote* (1)

Of the roughly 5.8 million Americans with heart failure, approximately 10% will have Stage D heart failure, defined as symptoms at rest despite optimal medical therapy. American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend 3 options for these patients: 1) a ventricular assist device (VAD); 2) a heart transplant; or 3) hospice care (2). Unfortunately, advanced therapies such as transplant and VAD are associated with significant morbidity and mortality. Patients with both therapies take numerous medications and are at lifelong risk for life-threatening infection.

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Patients with VAD are at risk for other complications as well, including bleeding, stroke, and device failure. But, given the limited pool of suitable cardiac donors and vast improvements in technology, it is of no surprise that the use of VAD has increased dramatically. Since the U.S. Food and Drug Administration's approval of the Heart Mate II continuous-flow (CF) left ventricular assist device (LVAD) (Thoratec Corp., Pleasanton, California), >10,000 of these devices have been placed in the last 5 years. More surprisingly, last year, more VAD implantations were performed than heart transplants—the first time this has ever occurred (3).

The vast majority of VAD implantations are performed with the intent that the patient will either die with the VAD

(aka destination therapy) or have the VAD until they receive a heart transplant (aka bridge to transplant [BTT]). VAD also theoretically should allow for and/or assist in the recovery of cardiac function (bridge to recovery [BTR]). Ventricular recovery would obviously be the ideal therapeutic outcome from a VAD. Animal models suggest that the combination of mechanical unloading with normalization of the neurohormonal milieu can result in significant reverse remodeling, challenging the dogma that heart failure is a progressive, incurable disease (4). But previous BTR trials using the older generation, pulsatile devices, have had mixed results. A single-center study of 39 consecutive patients with pulsatile VAD found only 1 patient to be suitable for explantation (5). The multicenter LVAD working group studied 67 patients, mostly of nonischemic etiology and supported by pulsatile VAD. Thirty-four percent had ejection fractions (EF) >40 within 30 days of implantation. Unfortunately, by 120 days, the majority of these patients had their EF decrease to their pre-VAD measurement and only 9% underwent LVAD explantation for recovery. Of note, in a subgroup of 20 BTT patients from the study, histologic analysis of the heart was performed at the time of LVAD placement and again at transplant. Unloaded hearts were found to have reduced myocyte size, lowered total collagen deposition, and decreased myocardial tumor necrosis factor- α content; all of this suggests positive remodeling with LVAD (6).

Several smaller studies suggest that rates of BTR may occur in up to 15% of patients. Pre-explantation EF as well as change in LV size and geometry were the greatest predictors of recovery (7,8). Unfortunately, the use of adjuvant neurohormonal blockade was not standardized in any of these trials. A more recent prospective study in 20 patients with LVAD tested the hypothesis that recovery could be enhanced by combining LVAD unloading with an aggressive pharmacologic regimen and use of the novel beta-2 agonist clenbuterol. Sixty percent of patients were successfully explanted, despite the fact that most patients had an EF of 14% to 15% at baseline and higher end-diastolic diameters than in the previous studies. Such results have yet to be reproduced in a larger trial (9).

Outside of clinical trials, BTR is rarely observed. According to the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) of mechanical circulatory support, less than 5% of patients in the United States have had their VAD explanted because of recovery of function. These VAD explantations have been generally limited to patients with acute processes in young patients with shorter duration of heart failure such as acute myocarditis, post-cardiotomy syndrome, and peripartum cardiomyopathy.

In this issue of the *Journal*, Drakos et al. (10) suggest a simple explanation for the lack of recovery noted in the registries: We simply are not looking hard enough. This single-center prospective study investigated the effects of CF-VAD unloading on myocardial structure as well as

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systolic and diastolic parameters based on echocardiographic findings. A total of 80 patients were enrolled with echocardiograms and right heart catheterizations done serially after CF-VAD implantation. Recovery in cardiac function was based on improvement of echocardiographic parameters during weaning trials performed serially throughout the year. At 6 months, over one-third of patients had a 50% relative improvement in EF when compared with pre-implantation levels of CF-VAD (from pre-CF-VAD LVEF to highest post-CF-VAD LVEF). More surprisingly, 19% of these patients maintained an EF greater than 40% after 6 months of mechanical unloading. The systolic and diastolic parameters improved along with a decrease in chamber volume size and mass. Unlike previous studies, this study only includes CF-VAD patients as opposed to the first-generation pulsatile VAD. Though CF-VAD have been shown to improve morbidity and mortality in comparison with pulsatile VAD, it is unclear which ones promote recovery; this study suggests that CF-VAD are better.

Unlike previous studies, Drakos et al. (10) recorded serial echocardiographic parameters over a full year. In fact, patients did not achieve full "benefit" from their VAD until 6 months after implantation, which may be a possible explanation for why these findings differ from earlier work. Also, unlike other studies, the investigators excluded patients that had acute heart failure, so they did not skew the data toward patients likely to have recovery.

The greatest improvement in the study was seen in younger patients and those with shorter durations of heart failure; this is consistent with previous studies. But, contrary to other studies, a relatively high proportion of ischemic patients demonstrated improvements in structure and function. Initially, this might seem counterintuitive, as one would think that ischemic patients would have the most scarring and least chance of recovery. One possible explanation is that many of the ischemic patients have a hibernating myocardium that recovers as coronary perfusion pressures improve and metabolic demands decrease.

Continuous mechanical unloading promoted positive and sustained remodeling over time as seen by echocardiographic changes in chamber dimension, LV mass, and EF. This was consistent with 2 previous studies (8,11). Such structural changes can potentially select patients for VAD removal (i.e., those with EF >40%); however, the number of patients studied at long-term follow-up was low. Echocardiographic data from the current study demonstrates that LV mass decreases, but does not go below the reference range. This implies that unloading does not lead to significant cardiac atrophy and is consistent with older studies (12). Clearly, pathologic data from cardiac explants would help to support this conclusion.

Though the findings are encouraging, many issues remain unresolved. The intent of the work was not to explant patients, and in fact no patients were explanted. The question remains: Would these patients retain the improvement in function once the VAD was removed?

Even if these patients did not go on to explantation, does the recovery in function ultimately translate into an improvement in destination therapy/BTT outcomes? Currently, BTT patients are automatically United Network for Organ Sharing status 1 (1A or 1B) on the transplant list indefinitely until they are transplanted. If mortality is different for those with some LV recovery in comparison with those with no recovery, it would be reasonable to stratify them on the list. Longer-term outcome studies will be needed to address this question.

Drug therapy was not standardized in the patients. In fact, less than one-third of patients were on beta-blockers. Whether standard heart failure therapies improve outcomes for VAD patients remains unknown and merits further study. Mechanical circulatory support may help optimize other more novel therapeutics, such as cell-based therapies, but combination studies using LVAD and cell therapy have been limited.

LVAD speed settings among patients varied significantly in the study. Thus, whether certain LVAD speeds promote recovery is unknown. It has also been speculated that full recovery of function will require gradual "weaning" of the LVAD. Next-generation centrifugal devices that allow for low speed settings for a prolonged period of time will be necessary to test this hypothesis.

Mechanical circulatory support has had a profound impact on the treatment of heart failure, but at a significant cost to an already strained health-care system; the estimated cost is \$86,000 per quality-of-life year (13). Given the fixed costs associated with implantation, pursuing strategies to improve morbidity and mortality after implantation should be of high priority. If the devices can reach their full potential as therapeutic tools to treat heart failure, it will be money well spent.

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