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EDITORIAL COMMENT

The Promise of Recovery*

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Chronic heart failure is a progressive disorder characterized by adverse structural, cellular, and molecular left ventricular remodeling. Advanced heart failure has generally been thought of as an irreversible process, but mechanical unloading with a left ventricular assist device (LVAD), particularly if combined with aggressive reverse remodeling heart failure medications, has been shown to lead to a reversal of the chronic heart failure phenotype, a process called "reverse remodeling." Reverse remodeling refers to the regression of pathologic myocardial hypertrophy and improvement in LV chamber size that can occur in response to the treatment of heart failure. Myocardial recovery is the normalization of structural, molecular, and hemodynamic changes sufficient to allow sustained explantation of the LVAD.

A rapidly increasing number of patients with advanced heart failure are now undergoing LVAD implantation (1) either as a bridge to transplantation or, increasingly, as destination therapy. This is particularly the case since the introduction of continuous-flow pumps, which have pretty much replaced the pulsatile pumps, because they are associated with better survival and lower morbidity. There are 2 types of continuous-flow pumps that are mainly used today: the axial and centrifugal types. Both the axial and centrifugal pumps have much longer longevity than the older pulsatile pumps, with a low rate of device failure. It has been uncertain whether the centrifugal pumps are able to provide unloading that is as sufficient/optimal as the axial flow pumps, and some have speculated that axial LVADs might provide better left ventricular volume unloading than centrifugal LVADs.

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In this issue of *JACC: Heart Failure,* Al-Sarie et al. (2) studied the impact of axial flow (AX) versus centrifugal flow (CR) continuous-flow pumps on the myocardial structural and functional response after mechanical unloading. They prospectively studied 133 consecutive patients with advanced heart failure who had undergone implantation with continuous-flow pumps and compared 107 patients who had undergone implantation with the AX Heartmate II device (Thoratec Corp., Pleasanton, California) and 26 patients who received the centrifugal-flow HeartWare device (HeartWare, Framingham, Massachusetts). Device speed was adjusted to achieve adequate flows and optimal left and right ventricular decompression with positioning of the interventricular septum in the midline with minimal mitral regurgitation. Aortic valve opening was desirable (but considered of lower priority compared with the preceding factors). The degree of mechanical unloading was assessed by both invasive hemodynamic data from right heart catheterization 6 to 8 weeks after LVAD implantation and by frequency of aortic valve opening seen with echocardiography at 1 to 2 months after LVAD implantation.

They showed that left ventricular ejection fraction (LVEF) increased significantly from 18% to 28% and 26% after LVAD implantation in the AX and CR groups, respectively. Twenty-two percent of patients in the AX group achieved a peak LVEF of 40% or more, whereas 18% of patients in the CR group achieved an LVEF of 40% or more. After using a model adjusting for age, sex, and cause of heart failure, LVEF did show a trend of more significant improvement in the AX group over time than in the CR group ($p = 0.003$). LV end-systolic volume index and end-diastolic volume index decreased significantly as early as 30 days after implantation in the 2 groups and showed no difference between the 2 groups, even

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after attempting to adjust for age, sex, and cause of heart failure. No significant difference in the frequency of aortic valve opening between the 2 groups was noted, suggesting that the left ventricle was unloaded to a comparable degree by both pumps. The left- and right-sided filling pressures were significantly decreased after 6 to 8 weeks of LVAD support with both pumps.

Patients in the AX group showed a more rapid improvement in structural and functional myocardial response after LVAD implantation. At subsequent time points, however, patients in both groups showed comparable improvement in structural and functional myocardial response, suggesting that long-term mechanical unloading with AX and CR LVADs provides similar improvement in structural and functional parameters. Overall, Al-Sarie et al. (2) concluded that the 2 pump types led to a similar degree of mechanical unloading as assessed by invasive hemodynamics and frequency of aortic valve opening.

The use of centrifugal LVADs is steadily increasing as a therapeutic option, and the results of this study suggest that patients receiving these pumps should be strongly pursued for myocardial recovery, as should those receiving AX pumps. The increased durability of both types of continuous-flow pumps, combined with the lengthening wait for a donor organ for transplantation, means that these patients are usually stable and waiting for a long period before transplantation, and the holy grail of myocardial recovery should be pursued as a therapeutic target. Even if the patient undergoes implantation as a bridge to transplantation, fewer and fewer of these patients are actually receiving transplant organs during the period of follow-up in the bridge-to-transplantation clinical trials (3). Furthermore, an increasing number of patients are undergoing implantation as destination therapy. These patients do not have the transplantation option, so they too should be strongly considered for myocardial recovery.

The adverse myocardial remodeling that occurs during the progression of heart failure is induced by pressure and volume overload, which drives the vicious cycle of progressive myocardial dysfunction in chronic heart failure. Hence, to reverse heart failure, it is important to be able to optimize the mechanical volume and pressure unloading induced by the LVAD to induce maximal hemodynamic unloading for structural and functional reverse remodeling and myocardial recovery. This study shows that both axial and centrifugal pumps reduce volume and pressure overload to a similar degree.

How the pump is run is critical to the success of the unloading. Currently, this is often not optimal, and many centers select a speed that simply minimizes patient symptoms (4), without properly unloading the left ventricle. Furthermore, many clinicians purposely leave the aortic valve opening to allow some pulsatility and do not adjust the pump for maximal unloading. It is important to run these pumps at speeds that create the best degree and duration of unloading. Furthermore, continuous flow LVADs are afterload dependent; therefore, increased afterload will decrease pump flow and reduce LV unloading. Hence, afterload (and blood pressure) reduction provided by heart failure medications will also increase pump flow and unload the heart further. Ascertaining the optimal unloading for each pump is an important next step to pursue further the promise of recovery.

LVAD support allows the administration of neurohormonal and other heart failure medications at high doses that are often not tolerated before pump implantation because of hypotension and renal dysfunction. Heart failure medications have been shown to cause reverse remodeling by reversing pathological hypertrophy, reducing fibrosis, and normalizing cellular metabolic functions, as well as improving mortality and functional status. Once the pump restores good flow to these patients with advanced heart failure and their renal function improves, they tolerate these medications at much higher doses. Combining mechanical unloading with LVADs and aggressive reverse remodeling pharmacological management, together with regular echocardiographic and hemodynamic testing of true underlying myocardial function (with the pump reduced to a speed at which it is not contributing), is important and can dramatically increase the frequency of sustained recovery from heart failure (5,6).

Strategies to thicken the myocardium to enhance the durability of recovery before explantation, such as clenbuterol administration (which induces “physiological hypertrophy”) or intermittently reducing the pump speed to intermittently load the heart are likely to be beneficial in improving the durability of recovery after explantation. LVADs also provide a relatively safe platform for the delivery of promising novel biological and cell-based therapies.

Although this study provides important new information, 1 important limitation that must be acknowledged is that Al-Sarie et al. (2) reduced the speed of the CR HeartWare device to 1,800 rpm for the second loading condition, which will essentially provide no net flow across the device, but they reduced the AX Heartmate II device to only 8,000 rpm, which will still provide significant forward flow through the device. The Heartmate II pump would have to be reduced to 6,000 rpm to provide no net

forward flow (7); hence, these 2 sets of data are not comparable. The majority of the data Al-Sarie et al. (2) provide compare the structural and hemodynamic response on pump, but when comparing the reduced speed data, this should be borne in mind.

THE PROMISE

The number of patients in the United States alone who are eligible for advanced heart failure therapies (LVAD/transplantation) is estimated to be between 250,000 and 300,000 (8). Even concentrating simply on patients with nonischemic cardiomyopathy, who have the greater likelihood of recovery and in most centers constitute about 50% of patients undergoing implantation (borne out in this study center), would result in approximately 125,000 good recovery candidates. The rate of recovery has been highly variable. Some reports from centers not optimizing pump speed, not testing for recovery, and not giving heart failure drugs (and possibly not explanting even if there is significant recovery) have low success rates of 5% to 10%, which would still translate to 6,250 to 12,500 patients. Other centers who optimize pump speed and testing and give aggressive heart failure medications have rates of 50% to 60%, translating to 62,500 to 75,000 patients. An ongoing multicenter clinical trial, RESTAGE-HF (Remission From Stage D Heart Failure), will give us a better idea of what the true percentage of recovery is, but given that the current rate of transplantation in the United States is 2,200 per year, the potential number that can achieve the holy grail of recovery from advanced heart failure is potentially very large and likely to have a significant impact.

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