Left Ventricular Assist Devices and the Failing Heart
A Bridge to Recovery, a Permanent Assist Device, or a Bridge Too Far?

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The field of cardiac mechanical assist devices has achieved a number of striking technical breakthroughs over the past 40 years.1 Emblematic of the type of important technical accomplishments that have been achieved in this field has been the development of the portable, battery-driven left ventricular assist device (LVAD) for patients with intractable cardiac failure. Although LVADs have been used primarily as a “bridge to transplantation,” a number of centers have now begun to implant LVADs as an alternative to transplantation.2 Indeed, as the technology in this field improves, it is entirely conceivable that LVADs will evolve into small, unobtrusive devices that will run on small, portable, long-lasting battery supplies that will not require external connection to the outside. This, in turn, will allow LVADs to serve as a very reliable alternative to transplantation for many patients with advanced heart failure who cannot receive transplants or who cannot be weaned from LVAD support.

Thus far, the clinical experience with LVADs as a bridge to transplantation has consistently shown dramatic improvements in cardiac output3,4 and New York Heart Association functional class.4,5 Importantly, these clinical changes have been attended by concomitant decreases in levels of neurohormones6,7 and cytokines,8 suggesting that LVAD support may alter the heart failure “milieu.” In an effort to explain these salutary changes in clinical status, investigators have turned to more basic studies and begun to examine myocardial ultrastructure before and after LVAD implantation. These latter studies have shown decreased myocyte necrosis9,10 and apoptosis,11 decreased myocytolysis,12 and improved myocyte contractility.12 The beneficial changes in the biology of the failing myocardium after LVAD support have also been accompanied by favorable changes in the LV chamber geometry,2 LV wall thickness,9 and LV volume,5 as well as a favorable leftward shift in the LV pressure-volume curve.5

Given the magnitude and multitude of beneficial changes observed within the myocardium after prolonged LVAD support, it is perhaps not surprising that clinical reports have begun to emerge showing that heart failure patients could be weaned successfully from LVAD support. Moreover, for some patients, there was no subsequent cardiac decompensation after LVAD explantation.13,14 Thus, there was considerable enthusiasm that LVADs might be used as a “bridge to recovery” of myocardial function; and indeed, some reports suggested that myocardial recovery occurred in up to 30% of the patients.11 In the present issue of Circulation, Mancini and colleagues15 report on a retrospective analysis of a large cohort of patients who were successfully weaned from mechanical support. Mancini et al also report on their experience using exercise testing to help identify which patients could be successfully weaned from LVAD support. Surprisingly, Mancini et al found that only 5% of the patients could be weaned successfully from LVAD support. The authors also reported on a smaller group of prospectively studied patients and were able to show that LVAD patients who were able to exercise to a VO2 >20 mL·kg−1·min−1 and/or a peak cardiac output of 10 L/min had a sufficient cardiac reserve to tolerate LVAD explantation. Given the relatively low incidence of myocardial recovery after LVAD support in this carefully done, albeit largely retrospective, study, the question that arises is whether we should view this report as “good news” or “bad news” for patients with heart failure.

Biology of the Failing Heart
Before we address the clinical significance of the report by Mancini et al, it is perhaps instructive to briefly review the extensive changes that occur in the failing heart. Although a complete discussion of the complex changes that occur in the heart during LV remodeling is well beyond the intended scope of this editorial, it is worth emphasizing that the process of LV remodeling extends to and impacts importantly on the biology of the cardiac myocyte, the volume of myocyte and nonmyocyte components of the myocardium, and the geometry and architecture of the LV chamber (Table). Although each of these various components of the remodeling process may contribute substantially to the overall development and progression of heart failure, what determines the reversibility of heart failure is whether or not the changes that occur at the level of the myocyte, the myocardium, or the LV chamber are reversible. In this regard, it is interesting to note that the changes that occur at the level of the myocyte and the LV chamber appear to be at least partially reversible in some experimental and/or clinical models.16–18 In contrast to the reversible changes that occur in the failing myocyte and the
Overview of Left Ventricular Remodeling

Alterations in myocyte biology
  - Excitation-contraction coupling
  - Myosin heavy chain (fetal) gene expression
  - β-Adrenergic desensitization
  - Hypertrophy with loss of myofilaments
  - Cytoskeletal proteins

Myocardial changes
  - Myocyte loss
  - Necrosis
  - Apoptosis

Alterations in extracellular matrix
  - Matrix degradation
  - Replacement fibrosis

Alterations in LV chamber geometry
  - LV dilation
  - Increased LV wall stress
  - Mitral valve incompetence
  - Wall thinning with afterload mismatch

remodeled left ventricle, many of the defects that occur within the myocardium, most notably those affecting myocyte survival with subsequent replacement fibrosis, may not be reversible and may therefore contribute importantly to the failure to respond appropriately to a variety of forms of therapy, including mechanical assist devices.

Viewed within the context of the present discussion, the results of the study by Mancini et al. are likely to be very realistic and perhaps not entirely unexpected. That is, as discussed above, a number of irreversible changes occur within the myocardium as heart failure advances. Principal among these changes is the progressive loss of myocytes, with subsequent replacement fibrosis. Germane to this discussion is the observation that some of the studies that have examined myocardial histology after LVAD implantation have failed to show complete cessation of myocyte necrosis during the period of LVAD support. Moreover, many of these studies have shown increased fibrosis after LVAD implantation, suggesting that there was ongoing cell death and replacement fibrosis during the period of LVAD support. Thus, although LVAD support may significantly attenuate disease progression during the period of mechanical support, the existing literature suggests that LVAD support does not abrogate disease progression in heart failure. It follows, therefore, that the frequency of myocardial recovery after LVAD support will vary somewhat from center to center and will reflect, at least in part, the degree of irreversible myocardial damage at the time of implantation and the extent of irreversible changes that occur within the myocardium during the period of LVAD support. Although the study by Mancini and colleagues suggests that the overall incidence of myocardial recovery after LVAD implantation may be disappointingly low, the good news in this and similar smaller studies is why myocardial recovery occurs at all and what the cellular and molecular changes are within the myocardium that allow this recovery to occur. We also need to understand whether specific types of adjunctive medical therapy might be used for patients in whom LVADs have been implanted. For example, it is conceivable that specific anti-inflammatory strategies might be employed to extend the use of LVAD support and/or promote weaning from LVAD support. Alternatively, medical strategies to improve organelle function (eg, sarcoplasmic reticular function) might be combined with LVAD support to provide a more effective bridge to recovery for specific patients. Given that LVAD implantation enables investigators to examine serial myocardial samples and organelle function within the same patient, and given the ability of gene “display” technology to examine a myriad of genes in the same sample, it is likely that answers to some of these questions will be forthcoming in the foreseeable future.

A second piece of good news in the report by Mancini and colleagues is that the authors describe a potentially reliable method for prospectively identifying those patients in whom LVAD support may provide a stable bridge to myocardial recovery. This, in turn, should allow optimal timing of LVAD support and possibly allow clinicians to use physiological testing to “tailor” medical therapy during the period of LVAD support. Indeed, if the findings by Mancini and colleagues can be applied successfully in other centers, this study will make an enduring contribution to our ever-enlarging armamentarium for treating patients with advanced heart failure.

References


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