Left Ventricular Assist Device-Induced Reverse Ventricular Remodeling

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Left ventricular assist devices provide chronic pressure and volume unloading of the dilated left ventricle in patients with end-stage heart failure. This is associated with reverse structural remodeling (normalization of the passive pressure-volume relationship), reverse molecular remodeling (increased expression of several genes involved in calcium metabolism that are down-regulated in heart failure), improved baseline contractility, and improved contractile response to increased heart rate and to beta-agonist stimulation. These findings indicate the profound degree of recovery of myocardial properties in hearts previously considered to have invincible end-stage heart failure.

Left ventricular assist devices (LVADs) are commonly used to bridge critically ill patients with heart failure to transplant.[1-4] One class of LVADs frequently used for this indication are pusher plate pumps that propel blood from the left ventricle to the aorta in a pulsatile manner. These pumps provide volume and pressure unloading of the left ventricle while simultaneously restoring total systemic blood pressure and blood flow.[1,5,6] Typically, the aortic valve remains shut as blood travels from the left ventricle to the LVAD and through the outflow conduit to the proximal aorta. In this manner, it can almost be considered that the left ventricle acts as a low pressure atrium for the LVAD.

Although it was generally believed in the past that the massively dilated and dysfunctional hearts of patients with severe end-stage heart failure are irrevocably damaged, there is increasing evidence that the hemodynamic unloading provided by these LVADs can normalize several aspects of heart structure and function.[6-12] We have termed this process of normalization of heart properties *reverse remodeling.*[6] Evidence supporting the notion of reverse remodeling and implications of this process are reviewed in this article.

Heart and Tissue Procurement

We have been studying various aspects of reverse remodeling under a protocol approved by the Institutional Review Board of Columbia-Presbyterian Medical Center that allows us to study hearts and tissues explanted at the time of LVAD implantation and heart transplantation, the latter from both patients who have required LVAD support and also from transplant recipients who did not require LVAD support. For many of the LVAD

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recipients, the approximately quarter-sized apical tissue block removed to attach the LVAD inflow conduit has been obtained at the time of LVAD implantation. Finally, hearts and tissue samples have been obtained from a small number of normal human hearts that could not be used for transplant because of technical reasons.

At our institution, we have used the pneumatic and electric LVADs manufactured by Thermo Cardiosystems, Inc (Woburn, MA). Techniques for inserting these devices have been described previously[7] and in other articles in this issue. Results pertaining to reverse remodeling have not differed between pneumatic and electric devices.

LVADs Provide Pressure and Volume Unloading of the Left Ventricle

The echocardiogram in Fig 1 was obtained from a patient approximately 7 days after implantation of a pneumatic LVAD.[6] These devices require periodic venting (to restore small amounts of air lost from the system), during which time device pumping is halted for approximately 45 seconds. The echocardiograms show the ventricular cavity in long axis during one of these venting cycles (Fig 1A) and within a few minutes after reinitiation of pumping (Fig 1B). The arrow indicates the position of the LVAD inflow conduit that is easily seen in Fig 1A. During device venting, the left ventricle is seen as a dilated (~6 cm), thin-walled (<1 cm) structure. In dynamic images, an ejection fraction of about 20% was observed in this case. When the device is turned on, the ventricle is seen to be collapsed and the wall is appropriately thickened. In dynamic images, the ventricle remains collapsed with periodic episodes of filling (at times when native LV contraction is out of synchrony with LVAD pumping). In addition, note that the right ventricle remains loaded independent of the device status. Finally, the aortic valve rarely opens, indicating that the path of blood flow is from the ventricle, to the LVAD, to the aorta.

In a series of patients, it was shown that pulmonary artery wedge pressure, which averaged 28 mm Hg (range, 20 to 38 mm Hg) at the time of LVAD insertion, had decreased to a mean value of 8 mm Hg (range, 6 to 12 mm Hg), measured with the device still operating after anesthesia (chest closed) at the time of heart transplant. At the same time, cardiac index had increased from its baseline value of 1.6 (1.2 to 2.3) L/min/m^2 pre-LVAD to 3.0 (2.7 to 3.5) L/min/m^2 during LVAD support. According to these findings, it is clear that the LVAD provides both pressure and volume unloading of the diseased left ventricle.

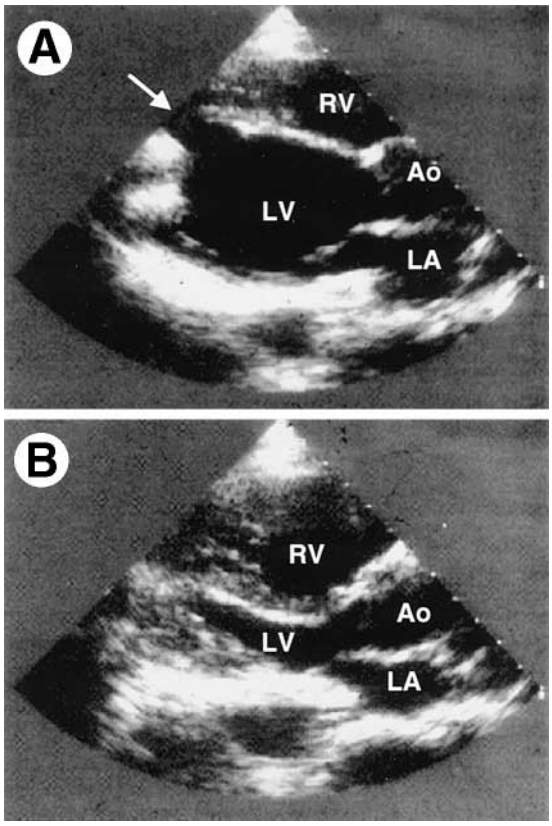

Fig 1. Echocardiograms of a patient 1 week after LVAD surgery. (A) LVAD operation is temporarily suspended (~45 sec) during a routine venting procedure. End-diastolic dimension is greater than 6 cm, indicating a dilated ventricular cavity. (B) This image showing internal dimension of 3 cm with thickened LV wall is taken within 1 minute after LVAD operation is restored. Thus, the LVAD provides substantial volume unloading of the heart. (Reprinted with permission from Levin HR, Oz MC, Chen JM, et al: Reversal of chronic ventricular dilation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. Circulation 91:2717-2720, 1995.[6])

Reverse Structural Remodeling by LVADs

Just before explantation at the time of heart transplantation, the hearts were perfused with 4°C cardioplegia solution and subjected to analysis of static pressure-volume relationships as described previously.[6] Briefly, this entails clamp occlusion of the aortic root and placement of a compliant water-filled latex balloon within the left ventricular chamber that is held in place by a metal adapter sutured to the mitral annulus. While measuring pressure within the balloon with a high-fidelity micromanometer, volume is varied from that which provides an intracavitary pressure of 0 mm Hg to a volume yielding a pressure of at least 30 mm Hg. The pressure and volume at each step-wise change are then plotted, resulting in the end-diastolic pressure-volume relationship (EDPVR) for that heart. Measurements obtained from the LVAD-supported hearts were compared with those obtained from hearts of patients not supported by LVADs and from normal hearts. In addition, LVAD-supported hearts were divided into 2 groups based on whether the LVAD exhibited prominent inflow valve regurgitation (IR) as determined on pre-explant echocardiography. An example of such an apical view echocardiogram is shown in Fig 2.[12a] This color Doppler examination reveals a large left ventricular cavity volume with a large intraventricular jet swirling within the ventricle. The jet near the septum (left side) shows the primary regurgitant volume and the jet along the free wall (right side) shows the blood swirling back toward the apex. Postexplant examination of this device revealed that one of the inflow valve leaflets had failed. Patients with such inflow valve regurgitation were encountered in 3 patients supported for greater than 180 days.

Representative averaged ex vivo EDPVRs are shown in Fig 3.[12a] Compared with those of normal hearts (squares) the EDPVRs of non–LVAD-supported hearts (circles) were shifted toward significantly larger volumes, a reflection of the gross dilation and structural remodeling that is typical of end-stage dilated cardiomyopathy. In contrast, LVAD-supported hearts exhibited EDPVRs that are shifted significantly toward lower volumes (downward triangles). Considering that the hemodynamic status (in terms of ejection fraction, LV chamber diameter, blood pressure, pulmonary capillary wedge pressure, and cardiac index) of the LVAD recipients at the time of LVAD implantation was worse than that of the non–LVAD-supported patients at the time of heart transplant, it is evident that LVAD support was associated with significant reverse structural remodeling of the left ventricle.

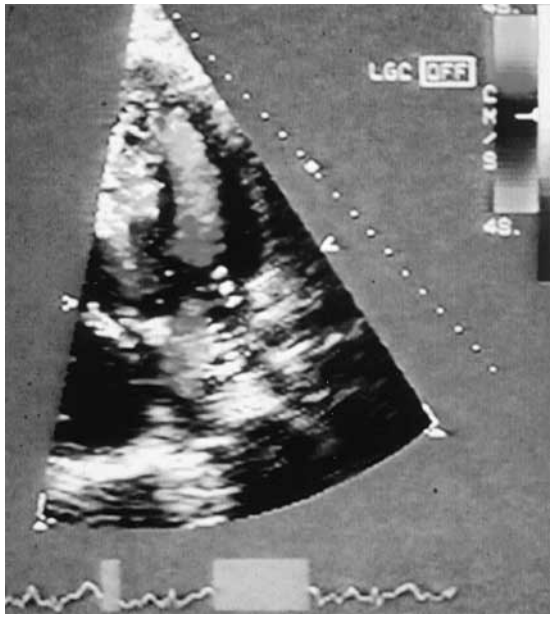

Fig 2. Apical echocardiographic view of the left ventricle with color Doppler mapping in a patient with prominent LVAD inflow valve regurgitation. The regurgitant jet along the septum is on the left side and the volume swirling back along the lateral wall is shown on the right side. (Reprinted from Ann Thorac Surg, 65, Moazami N, Argenziano M, Kohmoto T, et al, Inflow valve regurgitation during LVAD support may interfere with reverse ventricular remodeling, pp 628-631, Copyright [1998] with permission from Elsevier Science.[12a])

In patients with prominent inflow valve regurgitation (upgoing triangles), the remodeling process had been interfered with as evidenced by the fact that the EDPVRs of these hearts is more similar to those of the non–LVAD-supported transplant recipient hearts. We hypothesize that early in the course of the LVAD support, when the valve was operating normally, these hearts likely did exhibit reverse remodeling, but after valvular

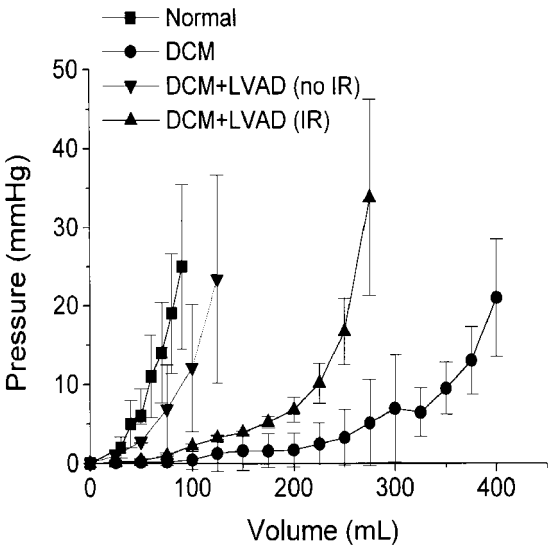

Fig 3. Ex vivo diastolic pressure-volume relationships from the explanted hearts of normal patients (squares), transplant recipients who did not receive LVAD support (dilated cardiomyopathy [DCM], circles), patients who had LVAD support in which there was no inflow valve regurgitation (IR, down-pointing triangles), and patients who had LVAD support in which there was inflow valve regurgitation (IR, up-pointing triangles). (Reprinted with permission from the Society of Thoracic Surgeons [The Annals of Thoracic Surgery 1998, 65, pp 628-631].)

malfunction occurred, the heart again redilated, resulting in the high volume EDPVR.

Influence of LVAD Support on Myocardial Contractile Performance

To test whether the chronic pressure and volume unloading by LVADs influences intrinsic myocardial performance, we have studied contractile strength of endocardial trabeculae of normal hearts, non-LVAD transplant hearts, from the LVAD core tissue (obtained at the time of LVAD implantation), and from LVAD-supported hearts at the time of transplantation.

Trabeculae of diameter less than 1 mm and length greater than 3 mm were excised, preserved in ice-cold Krebs-Ringer solution with 2,3-butanedione monoxime (BDM), and mounted in a muscle bath with one end to a force transducer and the other to a micrometer used to adjust length. The trabeculae were superfused with a standard oxygenated Krebs-Ringer solution at 37°C. Muscles were stimulated at 1 Hz and equilibrated for 1 hour at slack length. The muscle strip was then progressively stretched to L_{max}, the length of maximal force generation. After re-equilibration, stimulation frequency was increased every 2 minutes at 0.5-Hz increments to a maximum of 2.5 Hz (150 bpm). Then the response to isoproterenol (4×10^{-6} mol/L) was tested.

At 1-Hz stimulation frequency, absolute force generation by normal, pre-LVAD, post-LVAD, and non-LVAD transplanted hearts (normalized to cross-sectional area) were similar to each other, consistent with prior reports indicating that in this setting, there is no significant difference in force production between normal and diseased muscle.[13] However, at higher rates of stimulation, force declined in muscle from the pre–LVAD- and non–LVAD-supported hearts, whereas it increased in the normal and post–LVAD-supported hearts. Force tracings from the same patient both pre- and post-LVAD that exhibit this point are shown in Fig 4.

Before LVAD therapy in the heart failure state, inotropic response to isoproterenol is significantly blunted. In trabeculae from normal and post-LVAD hearts, beta-adrenergic responsiveness is restored. Force tracings in response to isoproterenol from the same patient both pre- and post-LVAD showing this point are seen in Fig 5.

Similar results with regard to force-frequency relationships and beta-adrenergic responsiveness have been obtained from patients with LVADs with both ischemic and idiopathic dilated cardiomyopathies. Also, results of preliminary experiments suggest quantitative differences in some of these responses depending on whether the patient was receiving inotropic support before transplantation. This is an important point because improved beta-responsiveness post-LVAD could simply be a reflection of the withdrawal of inotropic support and improved neurohormonal status established by LVADs[14] with resulting up-regulation of beta-receptors rather than some effect of chronic mechanical unloading of the LV to restore fundamental aspects of myocardial properties.

Nevertheless, these results suggest that 2 important mechanisms that regulate contractile strength (beta-adrenergic responsiveness and frequency of

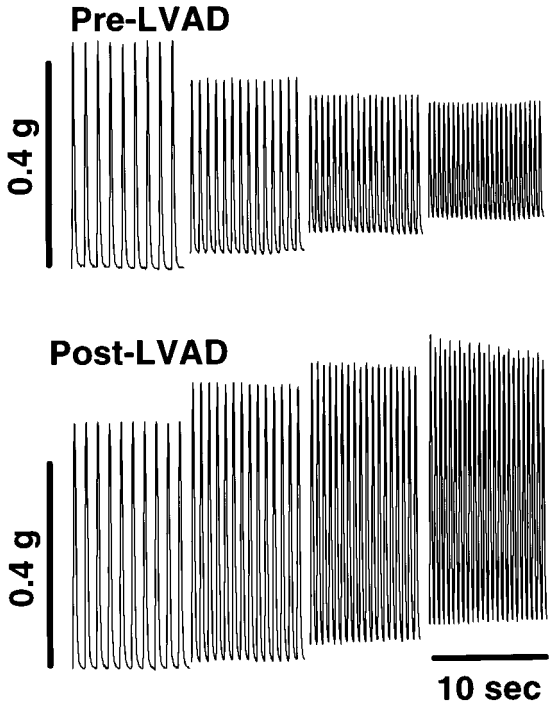

Fig 4. Force tracings from an endocardial trabecula excised from the apical myocardial tissue block removed during the insertion of an LVAD (top). The response to pacing at different frequencies (1, 1.5, 2, 2.5 Hz) shows progressively impaired relaxation and decreased systolic performance. After LVAD support (bottom) another trabecula from the same patient shows less impairment in diastolic properties and significant increase in force as frequency is increased.

contraction) are restored during LVAD support, though resting strength may not be significantly influenced.

Reverse Molecular Remodeling by LVADs

Myocardial contractile dysfunction in heart failure owing to a variety of causes has been partially linked to alterations in calcium handling. Downregulated gene expression of sarcoplasmic reticular calcium adenosine triphosphatase (ATPase) subtype 2 (SERCA2) and of the ryanodine-sensitive calcium (Ca^{2+}) release channel (RyR), and altered expression of sarcolemmal sodium-calcium (Na^+/Ca^{2+}) exchanger have been reported and appear to be associated with various aspects of contractile dysfunction.[15-19] The results of prior studies and results presented earlier suggest that LVAD-induced recovery of myocyte contractile performance in response to increased stimulation frequency is coincident with normalization of the magnitude and time course of the intracellular Ca^{2+} transient and calcium metabolism.[8] Accordingly, it can be hypothesized that normalized gene expression of Ca^{2+} handling proteins could underlie these phenomena. To test this hypothesis, we analyzed how LVAD support impacted on myocardial SERCA2, RyR, and Na^+/Ca^{2+} exchanger gene expression. Tissue samples were obtained from non–LVAD-transplant recipients, from LVAD recipients at the time of LVAD implant, from LVAD recipients at the time of transplantation, and from a limited number of normal hearts. These tissue samples were analyzed by standard Northern blot analysis. A representative Northern blot is shown in Fig 6. This blot was serially probed for SERCA2, RyR, Na^+/Ca^+ exchanger, and GAPDH. In general, band intensities for each of the 3 genes were greater in normal and post-LVAD samples than in the heart failure (including pre-LVAD) samples. Based on quantitative analysis of these blots, it was observed, consistent with previous studies, that there was a relatively large variability of

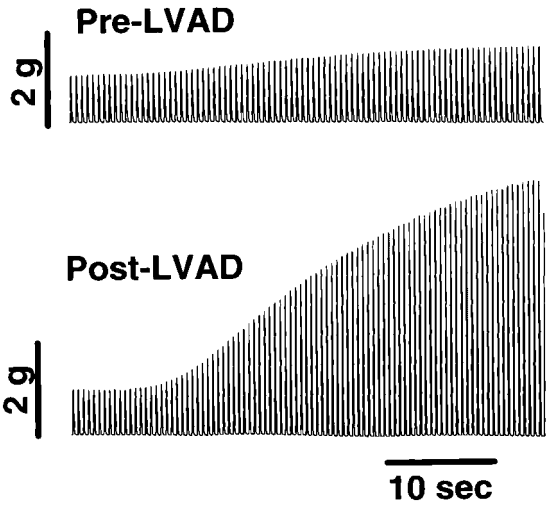

Fig 5. Force tracings from an endocardial trabecula excised from the apical myocardial tissue block removed during the insertion of an LVAD (top). This muscle strip shows little contractile response to isoproterenol. After LVAD support (bottom) another trabecula from the same patient shows an impressive contractile response.

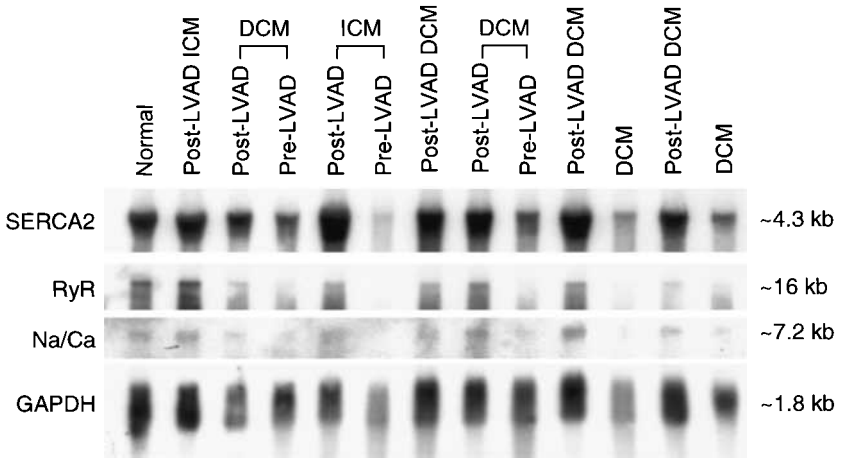

Fig 6. Representative Northern blot depicting myocardial messenger RNA for sarcoplasmic endoreticulum SERCA2, the RyR, the Na^+/Ca^{2+} exchanger, and GAPDH. Samples in this blot were randomly selected from normal tissue, from patients with heart failure both before and after LVAD support. Brackets represent paired pre- and post-LVAD samples from the same patient. Genes were probed serially and autoradiographs were developed for differing lengths of time depending on the band intensity.

expression of each gene in patients with heart failure and this variability was similarly present in the post-LVAD state. A quantitative comparison performed only on paired tissue samples (ie, from patients in which matched pre- and post-LVAD samples were available) determined that expression of each gene product increased ($P < .05$, $n = 13$ paired samples); if gene expression is normalized so that 1 is the average expression in normal human heart tissue, the following pre- versus post-LVAD expression levels were observed for each gene product: SERCA2, 0.78 ± 0.12 *v* 1.26 ± 0.13; RyR, 0.38 ± 0.15 *v* 0.86 ± 0.18; Na:Ca exchanger, 0.61 ± 0.21 *v* 0.90 ± 0.16. We propose that these near normalizations of gene expression of proteins involved in calcium handling may contribute to improved contractile performance observed at higher stimulation rates after LVAD support.

Discussion

As shown in the data presented earlier and in studies in other laboratories, LVADs have now been shown to induce reverse remodeling of several aspects of ventricular pathophysiology including (1) reversal of chamber enlargement and normalization of EDPVR[6]; (2) a global reduction in LV mass and regression of myocyte hypertrophy in patients after LVAD support[11,20]; (3) increased contractile properties, enhanced inotropic response to β-adrenergic stimulation, more normal contractile responses to increased rates of stimulation, and improved cytosolic Ca^{2+} transients (increased peak, accelerated decay)[8]; and (4) near-normalized expression of gene encoding for proteins involved in calcium metabolism. Despite the multitude of facets of reverse remodeling already identified, it is likely that there are many more as yet unexplored aspects of cardiac pathophysiology that are improved by LVAD support. Improved contractile performance, a bottom line indicator that global cellular processes are regaining normal properties, speak to this fact. As studies of this nature grow to be able to include greater numbers of patients, it will also become increasingly important to analyze results separately from patients with different heart failure causes; myocardial responses to LVADs may differ in the setting of chronic ischemic cardiomyopathy compared with other forms of dilated cardiomyopathy.

The precise mechanisms underlying the various aspects of reverse remodeling remain to be determined. The mechanisms underlying hypertrophy and chamber remodeling in response to pressure and volume loading of the myocardium involves intricately orchestrated up- and down-regulations of a multitude of intracellular signaling cascades; although having been investigated for over 20 years, these mechanisms are still not understood. It has been our working hypothesis that reverse remodeling involves the same mechanisms working in the opposite direction; however, additional mechanisms may be in effect. By restoring cardiac output, blood pressure, and renal perfusion, LVAD support leads to normaliza-

tion of the neurohormonal and cytokine environment that may have profound effects in normalizing cellular properties.

Recent evidence suggests that in some patients, LVAD support may lead to improvement of global pump function of sufficient magnitude to permit explantation of the device without subsequent transplantation.[21,22] This has led to the concept of using LVADs as a bridge to recovery. The potential of this possibility is strengthened by data showing the global extent to which reverse remodeling occurs. On the other hand, data suggest that there is only a very low incidence of full recovery during LVAD support as assessed by exercise testing with device output turned down and the outcome of a small group of patients that underwent explantation was not uniformly good. Accordingly, weaning from LVAD support is not currently the standard of care. Nevertheless, the goal of using LVADs as a bridge to recovery is a worthy pursuit because of the severe imbalance between the number of patients requiring transplant and the number of available donor hearts. Better understanding of the process of reverse remodeling will aid the development of adjunctive therapies, better patient selection criteria, and perhaps optimum LVAD use protocols to improve patient outcome after LVAD explantation.

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