With improved technology, increasing clinical experience, and expanding indications for use, left ventricular assist devices (LVADs) are assuming a greater role in the care of patients with end-stage heart failure. Early in the course of LVAD use as a bridge to transplant, it became evident that some patients exhibit substantial recovery of ventricular function, which led to the concept of reverse remodeling.

Methods and Results: Herein we summarize and integrate insights derived from a multitude of studies that have investigated how LVAD support influences ventricular structural, cellular, extracellular matrix, molecular, biochemical, and metabolic characteristics of the end-stage failing heart. The focus includes a review of the extent and sustainability of reverse remodeling, the important advances in understanding of the pathophysiology of heart failure derived from these studies and the implications of these findings for development of new therapeutic strategies.

Conclusion: In brief, studies of LVAD-heart interactions have led to the understanding that although we once considered the end-stage failing heart of patients near death to be irreversibly diseased, when given sufficient mechanical unloading and restoration of more normal neurohormonal milieu, a relatively large degree of myocardial recovery is possible. Comparison of effects on right and left ventricles have provided mechanistic insights by implicating hemodynamic unloading as primarily regulating certain aspects of reverse remodeling, neurohormonal factors as regulating other aspects, and joint regulation of still other aspects. As such these observations have driven a shift of thinking of chronic heart failure as a progressive irreversible disease process to a potentially treatable entity.

Key Words: Heart failure, extracellular matrix, hypertrophy, right ventricle, excitation-contraction coupling.
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LVAD, left ventricular assist device; LV, left ventricle; RV, right ventricle; ANP, atrial naturetic protein; BNP, brain naturetic protein; ET-1, endothelin-1; IL, interleukin; MMP, matrix metalloproteinases; TIMP, tissue inhibitors of metalloproteinases; iNOS, inducible nitric oxide synthase.

*To limit the number of citations, some references have necessarily been excluded from this listing.
profound, impacting on nearly every aspect of myocardial and systemic properties that is pathologically altered in the heart failure state; a detailed overview of studies performed to date is provided in Table 1. For the sake of brevity it is not possible to discuss all aspects detailed in this table nor possible to include every reference published on this rapidly growing field. This review attempts to summarize and integrate insights derived from these studies as they pertain to advancing understanding of the pathophysiology of heart failure, the extent and sustainability of reverse remodeling, and to their implications for development of new therapeutic strategies.

**Primary and Secondary Effects of LVAD Support**

LVADs were designed primarily to assume responsibility for pumping blood to restore normal cardiac output and blood pressure (Figs. 1 and 2) and allow reduction (or elimination) of the need for toxic levels of pressor and inotropic support. With LVADs of most designs, this is achieved by withdrawing blood from the left ventricle or atrium and returning it to the arterial system.

In addition, there are at least 2 beneficial secondary effects of LVAD support. First, based on their anatomic connections, LVADs are pumps functionally positioned in parallel to the normal left ventricle. As such, they divert blood from the left ventricle and provide profound LV pressure and volume unloading. This also results in reductions in pulmonary venous and arterial pressures and reduced pulmonary vascular resistance (ie, right ventricular afterload is reduced). Second, by normalizing blood pressure and cardiac output, LVAD support improves perfusion to all body organs, which results in improved autonomic function and normalization of the neurohormonal and cytokine milieu that is present in heart failure. The potential significance of these secondary effects may have been unanticipated by early LVAD designers, but their profound importance is now widely recognized. Heart failure is considered a systemic disease that affects many organs because of hypoperfusion and the abnormal neurohormonal and cytokine milieu; normalization of this milieu by LVADs promotes systemic recovery.

Not all secondary effects of LVAD support, however, are beneficial. LVADs provide pressure and volume unloading only to the LV. In the face of increased cardiac output, the right ventricle (RV) is often volume overloaded and unable to accommodate the resultant flow. Consequently, right heart failure (ie, normal or low cardiac output, normal or low pulmonary venous pressure with high central venous pressure) and RV distention occur in as many as 20% to 30% of LVAD recipients. In many instances this can be treated with inotropic agents or pulmonary vasodilators, but in some instances simultaneous right ventricular support is required.

As detailed later in this article, investigators have taken advantage of these differential effects on the LV and RV to clarify mechanisms of remodeling and reverse remodeling. Although the neurohormonal milieu is determined largely (though not entirely) by the blood perfusing the myocardium and is therefore common to the left ventricle and RV, hemodynamic benefits of LVADs are provided, for the most part, only to the left ventricle. Consequently, comparisons of effects on the right and left ventricles allowed identification of whether primary mechanism of specific aspects of recovery are due to hemodynamic factors, to neurohormonal factors, or to both.

**Ventricular Structural Reverse Remodeling**

Ventricular structure is characterized by LV muscle mass and the end-diastolic pressure-volume relationship...
Although studied for decades previously, it was not until the seminal work of Pfeffer and colleagues that it was demonstrated in experimental heart failure that this relationship shifts rightwards toward larger volumes in chronic heart failure, a phenomenon they called ventricular remodeling. It is known that such structural ventricular remodeling results from changes in cell width and length (hypertrophy), fiber rearrangement, and extracellular matrix changes in response to the abnormal stresses and neurohormonal stimulation present in heart failure. Similar shifts of the EDPVR in human heart failure were soon confirmed in both ischemic and idiopathic cardiomyopathies. Interventional studies in animals and humans suggested that the extent of remodeling could be limited, at least after acute myocardial infarction, with the use of vasodilators. However, in the 1980s and early 1990s, it was generally believed that after the heart was markedly dilated, no form of therapy could meaningfully reverse that process, which led to the generally held concept of irreversible, end-stage cardiomyopathy.

Among the initial case reports of patients undergoing prolonged LVAD support, a chest X-ray published by Frazier showed a small cardiac silhouette after prolonged LVAD support suggesting, in contrast to the preoperative severe chamber dilation, the presence of a nondilated heart. It was recognized that this finding could simply have been due to the unloading provided by the pumping LVAD, which decompressed the would-be dilated heart, particularly in the acute setting. However, this was subsequently shown not to be the case after chronic support through examination of the EDPVRs. LV EDPVRs were measured from human hearts explanted at the time of orthotopic transplantation in patients requiring LVAD support, from those not requiring LVAD support, and from several normal human hearts not suitable for transplant (Fig. 3A). Compared with normals, EDPVRs of non–LVAD-supported hearts were shifted toward markedly increased volumes (remodeling). In contrast, EDPVRs from LVAD-supported hearts were shifted far rightward in heart failure, shifts, over time, back toward normal. Shown in (A) are average EDPVRs from normal human hearts, from failing hearts not supported with LVAD, hearts supported with an LVAD for less than 40 days and hearts supported with in LVAD for more than 40 days. (B) Heart size, indexed by V30, the volume required to achieve an end-diastolic pressure of 30 mm Hg as a function of duration of LVAD support from individual hearts (see a insert for symbol key). Also shown are values from normals and from failing hearts not supported by LVAD. Underlying the reduction in heart size is regression of cellular hypertrophy. (C) Cross-section of normal human myocardium. In chronic heart failure (D), the myocytes are markedly hypertrophic. After LVAD support (E), LV myocardial hypertrophy regresses (individual myocyte cross-sectional area reduced). Increased interstitial fibrosis is also noted. All myocardial samples used for C–E were fixed in an unloaded state. All figures from Madigen et al.
hearts were more similar to normal. The near-normal position of these EDPVRs reflected a shift of the relations from high to significantly lower volume. We referred to this shift of the EDPVR back toward normal as reverse remodeling.16

The time course of reverse structural remodeling has been inferred by plotting the position of the EDPVR (indexed by the volume at a fixed pressure of 30 mm Hg, \( V_{30} \)) as a function of LVAD support (Fig. 3B).27 This relation assumed a roughly exponential time course with average time constant of 30.8 days, with the process reaching its maximal effect by about 90 days. On average, however, the hearts did not return to completely normal size. \( V_{30} \) averaged about 280 mL without LVAD support, about 150 mL after maximal reverse remodeling compared with about 100 mL in the normal hearts.

The right ventricle of the failing heart is also generally dilated, though not as significantly as the LV. RV \( V_{30} \) is about 80 mL in normal hearts and reaches about 150 mL in cardiomyopathy.18 In contrast, RV \( V_{30} \) of LVAD supported hearts also averages about 150 mL, indicating that the structural reverse remodeling is not generally observed in this chamber.18 Because central venous pressures remains elevated during LVAD support,17–22 the lack of reverse structural remodeling in the RV at the same time when reverse structural remodeling is strongly present in the LV signifies that reverse structural remodeling is primarily mediated the hemodynamic unloading and not by normalized neurohormonal milieu. Because LVADs also reduce RV afterload,17,23 the factor regulating reverse structural remodeling can even more specifically be targeted as the reduction in preload. Additional support for this hypothesis is provided by the findings that (1) on the rare occasion when an LVAD inflow valve failed the heart would be reloaded and would redilate (rightward shifted EDPVR) despite maintenance of normal forward cardiac output and blood pressure31 and (2) that indeed RV \( V_{30} \) regresses toward normal in hearts of patients receiving right ventricular device support.12 Similar univentricular effects are observed on regression of free wall mass and cellular hypertrophy (Fig. 3C–3E).18,27,29,30,32,35–39 The time course of change of LV myocyte cell dimension paralleled changes in mass and \( V_{30} \), but no such changes were observed in the RV.18

Finally, in addition to normalized myocyte diameter, LVAD support induces normalization of the cytoskeleton as evidenced by normalization of sarcomeric proteins, vinculin, desmin, and \( \beta \)-tubulin.38,67–71

**Improved Myocardial Function**

In addition to the effects on structure, studies of trabeculae and myocytes isolated from LVAD supported hearts also demonstrate improved intrinsic myocardial contractile properties. Dipla et al first described that LVAD support led to increased contractile strength, faster time to peak contraction, and reduced time to 50% relaxation in isolated cardiomyocytes.42 It was demonstrated in this same study that myocytes also exhibited improved contractile responses to increased frequency of stimulation (normalized force-frequency relationship, FFR) and to \( \beta \)-adrenergic stimulation. These findings were subsequently confirmed in isolated trabeculae.18,19,43–45 Recovery of the FFR correlated with improved expression of calcium cycling genes and improved calcium accumulating efficaASY of the sarcoplasmic reticulum.18,27,43,46 Improved \( \beta \)-adrenergic responsiveness correlated with improved \( \beta \)-receptor density and normalized phosphorylation of the calcium release channel.19,44,47 Interestingly, we observed that the FFR improved in LV myocardium but not in RV myocardium, which also correlated with chamber-specific normalized expression of genes involved with calcium cycling.18 In contrast, \( \beta \)-adrenergic responsiveness improved in myocardium of both RV and LV. These findings suggested that some aspects of functional recovery (eg, FFR and gene expression of calcium handling genes) are primarily regulated by hemodynamic factors, whereas other factors (eg, \( \beta \)-adrenergic signaling) are primarily regulated by normalized neurohormonal milieu.

**Extracellular Matrix**

In addition to structural and functional changes, LVAD support is also associated with changes in the characteristics and metabolism of the extracellular matrix. In contrast to other aspects, however, extracellular matrix properties do not change uniformly in a manner indicative of conversion back to the normal state. Indeed, several studies show that myocardial collagen content increases during mechanical unloading above the already abnormal levels observed in the chronic failing state.27,32,34,73 In contrast, results of a few studies indicated the opposite.36,74 In our recent study we showed that LVAD support was associated with a significant increase in total and especially crosslinked collagen deposition in LV myocardium,20 MMP-1 and MMP-9 levels and activity (matrix metalloproteinases, which are enzymes involved in breakdown of collagen), which are increased in the failing state, tended to decrease following LVAD support. Concomitantly, TIMP-1 (tissue inhibitors of metalloproteinases) levels increased tremendously after LVAD support, leading to a normalization of the MMP-1/TIMP-1 ratio. In addition, myocardial tissue levels of angiotensin I and II, known regulators of myocardial collagen synthesis, increased during LV unloading and the ratio of type I to type III collagen shifted (abnormally) to the more stiff type I collagen. In aggregate, these findings suggested that the high rate of collagen breakdown observed in end-stage heart failure is reduced during LVAD support, resulting in an overall increase in collagen content. We also observed that these biochemical changes lead to an increase in myocardial stiffness, which we speculated could be a factor contributing to the only rare occurrence of full recovery of function after LVAD support and the often progressive deterioration of pump function after LVAD explantation (as will be discussed later in this article). Findings in the RV were somewhat mixed, with most aspects trending in the same direction as in the LV, but typically not reaching statistical significance. This somewhat ambiguous picture lead
us to conclude that both neurohormonal and mechanical factors likely contribute importantly to extracellular matrix metabolism.

Molecular, Biochemical, and Metabolic Changes

As alluded to previously, the structural and functional improvements in myocytes and ventricular chamber have as their basis normalized expression of certain genes and posttranslational regulation of certain proteins that improve cellular functions and metabolism. It is well known that a multitude of changes in myocardial gene expression occur in heart failure that are generally considered to reflect a shift from the normal adult to a fetal gene program. Telio logically, this shift is believed to be driven by the mechanical and neurohormonal stresses of heart failure, features of which partially mimic the fetal environment. Compared with adult myocytes, fetal myocytes have a greater ability to undergo cell division. The changes associated with heart failure can thus be viewed as a response that reverts the genotype to a state in which the cells were more readily able to increase cell number and normalize wall stress. Because the transformation to the fetal state is incomplete, the mechanical and neurohormonal environment drives hypertrophy and, ultimately, apoptosis (programmed cell death).

The influence of LVAD support on gene expression, protein content, and protein function has been studied by several groups. As discussed previously, early studies showed normalization of expression and function in the LV (not the RV) of proteins involved with calcium handling known to be abnormal and contribute to contractile dysfunction in heart failure. Many studies have also focused on expression of genes involved with hypertrophy, cell cycling, and apoptosis. A majority of studies suggest that these genes shift toward normal during LVAD support and indicate a regression of hypertrophy and reduction in the amount of apoptosis (Table 1). However, not all such genes are normalized by LVAD support. Razegi et al showed that the PKB/Akt/GSK-3beta pathway is not activated during LVAD support and concluded that other signaling pathways must be responsible for the improvement of cellular function and cell survival.

Studies of the influence of LVAD support on myocardial metabolism have also yielded mixed results. On the one hand, improvement of overall myocardial mitochondrial function and enhanced caveolin expression (hypothesized to contribute to improved lipid metabolism) have been reported. On the other hand, gene expression of other proteins involved in metabolism that are downregulated in heart failure (eg, glucose transporter 1 and 4 and muscle carnitine palmitoyl transferase-1) are not normalized during mechanical unloading. Thus it appears that LVAD support only partially reverses depressed expression of genes involved in metabolism in the failing human heart.

More recently, microarray GeneChip platforms have been used to survey changes in transcription patter in response to LVAD support. Hall et al showed that 22 genes were downregulated, whereas 85 genes were upregulated after LVAD support. Genes involved in regulation of myocardial hypertrophy and vascular signaling were significantly downregulated. Using this technique, our group showed that calcium-handling genes were upregulated, whereas genes involved with regulation of myocardial fibrosis did not change on the transcription level. Margulies et al identified 3088 transcripts that exhibited abnormal abundance. As a consequence of LVAD support, only 11% of these genes exhibit partial recovery and only 5% showed true normalization. This latter study in particular reinforced the notion that although normalization of specific genes of interest can be identified after LVAD support, the normalization is not ubiquitous and expression of many genes (in fact a vast majority of genes), is still abnormal and may provide clues as to why function is not completely normalized in most LVAD patients. In the most recent study, Birks et al used microarray technology to assess gene expression profiles in LVAD patients who recovered to a degree that permitted LVAD explant compared with those in which recovery was insufficient. These investigators found distinct differences in expression of sarcomeric and cytoskeletal proteins between the 2 groups, which led to interesting new hypotheses about the mechanisms of recovery. Still, studies of protein content and protein function lag behind studies of gene expression in identifying the number of proteins that are either present in abnormal quantities or whose function is abnormal.

Mechanisms of Reverse Remodeling Are Unknown

The biology of how cardiac muscle responds to alterations in mechanical stress remains largely unknown. Most prior research has been devoted to understanding the impact of increased afterload as occurs in myocardial hypertrophy. Yet, after more than 40 years of physiologic, biochemical, and molecular research, it is still not fully understood how stress or strain regulate gene expression, assembly of sarcomeric and cytoskeletal proteins, and modify calcium cycling and function of other ion channels. Membrane bound macromolecules that link extracellular matrix and intracellular elements (integrins) and membrane bound components of a multitude of signaling cascades (eg, pathways involved in α- and β-adrenergic signaling, growth hormones, phosphokinases) have all been implicated in the hypertrophic response through their impact on many signaling cascades. Less well studied is the response of the normal heart to mechanical unloading and the development of atrophy. It has been our simplistic assumption that the mechanisms leading to normalization of myocardial abnormalities present in heart failure during mechanical unloading by LVADs reflects normalization of these very same signaling cascades invoked during hypertrophy as opposed to recruitment of pathways specific for the generation of atrophy. Although evidence available thus far is
consistent with our assumption, this is an assumption that has yet to be tested. So far, tissue derived from patients undergoing LVAD support provides the best opportunity to study this because of the paucity of experimental models of myocardial unloading or reverse remodeling.

Effects of Different LVAD Flow Patterns on Reverse Remodeling

In general, 2 different classes of LVADs are now in use for long-term support: pulsatile and non-pulsatile LVADs. During the last decade, pulsatile LVADs were dominant in clinical use, but nonpulsatile devices are now the dominant form in development as next-generation applications. Studies are beginning to compare the physiologic effects of pulsatile and nonpulsatile LVADs. For example, Loebe et al show that the inflammatory response measured by tumor necrosis factor-α and C5a was significantly more increased after implantation of a nonpulsatile LVAD than with a pulsatile LVAD. Potapov et al showed that biochemical marker of brain damage were similar between the 2 LVAD types in the first 14 days after implantation, similar to the study from Vatta et al, who demonstrated reversal of disruption of dystrophin with either pulsatile or nonpulsatile LVADs. Only 1 study evaluated hemodynamic effects during long-term support with nonpulsatile and pulsatile LVADs. It was found that LV pressure unloading was similar between these 2 types of LVADs, whereas LV volume unloading was significantly more pronounced with a pulsatile device. Most recently, Thohan et al showed that although there are differences between these 2 classes of devices with regard in magnitude of unloading, both forms of support were equally effective in normalizing cell size and tumor necrosis factor-α levels. These findings might provide important insights into the remodeling process with different LVAD support.

Clinical Evidence of LVAD-Induced Ventricular Contractile Recovery

Although recovery of LV function is commonly observed when LVADs are used in the setting of acute heart failure syndromes, the concept of recovery of ventricular function in patients with chronic heart failure after LVAD has been described only recently. It is noteworthy, however, that all of the research described concerning the relatively large degree of structural and functional reverse remodeling in chronic heart failure was entirely spawned by early clinical observations that significant recovery of LV function occurs during LVAD support. The first reported case of cardiac functional recovery after LVAD support involved an otherwise healthy young man with an idiopathic cardiomyopathy. At the time of intended transplant, the native heart was observed to have normal hemodynamic measurements with a normal ejection fraction. The transplant was aborted, the LVAD explanted and the patient became the first BTR with a HeartMate LVAD. After LVAD removal, however, the heart progressively redilated to its original pre-LVAD condition and unfortunately the patient succumbed to heart failure. The initial elation of investigators was dashed by the realization that the recovery could not be sustained when the heart was re-exposed to the hemodynamic load of the circulation.

Since our first experience, several groups have reported their clinical experiences concerning recovery of ventricular function post LVAD support. The results have varied, with some centers reporting a high frequency of LVAD explantation followed by sustained recovery and others only describing rare cases of myocardial recovery. Based on a retrospective chart review, we observed only 5 patients from among 111 patients with chronic heart failure who exhibited sufficient recovery to permit LVAD explantation without transplantation. All of these patients eventually developed recurrent heart failure, with 2 patients requiring a second LVAD for recurrent heart failure and the remaining 3 patients dying of progressive heart failure.

We also used exercise stress testing (including exercise hemodynamics, echocardiography, and oxygen consumption), to identify potentially recovered patients. Patients underwent cardiopulmonary exercise testing with the LVAD providing full support. Exercise was repeated in those patients who were able to tolerate weaning of flow to about 2 L/minute. Patients were considered for device explantation if they were able to exercise with minimal LVAD support and achieve a maximal oxygen consumption of 20 mL·kg·minute or peak cardiac output greater than 10 L/minute. Thirty-nine patients underwent cardiopulmonary stress testing approximately 3 months after LVAD implant according to this strategy. Weaning to partial support was achieved in only 7 of the 39 patients. Peak oxygen consumption declined in these 7 patients from an average of 17.3 mL·O2·kg·minute during full support to 13.0 mL·O2·kg·minute during partial support. The LVAD was explanted in only 1 patient demonstrating partial recovery due to device infection. This patient subsequently required reinsertion of another LVAD.

Another strategy for identifying potential responders has been through the use of dobutamine stress echocardiography. Preliminary data suggest that this technique may identify patients with sufficient recovery to tolerate device explantation. Kahn et al identified 9 of 16 patients with dilated cardiomyopathy in whom cardiac output increased and pulmonary capillary wedge pressure maintained below 15 mmHg in response to dobutamine; these 9 patients were successfully weaned. Six of these patients survived for at least 1 year, but all subsequently died or required transplant (Torre, personal communication).
mechanical circulatory support device database from 2004 showed that LVADs were used as bridge-to-transplant in 75.5% of cases, as destination therapy in 8.4% of cases and as BTR in 5.8% of cases. Of the 24 patients from the BTR group, 7 died before transplant, 2 did not recover after LVAD placement and had to be transplanted, and in only 8 patients LVAD explantation could be performed. Unfortunately, criteria used to select patients for BRT and follow-up reporting on freedom of recurrent heart failure after device explant are not described and may not be uniform at the different participating centers.

In contrast to these reports, the Berlin Heart Group reports a higher frequency of LVAD-induced myocardial recovery in patients with chronic idiopathic cardiomyopathy. More than 33% of their patients with dilated cardiomyopathy have undergone device explantation for recovery. Over a 10-year period, 33 patients with chronic nonischemic cardiomyopathy supported with an LVAD underwent explanation after recovery. The majority of these patients have sustained improvement with a 5-year survival of 85%. Recurrence of heart failure was observed in 32% of patients by 2 years after device explantation. Six patients required cardiac transplantation. One patient died of heart failure and 3 patients died of non-cardiac causes after device explantation. Predictors of sustained recovery included LV end-diastolic dimension less than 55 mm and ejection fraction greater than 45% during a 15-minute pump stop experiment and a less than 5 years history of heart failure and 3 patients died of non-cardiac causes after device explantation. Over a 10-year period, 33 patients with chronic heart failure and 3 patients died of non-cardiac causes after device explantation. Predictors of sustained recovery included LV end-diastolic dimension less than 55 mm and ejection fraction greater than 45% during a 15-minute pump stop experiment and a less than 5 years history of heart failure (positive predictive value of stable heart function > 3 years post explant of 92%). Hetzer et al also observed that optimal improvement in LV size and function occurred within approximately 90 days of LVAD implantation, but noted a gradual deterioration with longer periods of support.

The LVAD Working Group Recovery Study, a multicenter study including the 8 largest LVAD groups in the United States (Baylor, Cleveland Clinic, Columbia, Temple, Texas Heart Institute, and Universities of Michigan, Minnesota, Pittsburgh) was established in response to these contrasting reports of recovery during LVAD support. In this prospective study, 67 LVAD patients underwent monthly assessment of cardiac function using echocardiography at full and partial support. Fifty-five percent of the patients had dilated cardiomyopathy and 45% coronary artery disease. Serial echocardiographic assessment obtained during downtitrated LVAD support demonstrated significant improvement in LV ejection fraction and reduction in LV diameters as compared with pre-LVAD implantation. LVEF rose from an average of 17% preimplant to 34% at 1 month after implant during partial ventricular assist. Thirty-one percent of patients had ejection fractions > 40%. Three patients with acute heart failure (symptom duration < 1 week) and 2 patients with recent onset CHF (duration < 6 months) exhibited complete recovery and underwent successful LVAD explant. One patient with chronic heart failure had partial recovery but underwent device explantation because of device malfunction. This patient quickly deteriorated with ejection fraction falling from 35% to 20%.

### Strategies to Enhance Ventricular Contractile Recovery

Another group reporting success in bridging cardiomyopathic patients to full recovery and LVAD explant is the Harefield group. Led by Sir Magdi Yacoub, this group uses aggressive high dose heart failure medical therapy early post device implant in combination with clenbuterol, a β-2 adrenergic receptor agonist known in animal models to induce skeletal and cardiac muscle hypertrophy and improved contractile strength. Early after device implant, patients are treated with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and β-blockers followed by initiation of clenbuterol. Of 15 patients managed at Harefield with this protocol, 70% (11 patients) demonstrated sufficient recovery to allow device explantation. Clenbuterol was stopped just before device explantation and not resumed. After 3 years of follow-up, the average reported ejection fraction of these patients remains 60% to 65%. To date, only 1 patient is reported to have demonstrated clinical deterioration, and that was associated with significant alcohol intake. More recently, this group found that clenbuterol induces insulin-like growth factor I (IGF-I) in cardiac myocytes in vitro. They subsequently examined changes in IGF-I expression in patients who recovered after LVAD support combined with clenbuterol treatment. They found that patients with low IGF-I mRNA levels at implantation showed significant increase during recovery and those with high IGF-I mRNA at implantation remained high. In both groups, levels returned to normal by 1 year after explantation. They concluded that elevated myocardial IGF-I mRNA levels could play a role in recovery by limiting atrophy and apoptosis during reverse remodeling. At this time a multicenter study is planned to determine whether the results obtained at Harefield can be replicated by US centers (ie, Harefield Recovery Protocol Study).

### Conclusion

Shifts of ventricular and myocardial properties back toward normal observed during LVAD support are collectively referred to as reverse remodeling. The term can be used in a more focused manner by adding a qualifier and specifically denoting structural, molecular, biochemical or metabolic, reverse remodeling. Although many properties exhibit profound reverse remodel during LVAD support (eg, ventricular mass and structure), this is not a ubiquitous process. Important examples of myocardial or ventricular properties that do not regress toward normal during LVAD support include abnormal extracellular matrix metabolism, increased tissue angiotensin levels, myocardial stiffening, and partial recovery of genes involved with metabolism. Indeed, broad surveys of myocardial gene expression using gene chip technology reveal that expression of only a small percentage of abnormally expressed genes normalizes.
In addition, LVAD support cannot correct an aquired or inherited genetic defect that may underlie an idiopathic cardiomyopathy. For the case of ischemic cardiomyopathy, LVAD support is not known to lead to repopulation of the infarcted tissue with contracting myocytes. These realities may serve to establish theoretical and practical limits to the extend and sustainability of LVAD-induced reverse remodeling.

Nevertheless, studies of LVAD-heart interactions have led to the understanding that although we after considered the end-stage failing heart of patients near death to be irreversibly diseased, when given sufficient mechanical unloading and restoration of more normal neurohormonal milieu, a relatively large degree of myocardial recovery is possible. Comparisons of effects on right and left ventricles have provided mechanistic insights by implincating hemodynamic unloading as primarily regulating certain aspects of reverse remodeling, neurohormonal factors as regulating other aspects and joint regulation of still other aspects. As such these observations have driven a shift of thinking of chronic heart failure as a progressive irreversible disease process to a potentially treatable entity.

One intriguing concept generated by the findings of these studies is the conclusion that significant hemodynamic unloading, as provided only by LVADs, is necessary to induce profound reverse structural remodeling, in which case LVADs could assume a central role in any highly effective, potentially curative strategy for patients with severe heart failure. LVAD-Induced Reverse Remodeling

LVAD support is combined with one or more other treatment modalities, such as a drug therapy, cell therapy, or possibly a passive restraint device to prevent post-LVAD explant remodeling may prove particularly fruitful.

References


