

Reversal Mechanisms of Left Ventricular Remodeling: Lessons From Left Ventricular Assist Device Experiments

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ABSTRACT

The mechanical left ventricular assist device (LVAD) has become a reliable means of stabilizing the conditions of medically refractory patients with severe heart failure who are awaiting heart transplantation. At the same time, a substantial and growing body of evidence indicates that LVAD support triggers a multitude of adaptations within the failing human heart that seem to be triggered by hemodynamic unloading of the failing heart and changes in intracardiac and systemic neurohumoral activity. At the cell and tissue level, virtually every type of pathologic defect associated with failing human hearts demonstrates changes during LVAD support, and these adaptations are usually towards a less pathologic phenotype. This review summarizes the available literature concerning the phenomenology of so-called reverse remodeling. From this review it is clear that myocardial responses to LVAD support reveal the remarkable plasticity of even the most severely failing hearts. The composite literature on myocardial responses to LVAD support supports the thesis that mechanical overload is a primary factor sustaining the pathologic phenotype of the failing heart and suggests that the study of reverse remodeling provides a valuable opportunity to discover adaptive signaling pathways capable of mediating myocardial recovery.

Mechanical left ventricular assist devices (LVADs) have become a reliable means of sustaining medically refractory patients with heart failure awaiting cardiac transplantation. Immediately after their implantation, LVADs induce profound cardiac unloading including decreases in both preload and afterload. The profound decreases in cardiac-loading conditions are well illustrated by the immediate decreases in left ventricular end-diastolic volume and increases in relative wall thickness observed immediately after LVAD implantation.¹ Measurements of cardiac hemodynamics before and after

initiation of LVAD support affirm the striking and sustained decreases in myocardial preload and afterload and also demonstrate marked increases in effective cardiac output.^{2,3} Over time, LVAD support is associated with progressive decreases in the neurohormonal activation associated with advanced heart failure. Specifically, sustained LVAD support induces deactivation of the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the arginine vasopressin and intracardiac natriuretic peptide systems.^{2,4} Given the dramatic decreases in hemodynamic loading conditions and neurohumoral deactivation engendered by LVAD support, investigations of patients supported with LVADs permit unique studies elucidating the plasticity of the failing myocardium and the heart failure syndrome itself.

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Phenotype of the Failing Heart

The characteristic cellular abnormalities observed in failing cardiac myocytes are listed in Table 1. Many of

these features of the phenotype of advanced dilated cardiomyopathy are observed in parallel fashion at both the cellular and organ levels. For example, increases in volume and the relative elongation observed in myocytes from failing human hearts are reflected in increases in cardiac mass and the increase in relative wall thickness observed in the failing heart. Similarly, the abnormal contractility and slowed relaxation observed in failing myocytes lead to the systolic and diastolic abnormalities observed in the intact heart *in vivo*. Additional defects readily apparent at both the organ and cellular levels in most failing hearts include electrophysiological abnormalities, impaired beta-adrenergic responsiveness, and impaired contractile responses to increases in stimulation frequency (the negative force-frequency response). Further studies of failing human myocardium at the cellular level have suggested several mechanisms likely contributing to the pathophysiology of pump dysfunction, including the following: increased rates of apoptosis, pathological patterns of gene expression, and dysregulation of key signaling pathways. Beyond the cardiac myocyte, the failing heart is also characterized by abnormalities of the cardiac extracellular matrix (ECM) reflecting imbalances in the matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors of metalloproteinases (TIMPs), which regulate remodeling of the ECM.

“Reverse Remodeling” With LVAD Support

By providing human myocardial tissue both before and after LVAD support, the “bridge-to-transplant” use of LVADs offers a unique opportunity to study the phenomenology of “reverse remodeling” at the tissue level. In this context, studies to date have described alterations in virtually all of the characteristic features of the failing and remodeled cardiac myocyte listed in Table 1. These multilevel findings are summarized below, and instances where parallel observations have been made at the cellular and whole heart level are highlighted. It should be

Table 1. Cellular and Tissue Phenotype of Advanced Dilated Cardiomyopathy

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- Increased myocyte size
 - Abnormal myocyte shape (elongation, flattening, increased branching?)
 - Abnormal calcium handling
 - Impaired contractility
 - Impaired relaxation
 - Impaired responses to increased stimulation frequency
 - Electrophysiological abnormalities including action potential prolongation
 - Reduced β -adrenergic responsiveness
 - Pathological activation of signaling pathways including apoptosis
 - Abnormalities of the extracellular matrix (fibrosis, decreased cross-bridging)
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emphasized that *in vivo* extensions of tissue-based observations often address shortcomings and compromises inherent in *in vitro* studies. For example, patient-based studies entail a more comprehensive sampling of processes reflected at both the cell and organ levels while also permitting serial assessments that may better define temporal patterns of myocardial recovery and reverse remodeling.

Reversal of Morphological Hypertrophy

Given that both hemodynamic overload and neurohumoral activation have been implicated as primary triggers of cardiac myocyte hypertrophy, one would expect the unloading and neurohumoral activation associated with LVAD support to induce regression of myocyte hypertrophy. Indeed, several different studies have reported decreases in myocyte size after LVAD support is initiated.^{2,3,5-7} In the most comprehensive study to date, Zafeiridis et al used isolated cardiac myocytes to evaluate changes in myocyte size, shape, and heterogeneity after sustained LVAD support. These studies demonstrated that the average volume of failing human myocytes is nearly twice as great as that observed in nonfailing myocytes and that LVAD support is associated with a 60% regression of this pathological hypertrophy.³ Similarly, LVAD support induces a 62% regression of the increase in average myocyte length and decreases the marked heterogeneity of myocyte length associated with advanced heart failure. A recent report by Barbone et al⁶ demonstrated that decrements in myocyte size during LVAD support are not observed in the minimally unloaded right ventricle, supporting a primary role for mechanical factors rather than neurohumoral regulation in mediating the regression of hypertrophy observed in LVAD-supported patients. This reverse remodeling of cell dimensions was associated with marked reverse remodeling at the organ level, including a near normalization of LV end-diastolic diameter and LV mass among failing hearts receiving LVAD support. With respect to chamber dimensions, separate studies examining end-diastolic pressure-volume relationships have confirmed that decreases in echocardiographically defined LV dimensions reflect a true change in cardiac geometry rather than simply reflecting cardiac decompression.^{8,9}

Reversal of Contractile Dysfunction

Several different studies have demonstrated improvements in myocardial contractile function as measured in isolated myocytes and isolated muscle strips after employment of LVAD support. Use of *in vitro* techniques in these studies avoids the potentially confounding effects of LVAD-associated changes in loading conditions on *in vivo* measures of contractility. In isolated human cardiac myocytes, Dipla et al¹⁰ observed that 1 to 6 months of LVAD support was associated with significant improve-

ments in the fractional shortening of isolated myocytes, with even more marked improvements in the rates of shortening and relaxation. In isolated cardiac muscle strips, Heerdt et al⁹ demonstrated 38% percent improvement in developed force after LVAD support using a paired tissue analysis in which the pre-LVAD contractility of muscle strips from LV apical core were compared with the post-LVAD contractility of muscle strips from the LV free wall. In contrast, studies by Ogletree-Hughes et al¹¹ did not support alterations in developed tension or other contractile parameters under basal conditions, although improved adrenergic responses were evident (discussed further below). Several studies have examined *in vivo* LV contractile function after LVAD support. With the LVAD temporarily turned off, Frazier et al observed a mean change in LV ejection fraction from $11 \pm 5\%$ to $22 \pm 17\%$ after LVAD support.¹² Two separate reports from the Berlin Heart Institute likewise documented increases in LV ejection fraction after LVAD support, yet these studies clearly demonstrated that improved ejection fraction is not a universal finding among LVAD-supported patients.^{13,14}

Several pieces of evidence implicate improvements in defective cardiac myocyte calcium handling as a cellular mechanism contributing to improved basal contractile function after LVAD support. Studies in isolated myocytes have identified changes in the shape of the calcium transient that mirror changes in cellular shortening after LVAD support.¹⁰ Two separate studies have demonstrated LVAD-associated improvements in calcium uptake rates and binding in isolated sarcoplasmic reticulum membranes.^{9,12} Moreover, Heerdt et al⁹ reported LVAD-induced increases in mRNA abundance for sarcoplasmic reticulum adenosine triphosphatase (ATPase), ryanodine receptor, and sodium-calcium exchanger, which are key molecules regulating cellular calcium handling. However, altered mRNA abundance for sarcoplasmic reticulum ATPase and sodium-calcium exchanger was not observed in other studies, and changes in protein abundance for these molecules have not consistently correlated with changes in mRNA abundance for these molecules.⁹ Overall, the findings to date suggest that LVAD-induced changes in cellular calcium-handling likely reflect complex interactions between protein abundance, posttranslational modifications, and electrophysiological factors, which alter the functional balance among key regulatory molecules.

Improved Responses to Increased Stimulation Frequency

In addition to impaired contractile function under basal conditions, impaired contractile reserve is another hallmark of the failing heart. In this context, several studies have demonstrated that LVAD support is associ-

ated with improved *in vitro* contractile performance during increases in stimulation frequency. In isolated human cardiac myocytes, DiPaola et al¹⁰ reported that failing human myocytes from non-LVAD-supported hearts exhibit a stepwise decrease in shortening magnitude when stimulation frequency is increased in increments from 0.2 to 0.5 to 1.0 Hz. In contrast, failing myocytes with antecedent LVAD support exhibited better preserved shortening during increased stimulation frequency. Using isolated muscle strips from human hearts and pacing rates from 1.0 to 2.5 Hz, Heerdt et al⁹ likewise demonstrated negative force-frequency relationship in failing myocardium without previous LVAD support and positive force-frequency response in muscle strips from both nonfailing and LVAD-supported human hearts. This study also observed improved frequency-dependent contractile performance in each of experiments in which cardiac trabeculae from the same patient were studied before and after LVAD support. Although they affirmed that LVAD-support induces improved frequency-dependent contractions of LV trabeculae, recent studies by Barbone et al⁶ showed that improved contraction during increased frequency relationship is not consistently observed in right ventricular trabeculae. Given that the magnitude of hemodynamic unloading and remodeling induced by LVAD support is far less in the right ventricle compared with the left ventricle, these findings suggest that decrease of hemodynamic load is a primary factor underlying improved contractile function and contractile reserve observed after LVAD support.

Changes in Cardiac Electrophysiology

Prolongation of the cardiac action potential is yet another hallmark of the failing myocyte, and prolongation of action potential duration is reflected at the whole organ level in prolongation of the QT interval on the surface electrocardiogram. In medically refractory failing hearts requiring LVAD placement, Harding et al¹⁵ reported that cardiac unloading induces an immediate increase in the heart rate-adjusted QT interval (QTc) despite an immediate decrease in QRS duration that would otherwise be expected to decrease QTc. During sustained LVAD support, there was a secondary decrease in QTc duration that paralleled decreases in the cellular action potential duration measured in isolated human ventricular myocytes. These secondary decreases in action potential duration appear to reflect a reversal of the electrophysiological abnormalities characteristic of the failing human heart.¹⁶ Via modulation of voltage-dependent calcium fluxes, these changes in action potential duration may also translate into changes in contractile function observed after LVAD support. For example, shortening of action potential duration likely contributes to faster myocardial relaxation and improved force

frequency relationship after LVAD support. At the organ level, prolonged depolarization and heterogeneous depolarization (QT dispersion) contribute to arrhythmogenesis in failing hearts.¹⁶ From this perspective, one might speculate that decreases in QT duration might translate into decreased risk of spontaneous ventricular arrhythmias and sudden cardiac death.

Improved Beta-Adrenergic Responsiveness

Recognizing that impaired adrenergic responsiveness contributes to poor exercise performance and is a characteristic feature of the failing heart, several studies have explored the impact of LVAD support on myocardial beta-adrenergic responses. First, Dipla et al¹⁰ observed that isoproterenol induced much greater increments in shortening magnitude in isolated myocytes from LVAD-supported failing hearts compared with myocytes from failing hearts without previous LVAD support. These differences in adrenergic responses were observed even when LVAD and non-LVAD cells studied were matched on the basis of resting contractile performance. Subsequently, Ogletree-Hughes et al¹¹ observed that LVAD-supported failing muscle strips exhibited marked improvements in peak developed tension and in their positive and negative dP/dt responses to isoproterenol compared with failing human cardiac muscle strips without previous LVAD support. These investigators further demonstrated that these improved beta-adrenergic responses did not differ significantly from responses observed in human cardiac trabeculae from nonfailing hearts. Distinctions in adrenergic responses were observed even when there was no difference in basal contractility between nonfailing, failing, and failing/LVAD muscle strip preparations. Several reports have provided possible mechanisms for improved beta-adrenergic responses observed after LVAD support. First, at least 2 previous studies have demonstrated gradual decreases in circulating epinephrine and nor epinephrine during 1 to 2 months after initiation of LVAD support.^{4,13} Moreover, Muller et al^{13,14} reported decreases in circulating anti- β 1-adrenoreceptor auto antibodies during sustained LVAD support. Finally, LVAD support is associated with normalization of otherwise decreased myocardial beta-receptor density in failing human hearts.¹¹ Each of these factors, as well as unexplored changes in downstream adrenergic signaling mechanisms, may contribute to improved beta-adrenergic responsiveness observed after LVAD support of the failing human heart.

Adaptations of Key Signaling Pathways

Although many of the studies highlighted above implicate decreases in mechanical loading conditions as a

primary trigger of “reverse remodeling,” few studies to date have elucidated the signal transduction pathways that may be mediating changes in myocardial phenotype during LVAD support of the failing human myocardium. In recent studies, Flesch et al¹⁷ examined the family of nitrogen-activated protein kinases (MAPKs)—including p44/42 extracellularly regulated kinase, p38 kinase, and c-Jun N-terminal kinase (JNK)—in LVAD-supported human hearts. Compared with failing hearts without LVAD support, these investigators observed decreased p44/42 phosphorylation and activity, increased p38 phosphorylation abundance and activity, and decreased JNK1/2 abundance and activity among LVAD-supported hearts. These distinct changes in MAPK signaling molecules were associated with decreases in myocyte size and decreased rates of myocyte apoptosis based on an *in situ* DNA ligation assay. The findings reporting decreased apoptosis rates after LVAD support are in accord with observations by Bartling et al¹⁸ who reported a decrease in apoptotic myocytes (based on immunohistochemical staining and DNA laddering) in association with upregulation of the anti-apoptotic molecules Bcl-x_L, Mcl-1, and FasExo6Del/Fas.

Remodeling of the ECM

Conflicting descriptions exist of the effects of sustained mechanical support on the remodeling of the ECM. Reports range from those demonstrating no change in the relationship of matrix to myocyte,^{5,19} to reports of increased fibrosis,^{12,20-22} and even reports of decreased fibrosis.⁷ These disparities likely reflect differences in measurement techniques, including adjustments for dramatic shifts in myocyte mass as well as differences in etiology, sampling locations, duration of mechanical support, and/or adjuvant therapies. Recently, Li et al¹⁹ published a detailed description of the extracellular responses to LVAD-support. After 2 months of mechanical unloading, myocardial collagen content was unchanged; however, the degree of extracellular matrix cross-linking was increased. These findings were associated with a shift in the MMP-to-TIMP protein ratio that would tend to decrease the degradation of the myocardial ECM. Overall, the findings suggest that the changes in the extracellular fraction of the myocardium induced by mechanical unloading may be subtle. However, the shift in myocardial remodeling enzyme activity and abundance suggests that the ECM has a highly regulated plasticity similar to that found in myocytes. As with myocytes, changes in mechanical loading conditions appear to be a fundamental trigger for ECM remodeling. Indeed, the ECM has been implicated in mechanotransduction, which triggers myocyte adaptations to alterations in mechanical loading conditions.

Conclusion

In summary, a number of important lessons about cardiac remodeling can be derived from studies of LVAD-supported human hearts. Most obviously, LVAD support induces multilevel regression of the pathological phenotype of the failing human heart. Moreover, changes observed during LVAD support demonstrate that reverse remodeling can occur even in the most advanced cases of dilated cardiomyopathy. Although local and systemic neurohormonal factors may play a role, it is increasingly apparent that mechanical loading conditions are as important in sustaining the pathological features of the severely failing heart as they are in driving the progressive remodeling that occurs during transitions from normal to hypertrophic to failing heart. It is also likely that diverse signaling cascades contribute to the adaptations to myocardial unloading and the phenotypic transitions in the LVAD-supported heart. In this regard, it seems reasonable to wonder whether reverse remodeling involves simply a deactivation of those signaling pathways involved in forward remodeling or rather a unique activation of novel recovery pathways. Regardless of the specific signaling pathways involved, it is likely that some of these LVAD-induced myocardial adaptations might help promote enduring myocardial recovery, whereas others might actually be maladaptive for a nonsupport heart (eg, atrophy). In this context, distinguishing adaptive from maladaptive features of reverse remodeling will provide an important foundation for future therapeutic strategies.

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