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EDITORIAL COMMENT

# Myocardial Recovery After LVAD Implantation

## A Vision or Simply an Illusion?*

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In 1966, following a 4-h surgery, Dr. DeBakey implanted a left ventricular assist device (LVAD) in a patient experiencing post-cardiotomy shock. The patient was kept alive for 10 days until her own heart healed. This case has been recognized as the first successful use of an LVAD and has inspired the dream that myocardial recovery can occur when a failing heart is rested during LVAD. Over time, a consensus was established that myocardial recovery might occur in acute situations like the case from 1966. However, the question of myocardial recovery in patients with chronic heart failure (CHF) remained elusive. It was not until 1996 that the first report of ventricular reverse remodeling and apparent recovery was reported in a 19-year-old man with chronic heart failure (1); this "recovery" proved to be temporary, with re-emergence of the CHF phenotype within days of LVAD explant. It was not until 10 years later, in 2006, that the seminal and controversial work by Birks et al. (2) from the Harefield group impressed the heart failure community by reporting an extremely high success rate of LVAD explantation. In their study, 73.3% of the patients implanted with durable LVAD (HeartMate XVE, Thoratec, Pleasanton, California) and treated with neurohormonal blockade and clenbuterol exhibited myocardial recovery, including normalization of left ventricular (LV) ejection fraction and the ability to wean off and ultimately explant the device. However, due to the young patient population and the short antecedent duration of heart failure prior to LVAD implantation, there was skepticism that these findings could be generalized to the overall population of patients with CHF. As a result, a similar multicenter study was conducted in the United States; the results were negative (S. Maybaum, unpublished data). Unswayed, the Harefield group repeated their experiment when continuous-flow LVADs were introduced. Again, they demonstrated a high recovery rate (63%) (3). Since then, multiple single-center experiences on myocardial recovery reported wide ranges of rates of recovery (4). Recently, a group from Utah published an analysis of INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) data confirming the low rate of myocardial recovery for the overall LVAD population (1.3%) (5). However, they identified a subgroup of patients with a higher rate of myocardial recovery. These patients were characterized by age <50 years, nonischemic etiology, heart failure <2 years, lack of implantable cardioverter-defibrillator, creatinine <1.2 mg/dl, and LV end-diastolic diameter <6.5 cm. The ongoing debate and controversy lead to initiation of a prospective nonrandomized multicenter study: RESTAGE-HF (Remission From Stage D Heart Failure) (NCT01774656). The study has completed recruitment, and an interim analysis showed promising findings supporting high rate of clinical myocardial recovery with LVAD explantation in highly selected patients (S. Maybaum, unpublished data).

However, does the ability to explant an LVAD mean that the heart has recovered? Here, we need to differentiate between the phenomena of reverse remodeling and myocardial recovery. Reverse remodeling represents changes of anatomical and functional characteristics back toward normal in response to therapy. It has been shown that reverse remodeling results from removal of mechanical

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**TABLE 1 Significant Studies Evaluating Myocardial Recovery at the Cellular, Extracellular, Metabolic, and Genomic Levels**

| Study | Study Design | Main Finding | Implication for Recovery |
|---|---|---|---|
| Margulies et al., 2005 (12) | Study of transcriptional adaptations in failing and LVAD-supported hearts. (N = 199) | 1. More than 3,000 genes exhibit dysregulation in heart failure.<br>2. Among these dysregulated genes, a relatively small number exhibit a pattern of normalization, partial recovery, or overshoot after LVAD support. | Mechanical unloading with LVAD does not normalize the dysregulated genes from the failing myocardium, and more likely results in expression of a new gene expression profile. |
| Matkkovich et al., 2009 (13) | Comprehensive microarray profiling of miRs and mRNAs in myocardial specimens. (N = 27) | 1. 28 miRs were up-regulated with nearly complete normalization of the heart failure miR signature by LVAD treatment.<br>2. 444 mRNAs were altered, but only 29 normalized post-LVAD. | mrRs may demonstrate more dynamic expression changes in the setting of mechanical unloading.<br>This study did not utilize paired samples. |
| Drakos et al., 2010 (14) | Alterations in myocardial microvasculature, fibrosis, and hypertrophy before and after LVAD. (N = 15) | 1. 33% increase in microvascular density.<br>2. 36% decrease in microvascular lumen area.<br>3. Endothelial cell activation.<br>4. Significant increase in interstitial and total collagen content. | Finding of increased fibrosis on histology after LVAD support. |
| Diakos et al., 2014 (15) | Does LVAD leads to myocardial atrophy? (N = 44) | 1. Cardiomyocyte size decreased after LVAD unloading.<br>2. No sign of myocardial atrophy. | LVAD support is sufficient to induce cellular findings of cardiomyocyte normalization. |
| Diakos et al., 2017 (16) | The effects of mechanical unloading on myocardial energetics and the metabolic perturbation of heart failure. (N = 31) | 1. The failing myocardium had decreased glucose utilization.<br>2. After mechanical unloading, there was an increase of glycolysis; however, there was not a significant change in oxidative metabolism.<br>3. Despite mechanical unloading with LVAD therapy, TCA cycle abnormalities persisted. | The metabolic abnormalities found in the failing heart do not demonstrate normative changes despite mechanical unloading. |
| Farris et al. (11) | Myocardial tissue analysis in advanced heart failure patients before and after LVAD support. (N = 64) | 1. No differences in myocardial fibrosis.<br>2. No differences in capillary density.<br>3. Reduction of fibroblast-specific collagen expression. | Questioned the results by Drakos et al. (JACC 2010) on increased fibrosis and capillary density. |

LVAD = left ventricular assist device; miR = microribonucleic acid; mRNA = messenger ribonucleic acid; TCA = tricarboxylic acid cycle.

stresses on the LV and resolution of the neurohormonal derangements of CHF. Historically, reverse remodeling has occurred following the initiation of beta-blockers (6), angiotensin-converting enzyme inhibitors (7), and cardiac resynchronization therapy (8). However, LVAD support provides the most robust myocardial unloading and, accordingly, results in the largest degree of reverse remodeling (9). Reverse remodeling is often associated with improved function and, until recently, was considered to represent a true normalization of the cellular, extracellular, and transcriptional changes that occurred because of the initial myocardial insult.

However, recent data calls into question the ability of the failing myocardium to truly normalize. Topkara et al. (10) demonstrated in a reversible transgenic murine heart failure model that despite complete reversibility of the anatomical and functional changes, the myocardium remains susceptible to hemodynamic stresses leading to recurrent heart failure, and exhibits only partial normalization of the CHF genotype. Interestingly, they also identified expression of new genes not expressed in normal or failing myocardium, which they referred to as "reverse remodeling" genes (10). Their results question whether complete myocardial recovery can ever exist simply in response to an LVAD or pharmacological therapy. In fact, the extant published data has guided the evolution of the concept that the improved LV structure and function that permit LVAD explantation represent reverse remodeling with "remission" of the myocardial failure rather than "recovery" of myocardial function (**Table 1**).

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In this issue of the *Journal*, Farris et al. (11) add further evidence showing persistent CHF phenotypes in the extracellular matrix of hearts supported by LVADs. In their prospective observational study, the authors collected myocardial samples from heart failure patients ("loaded" failed myocardium), and additional samples were obtained at the time of transplant following a period of LVAD support and myocardial "unloading"; these patients were

supported for an average of 8 months. As in prior studies, ventricular function improved after LVAD support. However, there was no change in myocardial fibrosis or capillary density between "loaded" failing myocardium and the post-LVAD "unloaded" myocardium. The authors then isolated cardiac fibroblasts and macrophages from the tissue and sought to better characterize the changes in the cardiac fibroblast population. Interestingly, the authors demonstrated reduction of fibroblast-specific collagen expression despite the lack of change in the degree of fibrosis. Furthermore, when studying the isolated macrophage gene expression, a significant increase in the inflammatory markers was found following LVAD implantation. The authors conclude that despite the appearance of a reversed remodeled ventricle, the myocardium and, specifically, non-cardiomyocyte components of the extracellular matrix remain abnormal.

Where do these data fit in our evolving understanding of reverse remodeling and myocardial recovery? The current paper is in line with the messages reported by the genomic and transcriptomic studies of changes following LVAD support, which show that despite the normal appearance of the ventricle achieved with mechanical unloading, there is persistent abnormal gene expression. Reversal of the geometric alternations by mechanical unloading does not equate to reversal of the cellular and transcriptional machinery to normal. There is growing published data on the cellular, extracellular, metabolic, and genomic changes that occur following device implantation, and the results are mixed (**Table 1**). It is becoming clearer that complete normalization of abnormalities at the chamber, cellular, and genomic levels is not achievable by mechanical unloading, and therefore, the term *heart failure remission* is more suitable than recovery.

In summary, regression of the heart failure syndrome including clinical and anatomical normalization observed during myocardial unloading by LVADs does not imply that the underlying cellular biology and physiology of these hearts has also returned to normal. As the contributions of translational science blend with the important findings from cellular and animal studies, the granularity of our metrics for identifying and indexing recovery at the cellular and molecular levels becomes greater, and thus far, reveal how far from normal the reverse-remodeled myocardium really is. So, the question remains: is myocardial recovery a vision or an illusion?

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