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Cardiac Remodeling and Recovery: Lessons from Mechanical Ventricular Assist Devices

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Cardiac injury, regardless of etiology, typically leads to an increase in wall stress, decreased compliance, reduced systolic function, and progressive chamber dilation. This process is termed “remodeling”^{1,2} and is associated with a worse prognosis in patients with heart failure.^{1,3} Several drugs have been shown to have an effect on inducing reverse remodeling or reducing ventricular dilatation, including angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARBs), beta-blockers and, most recently, aldosterone inhibitors.³⁻⁵ Two mechanical interventions have also been associated with reverse remodeling: biventricular pacing (so-called cardiac resynchronization therapy)⁶ and mechanical ventricular assist devices (VADs).⁷ Left VADs (LVADs) induce the most complete reverse remodeling by far, returning the ventricle to nearly normal chamber size within days to weeks.

The use of VADs has evolved over the last 25 years and, currently, a significant number and type of devices with improved sophistication, durability, and reliability are available.^{8,9} The device most commonly used today is a pulsatile pump that is placed internally, either pre- or intraperitoneally, such as the HeartMate (Figure 1) or Novacor devices. These devices are able to fully support the circulation by draining nearly all the blood normally entering the left ventricle and pumping it back into the circulation by pusher plate compression of a blood reservoir in the pump. This support or output is pulsatile and synchronous with the intrinsic cardiac rate and rhythm. More recently, VAD technology has evolved to include axial or continuous flow pumps such as the Micromed-DeBakey (Figure 2) or Jarvic pumps.¹⁰ These pumps are able to almost totally decompress the cardiac ventricle, but use axial (continuous) rather than pulsatile flow.

There is significant evidence to suggest that the total reduction in wall stress that is achieved via mechanical unloading with VADs is able to induce significant structural, cellular, molecular, and functional reverse remodeling of the myocardium. This issue of *Cardiology Rounds* reviews the data regarding reverse remodeling and the potential for meaningful recovery of ventricular function associated with these devices.

Evidence for reverse remodeling

Neurohormones and natriuretic peptides

The pathogenesis of advanced heart failure is multifactorial and includes significant activation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system,⁴ which results in elevation of several neurohormones (angiotensin,¹¹ aldosterone,¹² norepinephrine,¹³ and natriuretic peptides).¹⁴ James et al demonstrated that within a 1-month period of LVAD support, there is near-normalization in all of these biochemical abnormalities and they remain normal unless right ventricular failure develops.¹⁵

Structural changes

As a result of the total decompression of wall stress and volume, ventricle dimension and mass are rapidly reduced – often by 70% – within days of VAD placement.¹⁶ Mitral regurgitation is also virtually eliminated, which further aids the reduction in ventricular size.



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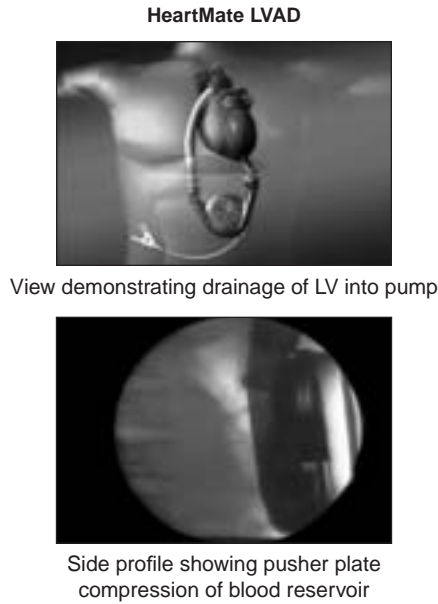
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Figure 1: Thoratec HeartMate XVE internal pulsatile pump.



Histology

One of the histological features typical of ventricular dilatation and remodeling is an elongation of the cardiomyocyte, rather than an increase in width, which is seen more typically with pressure overload and muscle hypertrophy.¹⁻³ Individual myocytes from patients with heart failure have been shown to have 3-4 times the length and total mass of a normal myocyte. Use of VADs is associated with a return to a near-normal length and mass, actually, finding many cells below normal in length and width (Figure 3).¹⁷ However, Yacoub et al have shown that the return of the myocyte to normal length and mass alone is not predictive of true functional recovery.¹⁸

Inflammation

There is a significant upregulation of many pro-inflammatory molecules in heart failure,^{3,4,19} including tumor necrosis factor alpha (TNF- α),²⁰ transforming growth factor beta (TGF- β),²¹ toll-like receptor four (TLR-4),²² many interleukins,²³ and matrix metalloproteinases (MMPs).²⁴ Significant downregulation of most of these proteins has been reported with LVAD support²⁵ and is thought to play a role in potential

Figure 2: MicroMed – DeBakey internal, axial flow pump.

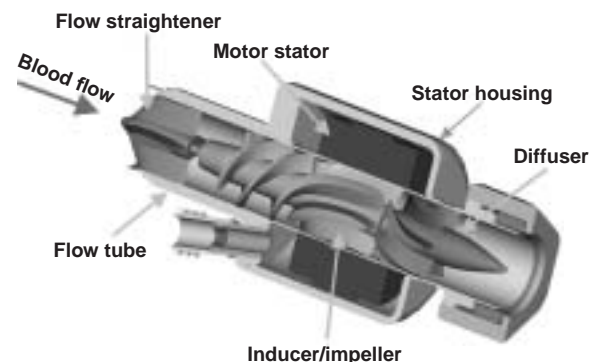
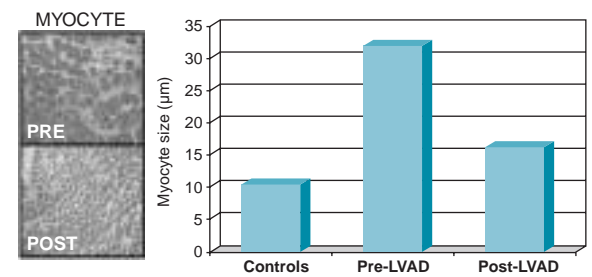


Figure 3: Regression in myocyte size following LVAD support.²⁶



recovery. Increased expression of these proinflammatory molecules has also been associated with myocardial fibrosis, a common finding in patients with heart failure due to ischemic or non-ischemic etiology. There are impressive reports of significant reductions in myocardial fibrosis with LVAD support, using homogenates of the heart to avoid bias or error in sampling, including both type I and type III collagen (Figure 4).²⁶

Structural proteins

Cytoskeletal and sarcomeric proteins play important roles in mechanosignal transduction and myocyte structure and function. Both types of proteins can be significantly downregulated with severe heart failure. Towbin et al demonstrated that dystrophin is an important gene involved in mechanosignal transduction initiated in the sarcomere, since mutation of this gene is associated with cardiomyopathy and ventricular dilatation.²⁷ Levels of dystrophin gene expression determined via immunostaining are severely reduced prior to LVAD implant, but normalize after several months of mechanical support (Figure 5).²⁸ Clearly, LVAD support can induce significant alterations in many important genes in heart failure.²⁹

Beta-adrenergic receptors

Chronic sympathetic nervous system stimulation is an important compensatory mechanism in chronic heart failure.^{4,13} However, it leads to downregulation of the beta-adrenergic receptors on the surface of myocytes, which further limits effective inotropic response to heart failure. Moravec et al have shown that this downregulation of beta-adrenergic receptors returns to near normal levels following LVAD support.³⁰ Normalization of beta-receptors allows a more effective response to sympathetic stimulation that may be needed after potential device removal.

Figure 4: Regression in myocardial Collagen Type I following LVAD support.²⁶

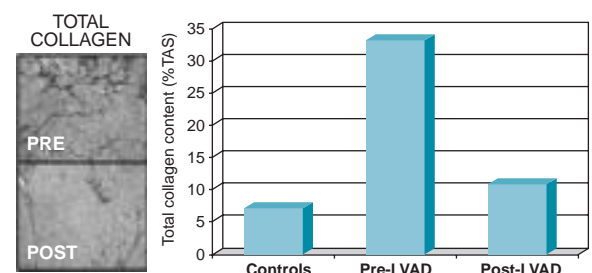
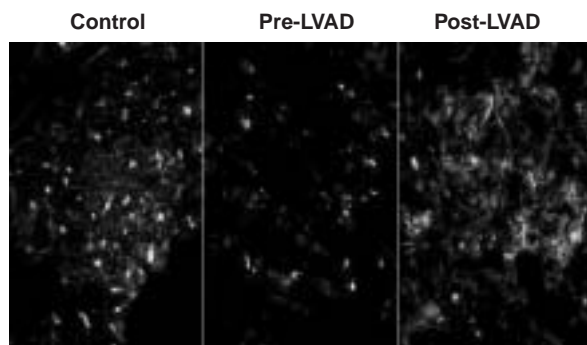


Figure 5: Changes in dystrophin gene expression by immunostaining in normal (controls) versus pre- and post-LVAD support.²⁷



Calcium handling proteins

Systolic function is largely related to intercellular calcium availability and handling. There are a number of calcium handling proteins (SERCA2a and the sodium-calcium exchanger, as well as total sarcomeric calcium content), whose quantitative expression by PicoTiterPlate polymerase chain reactions (PTPCRs) has been shown to downregulate significantly prior to LVAD implant, but nearly normalize following a period of mechanical unloading and support.^{29,31} There is less of a decrease in the ryanodine receptor, phospholamban, with heart failure.³¹ In fact, the inward calcium current has been shown to be the highest correlate of true recovery of the ventricle and of the ability to successfully explant the device.³²

Contractile function

Burkhoff et al demonstrated very depressed contractile function in myocardial trabeculae obtained from the heart at LVAD implant.³³ This study included analyses of pressure volume relationships, forced frequency response to continual electrical stimulation, as well as contractile response to isoproterenol. All of these parameters returned to near baseline, non-heart failure control levels following mechanical support (Figures 6 and 7). This study provides some of the strongest

Figure 6: Beneficial effects of LVAD support on force-frequency response to electrical stimulation of cardiac trabeculae pre- and post-LVAD support.³³

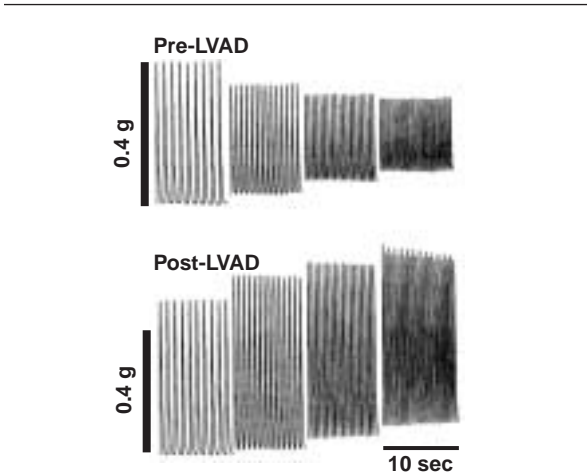
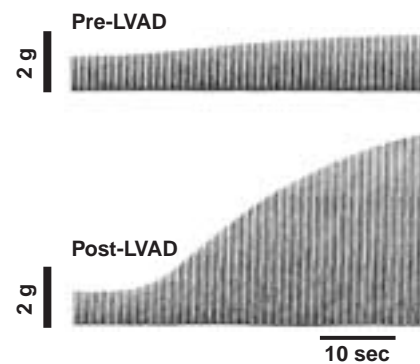


Figure 7: Contractile response of isolated cardiac trabeculae to isoproterenol infusion pre- and post-LVAD support.³³



evidence suggesting that the cardiac muscle has recovered substantially and may be able to assume adequate physiologic function after device removal.

Metabolism

One of the hypotheses explaining the transition to decompensation in hearts with chronic dilatation and reduced function is depletion of myocardial energy stores. These metabolic derangements have also been shown to revert to control levels with LVAD support.³⁴ There are also data demonstrating a return to near normal levels of myocardial energy stores,³⁵ mitochondrial function, and metabolic alterations that are disturbed in advanced heart failure.

Apoptosis

One controversial hypothesis to explain the development of heart failure is accelerated apoptosis.⁴ There are conflicting data regarding the irreversibility of the characteristic findings of apoptosis, the actual rate of this process, and the percentage of cells involved. Some data suggest that LVAD support may reduce these findings.³⁶

Electrical remodeling

In addition to extensive structural, cellular, and molecular remodeling, there is also evidence of electrical remodeling with LVAD support.³⁷ The calcium transient, defined by patch clamping techniques, may in fact be the best marker of true myocyte recovery.^{18,37} Restoration of a normal action potential may allow a clinical assessment of recovery and the decision to recommend device explantation.

Remodeling, not recovery

Collectively, the body of evidence suggests that LVAD support is able to achieve almost complete reverse remodeling. The return of myocytes to near normal size and the return to normal levels of calcium handling proteins, beta-adrenergic receptors, etc. and contractile force, suggest not only reverse remodeling, but also complete recovery. This should allow safe explantation of the device after a period of support, especially in patients with non-ischemic etiology. However, to date, only 5%-10% of all patients who have had a VAD implanted, have safely undergone device explantation.³⁸ The vast majority of these patients have had acute causes of heart

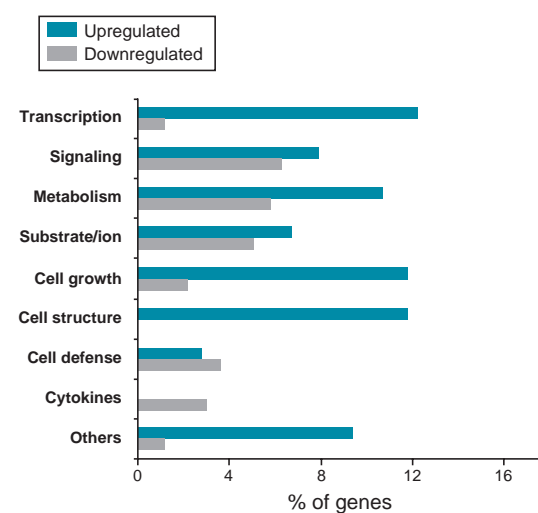
failure, most typically myocarditis, which has a natural history for substantial recovery with time and without therapy. The device, however, can provide a period of potentially life-saving support in these patients until recovery is evident.

Therefore, it appears clear that reverse remodeling does not equal recovery. Our group³⁹⁻⁴² and others^{43,44} have been interested in examining the molecular basis of reverse remodeling in heart failure. The VAD provides an extraordinary model to examine reverse remodeling since it provides rapid and, at times, complete reversal of structural, cellular, molecular, and functional changes induced by heart failure in a human model, rather than extrapolating data from animal models of over-expressed or knocked-out genes. One to two grams of tissue are obtained from the left ventricular apex at the time of LVAD implant for placement of the drainage cannula to the pump, and then again at the time of transplantation (explant) when the entire heart is available. These paired samples provide substantial tissue to allow examination of genes that are differentially up- or downregulated in response to total decompression of the ventricle and reverse remodeling.

To date, 19 patients in our program have had paired samples obtained at VAD implant and explant that have been analyzed by the Affymetrix U-133 microarray gene chip (Affymetrix, Santa Clara, California) in an unbiased approach to identifying the genes important in remodeling.³⁹ A number of statistical software programs (eg, Significance Analysis of Microarrays [SAM]) have been used to help sort the extensive data obtained from the 22,000 genes arrayed on the chip.⁴⁰ This approach has resulted in <1% false discovery rate.³⁹ Using restrictive cutpoints for defining significant differential expression of a gene, a total of 107 genes met these criteria. It is noteworthy that 85 of the 107 genes differentially regulated were upregulated, and only 22 were downregulated. This is somewhat counter-intuitive to the concept that the pathogenesis of most heart failure is due to an upregulation of gene expression, particularly, for example, neurohormones and inflammatory cytokines. However, our data would suggest that reverse remodeling is an active process. Quantitative polymerase chain reaction (PCR) studies have shown very close correlations between levels of gene message and actual protein expression.

The genes most notably upregulated are those involved in transcription, signaling, metabolism, cell growth, and cell structure (Figure 8).⁴¹ Genes significantly downregulated include those involved in cell signaling, cell defense, as well as inflammation. A series of upregulated genes involved in angiogenesis, including the proangiogenic genes, Sprouty-1 and angiotensin 2 receptor type 1, has been of particular interest.³⁹ Genes involved in angiogenesis that are consistently downregulated include neuropilin (a VEGF receptor), stromal-derived growth factor (SDF-1, a stem cell homing gene), angiopoetin, as well as transcription factor GATA-4 and MMP-9.³⁹ The patterns of gene expression in individual patients may vary, but they suggest a possible ventricular-vascular coupling that is important for recovery. The additional use of other computer software programs (eg, Infinity) makes it possible to examine entire signaling

Figure 8: Differential gene expression from paired samples of cardiac tissue obtained at LVAD implant and at transplant.⁴¹



pathways and is helpful in avoiding errors when using cutpoints for statistical significance. The cutpoint analysis may often miss the expression of important regulatory genes, such as those encoding transcriptional factors, upstream factors, and feedback loops, which govern other genes expression, yet may not have sufficient change in expression themselves to be detected using this method.

True recovery of ventricular function is still an important goal of LVAD use. There is increasing evidence that a unique beta-2 adrenergic agonist, clenbuterol, may be useful. This drug has been demonstrated to lead to a physiologic hypertrophy in all skeletal muscle, including the heart.^{45,46} Clenbuterol has been effective in increasing cardiac hypertrophy and performance in several animal models, including a *latissimus dorsi* wrapped around a compression chamber that demonstrated a significant increase in both force generation and cardiac hypertrophy over controls⁴⁶ and occurred without the fibrosis noted with catecholamine inotropes (eg, isoproterenol). This led to the use of clenbuterol in patients with end-stage heart failure who were being supported by an LVAD.^{47,48} An attempt was made to wean those with refractory heart failure of non-ischemic etiology and remove the device, while maintaining stable heart function. In a series of 15 patients, 10 (67%) were able to have the device explanted after an average of 13 months of clenbuterol treatment plus other therapies and LVAD support. This is 6-10 times better than other reports examining the likelihood of device explantation.³⁸ At 2 years of follow-up, the average ejection fraction in these 10 patients was 60%.

Tissue from several of these clenbuterol-treated patients who demonstrated actual recovery rather than just remodeling was examined in a manner similar to the one described above in patients who had no evidence of recovery and went on to transplantation. Of importance, 4 genes were identified that appeared to distinguish patients who were recovering from those who were not, including insulin-like growth factor (IGF-1), collagen

type 4 and 6, vimentin, and phosphodiesterase 4D. Of these 4 genes, the latter was downregulated, while the other 3 were upregulated.³⁹ Two other genes – angiotensin 2 and SDF-1 – were significantly upregulated in patients who recovered and downregulated in non-recovered patients, which seemingly implies that they have a more critical control function since their expression was in the opposite direction in those who recovered.

Importantly, in our program, 2 patients who had ventricular recovery in the absence of clenbuterol also showed upregulation of SDF-1; however, there was a 2-fold greater change in SDF-1 expression in the patients who received clenbuterol. All these changes suggest that stem cell homing may be part of the explanation for the actual recovery, not just remodeling seen with clenbuterol. It was reported that a number of individual myocytes were smaller than normal size in hearts examined after periods of LVAD support.¹⁷ This may either represent myocardial atrophy from disease because the ventricle did not function mechanically for months or may potentially represent cardiac hyperplasia, in which smaller progenitor cells responding to increased SDF-1 expression have, in fact, homed to the heart. This hypothesis would explain why a heart – so severely injured as to require LVAD support – is able to recruit a new population of myocytes for sustained supranormal ventricular function when treated with clenbuterol,

It may well be that the ventricle can be reconditioned by changing the levels of pump support (fixed rate or automatic mode and varying rates) so that it assumes greater preload and mechanical function gradually over time, once recovery of normal left ventricular dimension and myocyte size has been achieved.⁴⁹

Conclusion

LVADs may be the ideal platform to study the potential benefit of stem cell therapy for myocardial repair and recovery.⁵⁰ The device may potentially allow safe implantation of stem cells directly into scarred myocardium, and to the most remote areas. In addition, this technique allows acceptable tolerance of any pro-arrhythmic effects reported in trials of intracoronary-infused skeletal myoblasts. More importantly, it provides the ability to examine labeled stem cells at device explantation either at transplantation or during recovery. There are undoubtedly multiple mechanisms involved in remodeling and reverse remodeling. A subset of genes may actually be critical to induce not only remodeling, but also true functional myocardial recovery. Myocardial recovery now appears to be a more reasonable goal with LVAD support.

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