Molecular- and Organelle-Based Predictive Paradigm Underlying Recovery by Left Ventricular Assist Device Support

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Recent reports have demonstrated a 2-year survival rate of HF is a major cause of morbidity and mortality in the United States, and heart transplantation remains as the gold standard therapy. Because of scarcity of donor organs, the application of mechanical circulatory support devices has become a crucial approach in HF therapy as a bridge to transplantation. Therefore, mechanical circulatory support devices have existed both conceptually and experimentally for >40 years, along which an exponential evolution of mechanical circulatory support device technology has occurred. To mimic human physiology, the first generation of left ventricular assist devices (LVADs) were pulsatile volume displacement pumps (HeartMate XVE LVAS, Thoratec PVAD, and Novacor, etc.). Insights demonstrating the inessentiality of the pulsatile nature of LVADs for survival from a physiological standpoint propelled the design of second-generation continuous flow devices (HeartMate II [Thoratec Inc], the Micromed DeBakey VAD, Berlin Heart Incor [Berlin Heart AG], and the Jarvik 2000 [Jarvik Heart Inc]), which emerged with superior safety and durability. Consequently, the HeartMate II was approved for bridge to transplantation and destination therapy in the United States. Recent reports have demonstrated a 2-year survival rate of 87% in destination therapy patients under intense surveillance, comparable with open heart transplantation survival statistics. In parallel, these promising outcomes of LVADs in HF therapy have spawned the translational research field of LV reverse remodeling, which has already shown great promise for elucidating underlying molecular and cellular mechanisms.

Clinical Insights Into Bridge to Recovery
HF is a highly complex clinical syndrome marked by a multitude of derangements, both in adult and pediatric populations. The clinical phenotype of HF begins with an injury or supranormal stressor on the heart and, through prolonged dyshomeostasis, eventuates in cellular and organ failure. The compensatory adaptive mechanisms including neurohormonal activation (eg, the adrenergic system along with aldosterone, renin, and angiotensin) may initially maintain cardiac output, but the inability to sustain this eventually results in HF together with the release of proinflammatory cytokines. The response to neurohormonal activation, direct mechanical stretch, and LV volume overload results in progressive maladaptive remodeling (Figure 1). These derangements are potentially reversed during LVAD mechanical unloading. The current gold standard therapy for HF is open heart transplantation, yet it carries a 50% 10-year survival along with all complications related to long-term immunosuppression and increased medical costs. With the evolution of LVAD technology and reliability, there has been anecdotal evidence of sufficient LV recovery by LVAD support to a point allowing device removal (ie, bridge to recovery [BTR]). The Harefield group was the first to study a homogenous population of patients with HF, in which they applied a defined pharmacological protocol along with LVAD unloading to induce recovery. This involved high-intensity neurohormonal blockade followed by induction of physiological hypertrophy with a high-dose clenbuterol, a direct β-agonist, to optimize LV recovery. The procedure resulted in 63.2% of patients successfully recovering after LVAD explantation. Reliable and robust predictive parameters and patient selection criteria for successful BTR have not yet been established. Patients with nonischemic cardiomyopathy (NICM) have been targeted in studies as the group most likely to undergo successful BTR. However, this NICM population itself has heterogeneous underlying causes, such as viral myocarditis,
Morphological, Molecular, and Cellular Insights of Reverse Remodeling After LVAD Support

Morphological and Molecular Insights

During the past 2 decades, molecular and cellular recovery after LVAD mechanical unloading (Figure 2) has been extensively investigated in an effort to understand the pathophysiology and critical pathways for potential therapeutic applications (Table).\(^5\)\(^-\)\(^7\),\(^17\) The current consensus is that morphological, cellular, and molecular reversal after LVAD implantation precedes clinical recovery. However, these features alone have not been able to predict clinical recovery reliably.\(^7\) With regard to morphological changes, several early histological studies described a conclusive decrease in cell volume and morphological restructuring to a prediseased state.\(^5\)\(^-\)\(^7\),\(^17\) LVAD support also led to enhancements in cardiomyocyte force in conjunction with accelerated contraction and relaxation times.\(^8\) Nevertheless, whether interstitial connective tissue remodeling can be reversed after LVAD support remains controversial.\(^5\)\(^,\)\(^6\)

As a governing determinant of cardiac function, calcium (Ca\(^{2+}\)) handling of the cell is disturbed during HF, which may contribute to the decreased contractility. In this regard, there seems to be increased gene expression of the sarcolemmal...
Na\textsuperscript{+}Ca\textsuperscript{2+} exchanger and sarco-endoplasmic reticular Ca\textsuperscript{2+} ATPase subtype 2a after LVAD implantation, but corresponding protein expression remains unclear. Furthermore, levels of the Ca\textsuperscript{2+} regulatory protein phospholamban seems to be unchanged after LVAD implantation, whereas L-type Ca\textsuperscript{2+} channel function and ryanodine receptor function are improved through post-translational modifications after LVAD implantation\textsuperscript{5,6}.

Cardiac function is also orchestrated by the neurohormonal system, and there is clear evidence that increased levels of neurohormones during HF (such as epinephrine, norepinephrine, renin, angiotensin II, aldosterone, and arginine vasopressin) are decreased with successful LVAD support\textsuperscript{5,6,17}. Other key hormonal players in maintaining arterial blood pressure and volume homeostasis are cardiac atrial natriuretic peptide and B-type natriuretic peptide\textsuperscript{5,6,17}. Both atrial natriuretic peptide and B-type natriuretic peptide are important HF biomarkers that are released by the atrium and LV, respectively, on pressure overload. Because LVAD therapy immediately relieves the burden on the overloaded heart, both atrial natriuretic peptide and B-type natriuretic peptide levels show a downward trend. In addition, β-adrenergic receptor density and response to stimulation can be restored after LVAD support, most likely through alterations in intracellular rather than hemodynamic factors\textsuperscript{5,7} and also reversed phosphoinositide 3-kinase-γ activation and alterations in adenylyl cyclase.

Certain aspects of mitochondrial structure and function have been investigated. Metabolism is disrupted during HF, yet studies on the effects of LVAD support on metabolic pathways are limited. Decreased creatine kinase activity during HF is restored after LVAD support, indicating improved energy production. Moreover, the composition of cardiolipin, an integral component of the mitochondrial inner membrane that facilitates the function of numerous energetic enzymes, is normalized, after LVAD support in ischemic cardiomyopathy, but not in dilated cardiomyopathy\textsuperscript{5,6,17}.

The inflammatory response characteristic of HF progression, including the upregulation of proinflammatory cytokines such as tumor necrosis factor-α, interleukin-6, interleukin-8, and several heat shock proteins, was reversed after LVAD implantation\textsuperscript{6}. In addition, apoptotic cell death during HF can be attenuated by LVAD support, though controversial results from different studies have been reported\textsuperscript{5,6,17}.

**Transcriptional Modifications**

Because gene expression and protein expression are not always synchronized, maladaptive hypertrophy and HF are also characterized on a transcriptional and epigenetic level targeting the activation of gene expression\textsuperscript{5}. Hypertrophy and HF are both correlated to the activation of genes encoding transcriptional factors (c-jun, c-fos, c-myc), hormonal passengers (atrial natriuretic peptide, B-type natriuretic peptide), β-myosin heavy chain, and skeletal α-actin. One of the first studies measuring the expression of cardiac genes in HF samples found that sarco-endoplasmic reticular Ca\textsuperscript{2+} ATPase subtype 2a, the ryanodine receptor, and the sarcolemmal Na\textsuperscript{+}Ca\textsuperscript{2+} exchanger were all upregulated after LVAD support\textsuperscript{18}. A similar study by Hall et al\textsuperscript{19} using microarray analysis of mRNA transcripts in patients with HF after LVAD support in combination with pharmacological therapy revealed a significant association of both the integrin and cAMP pathways with the functional recovery in cardiac contractility and metabolism. Nevertheless, some studies have failed to demonstrate...
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(Continued)
a normalized gene expression during mechanical unloading. Margulies et al. analyzed 199 human myocardial specimens and found that the abundant changes in transcripts during HF did not respond to LVAD support.

Intracellular Transduction Pathways

Several signal transduction pathways implicated in the progression of HF and LVAD-induced recovery are summarized in the Table.5–7,17 One of the first signaling pathways that provided insight as an underlying mechanism of HF is the calcium/calmodulin-activated protein kinase and phosphatase (calcineurin).5 Another prominent signaling pathway is the phosphoinositide 3-kinase/Akt (also known as protein kinase B) pathway, which stimulates several tyrosine kinase receptors such as insulin-like growth factor, fibroblast growth factor, transforming growth factor, as well as G-protein–coupled receptors. Finally, the mitogen-activated protein kinase cascade, which includes extracellular signal–related kinases, c-Jun N-terminal protein kinases, and p38 mitogen-activated protein kinase subfamilies, is a highly conserved signal transduction pathway.5 Moreover, receptor tyrosine kinases are involved in the transmission of hypertrophic and survival signals in the cardiomyocyte.

LVAD induces significant perturbations of these key signal transduction pathways.21 For example, the activation of Akt, glycogen synthase kinase-3β, and phosphorylation of P70S6K (as part of a prohypertrophy signaling pathway) in patients with HF are downregulated after LVAD, whereas both c-Jun N-terminal protein kinase– and p38-mediated signaling remained unchanged by LVAD implantation. Extracellular signal–related kinase is downregulated by mechanical unloading, whereas c-Jun N-terminal protein kinase signal transduction exhibited no change.5–7,17 Lastly, unloading of the heart resulted in an upregulation of Her2/neu and Her4, particularly in patients with ischemic cardiomyopathy. At the same time, glycoprotein 130, the common signal transducer of interleukin-6 cytokines,22,23 which plays an important role in receptor tyrosine kinase signal transduction, was decreased after LVAD implantation.

In conclusion, a comprehensive profile of the pivotal elements in signal transduction pathways (and their post-translational modifications) in maladaptive hypertrophy and HF progression are only beginning to be discovered, and future investigations in this area will likely unveil many potential therapeutic targets.

### Table. Continued

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<td>Many altered genes during HF</td>
<td>Only small percentage of transcripts show reversal</td>
<td>Reverse remodeling may occur without normalization of abnormal gene expression</td>
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<tr>
<td>MicroRNA expression</td>
<td>Many microRNAs in HF are up- or downregulated</td>
<td>Many microRNAs show normalization than genes</td>
<td>May be more sensitive to study reverse remodeling</td>
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Akt indicates protein kinase B; ANP, atrial natriuretic peptide; AT, angiotensin; BNP, brain natriuretic peptide; Erk, extracellular signal-regulated kinases; FGFR, fibroblast growth factor; GSK-3β, glycogen synthase kinase-3β; Her2/neu, human epidermal growth factor receptor 2; HF, heart failure; IGF, insulin-like growth factor; IL, interleukin; JNK, c-Jun N-terminal kinase; LVAD, left ventricular assist device; MAP, mitogen-activated protein; PI3K, phosphoinositide 3-kinase; PTM, post-translational modification; RTK, receptor tyrosine kinase; RV, right ventricle; SERCA2a, sarco-endoplasmic reticular Ca2+ ATPase subtype 2a; and TNF, tumor necrosis factor.

### Organelle-Specific Insights in HF and Reverse Remodeling

**Mitochondria in HF and Reverse Remodeling**

Many reports from both animal and human clinical studies strongly indicate that mitochondrial dysfunction is crucial in the pathophysiology of HF.24 Next to supplying energy in the form of ATP, mitochondria are also involved in the regulation of intracellular Ca2+ fluxes, redox potential, biosynthesis, reactive oxygen species (ROS) generation/signaling, cell death pathways, and protection against stressors, such as ischemia reperfusion injury.25 Mitochondrial energy supply involves the coupling of electron transfer and oxygen consumption through the mitochondrial electron transport chain complexes I, II, III, and IV with the phosphorylation of ADP to ATP by F0F1-ATP synthase, also known as complex V. In the process of oxidative phosphorylation, the coupling efficiency between respiration and phosphorylation is often measured as the respiratory control index (RCI). In isolated mitochondria, the active respiratory state is often referred to as state 3 respiration, whereas the slowest rate when all the ADP has been phosphorylated to ATP is referred to as state 4. The RCI can be determined as a ratio of state 3/state 4. A lower RCI indicates a disturbed coupling of oxidation and phosphorylation, causing an inefficient energy production during which oxygen is prematurely reduced as ROS. Under basal conditions, the catabolism of fatty acids through β-oxidation provides ≈90% of the total ATP used in the heart. In addition to fatty acids, other substrates used for oxidative phosphorylation include glucose, pyruvate, lactate, and ketone bodies.24 Thus, several mitochondrial energy pathways including oxidative phosphorylation, the tricarboxylic acid cycle, and fatty acid oxidation are essential for maintaining the contractile function of the heart.24 Both basic research and clinical studies have reported a shift toward glucose oxidation at the expense of fatty acid oxidation in hypertrophied and failing hearts. Consequently, ATP levels in failing hearts rapidly decline, leading to cardiac energy deficits. Concomitantly, studies involving transgenic alterations in mitochondrial proteins (eg, adenine nucleotide translocator and respiratory complex enzymes) during the progression of HF indicate a crucial role for mitochondria.24

Supranormal mitochondrial ROS production is implicated in many pathological conditions such as contractile dysfunction, calcium dysregulation, cell death, and ventricular hypertrophy and dilation. ROS, including superoxide, hydroxyl...
radicals, and hydrogen peroxide, are normal byproducts during mitochondrial metabolism. The majority of reports describing pathological ROS release in HF have come from studies conducted in animal models. In agreement, it has been demonstrated that ROS levels are elevated in the failing human heart. Contractile dysfunction can result from disturbed mitochondrial oxidative phosphorylation with insufficient energy production, where oxygen is prematurely and incompletely reduced, causing increased ROS release from electron transport chain complexes I and III. During HF, elevated ROS release by itself can further induce more ROS release. The release of ROS from the mitochondria can lead to extensive oxidative damage to a variety of intracellular molecules such as proteins (eg, mitochondrial respiratory enzymes, matrix enzymes), DNA, and specific lipids (eg, membrane phospholipids such as cardiolipin). Furthermore, ROS also modulate multiple overlapping signaling pathways in the progression of ventricular hypertrophy. It is evident that an excessive generation of ROS serves as an important mechanism in the pathophysiology and progression of HF.

More recently, it has become apparent that cell death by apoptosis and necrosis are both important contributors in HF. Multiple studies have demonstrated the significant importance and magnitude of cardiac apoptosis during HF. The intrinsic apoptotic pathway features profound interactions between mitochondria, nucleus, and other subcellular organelles. The release of specific mitochondrial proteins from the intermembrane space (eg, cytochrome-c, endonuclease G, apoptosis-inducing factor, and Smac) triggers these events that subsequently cause DNA fragmentation and the activation of apoptotic protease activating factor 1 and caspases. This chain of events ultimately culminates in cell death. In contrast to apoptosis, the exact contribution of necrosis in HF has not been extensively studied. However, evidence has shown that HF could be rescued by deletion of the pro-necrotic factor cyclophilin D, but not by the antiapoptotic factor B-cell lymphoma 2, implicating that necrosis is also a major component in the progression of HF. Consequently, the mitochondrial release of these pro–cell death factors also involves the mitochondrial permeability transition pore. Mitochondrial permeability transition is related to several detrimental mitochondrial events such as mitochondrial membrane potential (ΔΨm) deterioration, ROS overproduction, Ca2+ overload, and impaired NO signaling. Accordingly, mitochondrial permeability transition pore opening has previously been reported in HF resulting from Ca2+-induced cardiomyopathy and diabetic cardiomyopathy.

Surprisingly, there are relatively few studies available that investigate the role of mitochondrial function in reverse ventricular remodeling by LVAD support. An early study by Lee et al investigated mitochondrial respiratory function in patients with advanced HF before and after LVAD support. Progression of HF was associated with extremely low RCI. However, the RCI were significantly improved after LVAD support, suggesting an important role of the device in benefiting oxidative phosphorylation and electron transport. Another study by Mital et al examined the effects of NO on mitochondrial respiratory control during reverse ventricular remodeling, a coupling that is usually disrupted during HF progression. The study reported that chronic LVAD support potentiates endogenous NO-mediated regulation of mitochondrial respiration as measured by improved MVO2 consumption. This effect could in turn be abrogated by NO synthase inhibition. As aforementioned, Heerdt et al observed that LVAD-supported hearts exhibited a normalization of cardiolipin content within the inner mitochondrial membrane. Cardiolipin is essential for normal functionality of the mitochondrial respiratory chain, as well as substrate transport. In conclusion, it is evident that the pathological proteomic mitochondrial phenotype is reversible, which may be an important underlying mechanism in reverse ventricular remodeling by LVAD.

**Proteasome in HF and Reverse Remodeling**

The proteasome is usually referred to as the 26S complex, which consists of a 20S catalytic core particle and 1 or 2 19S regulatory particles. The main function of the 26S proteasome is to degrade proteins that are damaged or have reached the end of their functional lifetime. As a part of the ubiquitin-proteasome system (UPS), the proteasome maintains cardiac protein homeostasis and thus plays a significant role in LV remodeling and HF.

During the years, clinical studies have observed detrimental side effects in the heart when proteasome inhibition was used for the treatment of cancer. For example, a large clinical trial of 315 patients using the proteasome inhibitor bortezomib to treat multiple myeloma revealed significant cardiotoxicity and occurrence of HF. During ventricular remodeling and HF, ubiquitinated proteins accumulated, suggesting impaired proteasomal activity. Further investigation on human pressure-overloaded hearts also revealed a correlation between ventricular hypertrophy and a depressed proteasomal activity. In a rodent model, our group recently found that ventricular hypertrophy by prolonged β-adrenergic stimulation is concomitant with decreased 20S caspase-like and trypsin-like activities, with an unchanged chymotrypsin-like activity. This functional alteration may be attributed to an increased incorporation of inducible subunits in 20S proteasomes. Besides removal of damaged proteins, proteasomes also play critical regulatory roles by degrading pivotal components of biological pathways, such as prohypertrophic signals (eg, Akt and extracellular signal-related kinase 1/2). Inhibition of the proteasome pathway in sympathetically stimulated mice resulted in the prevention or reduction of maladaptive ventricular hypertrophy.

Although there is increasing evidence that the UPS plays a significant role in ventricular remodeling and HF, there are still relatively few studies describing whether and how the UPS is affected by ventricular unloading after LVAD implantation. Kassiotis et al reported that the progression of autophagy in the failing heart is reversed after LVAD support. In this study, the investigators further observed that 20S proteasome activity was increased by mechanical unloading. Subsequently, Wohlschlaeger et al reported a depression of the UPS during HF, which was reversed after LVAD therapy. Both studies strongly suggest a significant role for the UPS in ventricular hypertrophy and HF, as well as in reverse cardiac remodeling. Although the UPS plays a crucial role in the pathophysiology of maladaptive ventricular remodeling and HF, further studies are necessary to define its causative or compensatory role.
LVAD therapy offers a platform to increase our understanding of the UPS in maladaptive remodeling and HF.

**Future Perspectives and Directions**

Standard HF therapy has shifted from traditional heart transplantation to LVAD implantation with a focus on destination therapy and BTR. Nevertheless, clinical parameters to predict LV recovery after LVAD support are still ill defined. Hence, we think that the development of novel patient selection criteria requires that HF is targeted by a systems biology approach incorporating transcriptomics, proteomics, metabolomics, cell biology, and bioinformatics (Figure 3). A plausible initial approach would be the exploration of molecular or organellar assays in combination with pre-existing clinical parameters as predictive measures. Collection of blood and ventricular tissue samples during LVAD implantation are suitable means for accomplishing this (Figure 3). In addition to molecular and cellular alterations (Table), there is growing evidence that mitochondria and the UPS have important roles in LV remodeling, HF progression, and reverse cardiac remodeling. A plausible initial method for integrating organellar-based profiles would be to implement mitochondrial functional assays (e.g., mitochondrial ΔΨ, susceptibility to mitochondrial permeability transition, RCI, and electron transport chain activities) and proteasome activity assays into the current panel of clinical parameters. In line with mitochondrial function, metabolism is also an important determinant of HF. Accordingly, we propose a comprehensive comparison of essential metabolites using blood samples before and after LVAD implantation. These omics data can be further interrogated using state-of-the-art bioinformatics tools to provide insights into disease. This bidirectional translational medicine approach will enable us to study HF and identify patients who would benefit from BTR, destination therapy, or bridge to transplantation. This molecular- and organelle-based predictive paradigm may advance personalized medicine through individual patient profiling.

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**Disclosures**

None.

**References**


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