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Reverse Remodeling with Left Ventricular Assist Devices

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Abstract

This review provides a comprehensive overview of the past 25+ years of research into the development of left ventricular assist device (LVAD) to improve clinical outcomes in patients with severe end-stage heart failure and basic insights gained into the biology of heart failure gleaned from studies of hearts and myocardium of patients undergoing LVAD support. Clinical aspects of contemporary LVAD therapy, including evolving device technology, overall mortality, and complications are reviewed. We explain the hemodynamic effects of LVAD support and how these lead to ventricular unloading. This includes a detailed review of the structural, cellular and molecular aspects of LVAD-associated *reverse remodeling*. Synergisms between LVAD support and medical therapies for heart failure related to reverse remodeling, remission and recovery are discussed within the context of both clinical outcomes and fundamental effects on myocardial biology. The incidence, clinical implications and factors most likely to be associated with improved ventricular function and remission of the heart failure are reviewed. Finally, we discuss recognized impediments to achieving myocardial recovery in the vast majority of LVAD-supported hearts and their implications for future research aimed at improving the overall rates of recovery.

Introduction

Left ventricular assist devices (LVADs) are a mainstay of care for many patients with end-stage heart failure either as a bridge to transplant, bridge to recovery or as destination therapy. Approximately 3000 LVADs are implanted worldwide each year and, with current selection criteria, devices and surgical techniques, 1- and 2-year survival rates are 82% and 72%, respectively.[1] While survival rates and the incidence of pump thrombosis have improved over the decades as a result of technological advances and improvements in clinical management, significant challenges remain, particularly as they relate to stroke, infection, gastrointestinal bleeding and right heart failure.

In addition to remarkable contributions to the care of end-stage heart failure patients, clinical and basic studies of LVAD patients and their tissues have produced a wealth of information about the biology of heart failure and the potential for myocardial *reverse remodeling*,[2] *remission*[3] and *recovery*.[4] These studies have focused on the primary myocardial effects

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of LVADs related to direct mechanical and metabolic ventricular unloading, in addition to secondary salutary myocardial effects of LVAD support related to improved end-organ perfusion and suppression of the activated systemic inflammatory and neurohormonal systems.

In this review, we first provide a brief overview of the evolving LVAD technology. Next, we discuss the hemodynamic effects of LVAD support and how these lead to ventricle unloading. This is followed by a detailed review of the structural, cellular and molecular aspects of LVAD-associated *reverse remodeling* with focus on what has been learned concerning the potential for myocardial recovery. Finally, we review the incidence, clinical implications and factors most likely to be associated with improved ventricular function and remission of the end-state heart failure state.

Evolving Left Ventricular Assist Device Technology

The past thirty years have seen progressive improvements in mechanical circulatory support devices, with significant improvements in efficacy and portability, dramatic increases in durability and progressive reductions in associated adverse effects. The first generation of LVADs, exemplified by the HeartMate XVE, were pulsatile devices, and were limited in use due to their size and a high rate of mechanical failure. Despite these drawbacks, the HeartMate XVE was a significant improvement over medical therapy, both for patients being bridged to transplant (BTT) and those undergoing implantation as destination therapy (DT).[5, 6] The adverse events associated with the pulsatile LVADs spurred the development of second-generation LVADs, which employed continuous-flow technology. The transition to continuous-flow physiology had several advantages, including a significant decrease in the pump size and enhanced durability due to fewer moving parts and elimination of the need for biological valves. These improvements translated to significantly better outcomes for DT patients, with 46% of HMII patients achieving 2-year survival free from disabling stroke or device replacement as compared to 11% of HeartMate XVE patients.[7] The other widely used, second-generation LVAD, is the HVAD. The observational ADVANCE trial demonstrated 90.7% success (transplantation, explantation for recovery or ongoing device support) at 6 months for HVAD BTT patients.[8] These two devices were randomized against each other in DT patients in the ENDURANCE trial, which demonstrated similar overall event-free survival at 2 years.[9] The HM3 is a third-generation LVAD, with a fully magnetically levitated centrifugal-flow rotor, eliminating friction-generating mechanical bearings which are thought to contribute to thrombus development within the HMII pump. In the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) trial, the HM3 was superior to the HMII in terms of event-free survival, with a marked reduction in the incidence of hemocompatibility-related adverse events (HRAEs), most notably pump thrombosis.[10, 11] Despite overall improvement in outcomes, the adverse event profile of contemporary LVADs remains significant and include right ventricular failure, device-related infections, gastrointestinal bleeding, de novo aortic insufficiency, and stroke.

LV unloading and hemodynamic effects of LVAD support

LVADs pump blood from the left ventricle to the aortic root, thus providing a mechanical pump that works in parallel with the native left ventricle. The flow (Q) generated by an LVAD depends on the pressure gradient (or pressure head, H) from the tip of the inflow cannula to the tip of the outflow graft and the rotational speed of the device (revolutions per minute, RPMs) according to each pump's unique relationship between pressure head - flow relationship: the HQ curve (Figure 1A). In general, the greater the pressure head, the lower the flow and, for a given pressure head, the flow increases with increased RPMs. Modern LVADs are continuous flow devices, meaning they pump blood throughout the entire cardiac cycle; however, since aortic and ventricular pressures vary during the cardiac cycle (Figure 1B), the pressure-gradient the pump is exposed to varies during the cardiac cycle (Figure 1C), so that the flow rate varies during the cardiac cycle (Figure 1D). The impact on the LV is a flow-dependent unloading of the LV that is indexed by a decreased LV end-diastolic pressure, end-diastolic volume and pressure-volume area (PVA, a correlate of myocardial oxygen consumption) which are readily illustrated on the ventricular pressure-volume diagram (Figure 1E). The loop shape also transitions from a normal rectangular to a triangular shape due to loss of isovolumic contraction and relaxation phases. Simultaneously, total cardiac output to the body (CO, the sum of the native heart output and the LVAD flow) and mean arterial blood pressure increase (MAP), while pulmonary capillary wedge pressure (PCWP) generally decreases in parallel with the reduction of end-diastolic pressure. Depending on LV contractility, LVAD RPM and volume status, the LVAD may overtake the LV such that LV pressure is always lower than aortic pressure and the aortic valve remains closed (as in Figure 1B), a phenomenon referred to as LV-aortic pressure uncoupling.

Clinical studies of both centrifugal and axial flow devices, which have different HQ curves, show similar hemodynamic effects.[12] Patients vary greatly with regard to their baseline hemodynamic profile on LVAD support. Among many factors, this variability largely reflected differences in volume status and right ventricular contractility. Consistent with theory detailed above, increased RPMs generally results in decreased PCWP, and increased CO and MAP. There are only small and inconsistent changes of CVP, likely reflecting the competing effects of increased LVAD flow to increase venous return to the right ventricle (i.e., increased RV preload) and decrease PCWP (i.e., decreased RV afterload).[12] Thus the higher the LVAD RPMs, the greater the degree of hemodynamic unloading.

In addition to these hemodynamic effects, increased LVAD speed affects LV and RV anatomy as summarized in Supplemental Figure 1.[13] With the HeartMate II LVAD (HMII, Abbott Laboratories, Chicago), increased RPMs decreases LV volumes and drives the LV to a more conical shape. In contrast, RV volumes remain mostly stable until, at the highest speeds, the interventricular septum becoming more convex (bulging into the LV) and RV volume increases. With the HVAD device (Medtronic, Minneapolis), LV volumes also decrease with increasing RPMs, but the LV chamber remains more spherical as in the baseline heart failure state. The difference may be explained by device position. The HMII is an intra-abdominal device that displaces the LV apex inferiorly while the HVAD is connected to the LV apex, limiting the longitudinal change of the LV. The HeartMate 3

(HM3) LVAD, also attached to the apex, produces changes that are intermediate between the HMII and HVAD LVADs.

Echocardiography and hemodynamics can be used separately or simultaneously to determine the adequacy of LV unloading and to optimize LVAD function. Unloading parameters, specifically LV size, frequency of aortic valve opening and the degree of mitral regurgitation, can be measured dynamically across a range of LVAD speeds in an echocardiographic ramp test to determine the optimal speed setting.[14–16] The addition of hemodynamic measurements to the ramp study through simultaneous right heart catheterization imparts an understanding of the relationship between volume unloading and pressure unloading.[12, 13] Evidence suggests that achieving an optimal hemodynamic profile is associated with significant reductions in the incidence of adverse events.[17, 18]

Biological effects of mechanical unloading of the LV

Soon after introduction of LVADs into clinical practice, it became evident that LV dimensions of end-stage failing hearts were decreasing over time. To determine whether these changes simply reflected the primary unloading effects of the LVAD, or whether this reflected a fundamental change of LV size and structure, end-diastolic pressure-volume relationships (EDPVR) were measured from hearts explanted at the time of heart transplant (Figure 2A).[2, 19] Results showed that the EDPVR of LVAD-support hearts were significantly left shifted towards lower volumes compared to non-supported hearts; on average, however, the LVAD-supported hearts remained larger than normal hearts. When indexed by the volume at which the EDPVR attained a pressure of 30 mmHg (V_{30}), it was shown that the size of the heart was related to the duration of LVAD support, following a roughly exponential time course with a time constant of ~30 days (Figure 2B).[19]

These studies of explanted human hearts, and associated studies comparing characteristics of paired pre- and post-LVAD myocardial tissue samples, ushered in an era of intense investigations into the effects of LVAD support on size, structure, cellular, extracellular and molecular characteristics of the failing myocardium.[20] These studies provided unique insights into mechanisms of reverse remodeling and consistently demonstrated ventricular structural and functional improvements are accompanied by favorable changes in the biology of the human myocardium at the cellular and molecular levels. Early work from patients supported with pulsatile-flow LVADs focused on the impact of mechanical unloading on individual aspects of the maladaptive LV remodeling phenotype. However, recent advances in RNA sequencing, mass spectrometry, and metabolomics as well as greater appreciation of cellular heterogeneity of the healthy and disease human heart allowed researchers to investigate LVAD-induced changes in RNA and protein signatures at the global scale in a cell-specific manner (detailed below, Figure 3). Despite the favorable changes observed at the cellular and molecular levels, it is important to recognize that the vast majority LVAD-supported patients do not exhibit fully recovery and move on to receive heart transplantation, highlighting the importance of correlating the changes at the cellular and molecular structure with echocardiographic and hemodynamic indices of cardiac function in LVAD patients. LVAD-induced alterations in the cellular and molecular structure of the failing myocardium also need to be evaluation in an evolving era of

LVAD technology and heart failure therapies including beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor neprilsyn inhibitors, aldosterone blockers, sodium glucose co-transporter inhibitors, and cardiac resynchronization therapy, all of which may have profound impact on the reverse remodeling phenotype.

Impact of Mechanical Unloading on the Failing Cardiomyocyte

Reversal of Cardiomyocyte Hypertrophy

Cardiomyocyte hypertrophy is widely believed to be a compensatory response to stress induced by hemodynamic overload and/or neurohormonal activation, which may become maladaptive if the stress signal remains sustained.[21] Studies have consistently showed that mechanical unloading with LVAD leads to a reduction in cardiomyocyte size while the magnitude of this reduction has been debated.[19, 22–24] Some early work from patients with pulsatile-flow LVADs have suggested that prolonged unloading could lead to an extreme reduction in cell size resulting in the atrophy of cardiomyocyte, similar to what has been observed in animal models of heterotopic heart transplantation and mechanical unloading.[22, 25, 26] These observations led to the utilization of β1-agonist clenbuterol in LVAD-supported patients, in an effort to pharmacologically prevent cardiomyocyte atrophy and to promote myocardial recovery in clinical trials.[27, 28] However, other studies with pulsatile devices[19] and more recent data from patients supported with newer generation continuous-flow LVADs[29] did not suggest a reduction in cell size beyond that of non-failing cardiomyocyte and therefore did not support this hypothesis.

One of the characteristic features of pathological cardiomyocyte hypertrophy is the switch to the fetal gene expression profile including atrial natriuretic peptide (NPPA), brain-natriuretic peptide (NPPB), beta-myosin heavy chain (MHY7), and alpha-skeletal actin (SKA). Consistent with LVAD-induced reduction in cardiomyocyte size, mechanical unloading also leads to reduction in myocardial expression of fetal gene isoforms. While the upstream signaling cascades for LVAD-induced reduction in cell size are only beginning to be understood, GATA binding protein 4 (GATA-4), a master transcriptional regulator of stress-induced cardiomyocyte hypertrophy, has been shown to be downregulated with LVAD support.[30] Similarly, activation of mitogen activated protein kinases (MAPKs) that are linked to cell growth including ERK-1/2 and JNK-1/2 were also shown to be reduced with mechanical unloading.[31] GSK-3β, a negative regulator of calcineurin/NFAT signaling and cardiomyocyte hypertrophy, has been shown to be activated during LVAD support, yet this finding has not been validated by other investigators.[29, 32, 33]

Improvements in Calcium Cycling and Cardiomyocyte Contractility

Altered calcium cycling resulting in reduction in cardiomyocyte contractility is a central cause of heart failure.[34] Cardiomyocytes isolated from explanted human hearts before and after LVAD support demonstrate a significant improvement in myocyte contractile properties such as magnitude of contraction, time to peak contraction, and time to 50% relaxation, yet this improvement appears to be only partial compared to non-failing cardiomyocytes.[35] LVAD-induced improvements in cardiomyocyte contractility is associated with a significant increase in calcium entry through sarcolemma during action potential and an increase in

sarcoplasmic reticulum calcium content.[36] These favorable changes are also accompanied by normalization of calcium cycling genes including Na/Ca exchanger (NCX), sarcoplasmic endoreticular Ca2+ ATPase (SERCA), and ryanodine receptor 2 RyR2[20], as well as protein kinase A mediated hyperphosphorylation of RyR2.[37] Additional evidence for LVAD-induced improvement in excitation-contraction coupling arises from ultrastructural examination of LVAD-supported cardiac tissues also suggested a higher likelihood of functional recovery in hearts with preserved T-tubule structure and a shorter physical distance between sarcolemma and ryanodine receptors.[38]

β -adrenergic signaling is a direct regulator of cardiac contractility through changes in both inotropy and chronotropy. Heart failure is characterized by sympathetic hyperactivity resulting in a decrease in myocardial β−1 adrenergic receptor density and uncoupling of G proteins from the β receptors, a process involving GRK2 mediated phosphorylation of the β receptor. Mechanical unloading with LVAD results in upregulation of β-adrenergic receptor density and increased responsiveness to β-adrenergic stimulation.[39, 40] Restoration of β-adrenergic responsiveness was accompanied by decreased GRK activity on LVAD support, which was mediated primarily by a reduction in GRK2 but not GRK5 expression.[41, 42]

Reorganization of Cytoskeletal Structure

Cytoskeletal proteins form the scaffold of cardiomyocytes providing stability and mechanical integrity of sarcomeres necessary to maintain uniform transmission of force.[43] Genetic mutations in cytoskeletal proteins cause muscular dystrophy frequently associated with dilated cardiomyopathy and heart failure, and disorganization of cytoskeletal organization is linked to contractile dysfunction.[44] Vatta et al. reported a disruption in the N-terminal region of dystrophin protein in patients with end-stage cardiomyopathy, which was reversed after mechanical unloading with LVAD in 4 out of 6 patients.[45] Myocardial gene expression analysis in LVAD supported patients with recovery of LV function suggested an increase in the transcript levels of several sarcomeric and non-sarcomeric cytoskeletal genes including lamin A/C, spectrin, β-actin, α-tropomyosin, α1-actinin, and α-filamin and a decrease in vinculin, troponin T3 and α2-actinin.[46] At the protein level, abundance of cytoskeletal proteins including desmin, vinculin, and α-actin was significantly reduced in ischemic failing hearts following mechanical unloading.[47] However, immunohistochemical staining of myocardial cytoskeletal myofilaments in patients before and after LVAD support showed only slight improvements in structural organization of actin, tropomyosin, troponin C, troponin T, titin proteins, suggesting that disarrangement of cytoskeletal protein structure could be persistent with mechanical unloading.[48]

Alterations in Mitochondrial Structure and Cellular Metabolic Pathways

The majority of the ATP consumed by the cardiomyocyte is derived from oxidative metabolism in the mitochondria, also known as “powerhouses” of cell.[49] As such, abnormalities in mitochondrial structure and function is closely linked with pathophysiology of heart failure. Mechanical unloading with LVAD leads to a reduction in cardiomyocyte mitochondrial content determined by mtDNA copy number normalized to nuclear DNA.[50] The reduction in mitochondrial number is, however, accompanied by favorable changes in the mitochondrial ultrastructure including size uniformity, organized cristae structure, and

reduction in abnormally small and fragmented mitochondria following LVAD support.[51] Frequency of deletion mutations in the mitochondrial DNA were reduced in patients supported with LVAD.[52] As a result, mitochondrial oxidative stress measured by hydrogen peroxide emission ex-vivo was significantly reduced in LVAD supported failing hearts.[53]

Altered energetics is believed to be central to the development and progression of HF, exhibiting a “fetal pattern” of substrate use characterized by enhanced glycolysis and a reduction in fatty acid oxidation. Transcriptional analysis of unloaded human hearts have suggested LVAD-induced upregulation of genes involved in fatty acid, pyruvate and glucose metabolism as well as genes in the mitochondrial complex.[54] Favorable changes in the metabolic gene expression profile was accompanied by restoration of myocardial metabolite levels of C2–C10 acylcarnitines, Krebs cycle intermediates, as well as amino acids to levels of non-failing control hearts, suggestive of improved fuel utilization and metabolic homeostasis with LVAD support.[54] Other investigators have suggested that, while the levels of glycolytic metabolites and amino acid in the failing human myocardium are restored with LVAD support; the levels of Krebs cycle intermediates remain largely unchanged, suggestive of “glycolysis-oxidative phosphorylation mismatch”.[55] While the precise mechanisms responsible for the dissociation between glycolysis and tricarboxycycline acid cycle metabolism are unclear, subsequent work suggested that the glycolysis-oxidative phosphorylation mismatch is accompanied by an increase in the levels of rate-limiting enzymes of pentose phosphate pathway and 1-carbon metabolism in LVAD supported hearts, resulting in higher levels of reduced nicotinamide adenine dinucleotide phosphate and improved cytoprotection.[56]

Mechanical unloading improves fatty acid oxidation through upregulation of carnitine palmitoyltransferase I (CPT1) mRNA levels, a critical regulator of mitochondrial fatty acid transportation and reduced myocardial accumulation of toxic lipid intermediates including diacylglycerol and ceramide.[57] Nearly all chain lengths of ceramides are reduced by LVAD support along with a reduction in protein levels of ceramide synthase 2 (CERS2).[58] Consistent with improved fatty acid utilization and oxidation, the levels of circulating long-chain acylcarnitines were significantly reduced following LVAD support.[59]

Reduction in Cardiomyocyte Cell Death and Autophagic Signaling

Heightened necrotic and apoptotic cell death is thought to contribute to cardiomyocyte loss and progressive decline in LV function during heart failure. Early studies from patients supported with pulsatile-flow LVADs suggested attenuation of ventricular apoptotic DNA fragmentation and upregulation of anti-apoptotic signaling genes including bcl-XL and FasExo6Del/Fas in the failing human hearts after mechanical unloading.[60] However, terminal deoxynucleotidyl transferase dUTP nick-end (TUNEL) labeling of apoptotic nuclei consistently demonstrated an overall low incidence of cardiomyocyte apoptosis in the failing human heart, which was largely unchanged following mechanical unloading.[61–64]

Mechanical unloading with LVAD leads to a reduction in the levels of autophagy markers in the failing human heart including Atg5–12, Beclin-1, and LC3-II.[62] Mice with cardiac-restricted overexpression of beclin-1 develop augmented pathological remodeling characterized by cardiomyocyte hypertrophy, increased myocardial fibrosis, and reduced

fractional shortening following pressure overload. Conversely, heterozygous disruption of beclin-1 was protective from pathological remodeling induced by pressure-overload.[65] Taken together, these observations suggest that LVAD-induced reduction in autophagic response could be an adaptive response.

Enhanced Cardiomyocyte Regeneration

Adult human heart has extremely limited capacity for regeneration evidenced by low incidence of cardiomyocyte turnover that diminishes with age.[66] Cell-cycle arrest remains a major barrier to cardiomyocyte renewal. Mechanical unloading with LVAD was shown to reduce the number of polypoid cardiomyocytes and cardiomyocyte DNA content, while the number of binucleated cardiomyocytes were increased.[67] In addition, markers of cell-cycle reentry including phosphorylated Histone H3 and Aurora B kinase were shown to be upregulated in cardiomyocytes following LVAD support.[50] While the signaling mechanisms responsible for cell-cycle reentry remains largely unknown, these early observations suggest that at least a proportion of cardiomyocytes are not terminally differentiated and could potentially regenerate with mechanical unloading.

Impact of Mechanical Unloading on the Non-Myocyte Compartment

Changes in Extracellular Matrix

The extracellular matrix (ECM) plays a crucial role in cardiac homeostasis by providing structural support and regulating signal transduction in resident myocardial cells.[68] Ischemic and non-ischemic heart failure are characterized by activation of fibroblasts which triggers synthesis and deposition of ECM proteins resulting in expansion of interstitium. While several reports suggested a reduction in myocardial collagen content with mechanical unloading[23, 69, 70], the majority of evidence from studies utilizing digital microscopy as well as biochemical and functional characterization of myocardial collagen in larger number of patients demonstrate no change[63, 71] or a significant increase[24, 40, 71–74] in myocardial fibrosis following LVAD support. Biochemical characterization of myocardial collagen using hydroxyproline and Sircol collagen assays showed an LVAD-induced increase in the total myocardial collagen content, undenatured soluble collagen, as well as cross-linked collagen determined by an increased ratio of insoluble to soluble collagen fraction.[40, 73, 74] LVAD-induced increase in the cross-linked collagen resulted in an increase in myocardial stiffness determined by passive LV pressure volume relationships.[40]

Changes in myocardial collagen content is mediated by ECM turnover enzymes including matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). Studies using gelatin zymography suggested a decrease in MMP-2 and MMP-9 activity in LVAD supported failing hearts, which was accompanied by a significant reduction in MMP-1, increase in TIMP-1 protein levels, and a net decrease in MMP-1/TIMP-1 ratio favoring collagen deposition.[40, 73] Myocardial mRNA levels of MMP-2 and MMP-9 were downregulated with LVAD support and accompanied by a reduction in circulating MMP-9 protein levels.[70]

Neurohormonal inhibition appears to be a major determinant of LVAD-induced ECM remodeling, as treatment with ACE-inhibitors resulted in significant reduction of cross-

linked collagen, normalization of MMP-1/TIMP-1 ratio, and COL1A1 gene expression in the failing human heart.[75, 76] ECM remodeling could be affected by other factors such as the degree and duration of mechanical unloading, as the longer durations of LVAD support resulted in lower myocardial collagen content. [74]

A central question remains whether myocardial fibrosis is a determinant of myocardial recovery in LVAD supported patients. Animal models of myocardial recovery with improvements in cardiac structure and function exhibit persistent or increased myocardial fibrosis, suggesting that reversal of fibrosis may not be central to the process of reverse remodeling.[77–79] On the contrary, histopathological studies from explanted human hearts suggested that patients with less cardiac fibrosis at the time of LVAD implantation were more likely to demonstrate improvement ejection fraction and undergo device remodel for recovery.[80, 81] It is important to note, however, that lower myocardial fibrosis may serve as surrogate for non-ischemic HF etiologies, which have higher recovery potential than ischemic HF. Nevertheless, these observations suggest that while mechanical unloading with LVAD may not reduce myocardial fibrosis, patients with lower myocardial collagen deposition at the time of LVAD implantation could be more likely to recover on device support. Future research will determine the precise role of extracellular matrix composition in LVAD-induced reverse remodeling.

Endothelial Cell Activation & Microvascularizarion

It has been well established that microvascular density in the failing human heart is reduced. LVAD support is associated with a 33% increase in myocardial microvascular density measured by CD34 staining in the failing human heart.[24] Ultrastructural examination suggests signs of endothelial cell activation in LVAD supported hearts including reduplication of basal lamina, increase in the number of cellular projections, and increased number of organelles protruding into the luminal area.[24] While the signaling mechanisms responsible for LVAD-induced changes in endothelial cell phenotype and myocardial microvascular density are unknown, it is plausible that angiogenetic pathways including Angiopoietin-2 (Ang-2) signaling which have been implicated in the development of mucosal arterio-venous malformations and mucosal bleeding events, could also be activated in the failing human myocardium.[82] Ang-1 promotes normal vessel growth while Ang-2 promotes abnormal growth associated with vascular destabilization and inflammation.[83] Therefore, LVAD-induced changes in endothelial structure and microvascular density could be maladaptive and contribute to increased fibrosis observed in LVAD supported hearts.

In addition to changes in the endothelial cell phenotype, mechanical unloading has a profound impact on the macrovascular structure. LVAD support resulted in thinning of internal elastic media and reciprocal thickening of the external elastic media in coronary arteries.[84] Importantly, mechanical unloading induced expansion of the coronary artery adventitia, which was accompanied by a significant increase in collagen deposition and vasovasorum density in this layer.[84] While the functional impact of these findings merit further research, fibrotic changes observed in the coronary arteries in LVAD supported patients may cause myocardial ischemia and hinder myocardial recovery.

Changes in Cytokine Signaling and Cardiac Macrophage Phenotype

Chronic heart failure is associated with activation of innate and adaptive immune systems compromising of cellular and non-cellular components.[85] Mechanical unloading with LVAD is associated with significant reductions in myocardial pro-inflammatory cytokine levels including TNF-α, IL-6, IL-1β, Fas, and FLICE.[86–88] However, circulating levels of TNF-α as well as several other chemokines including monocyte chemoattractant protein 1 (MCP-1), IP-10, IL-8, and C-reactive protein (CRP) remain persistently elevated after LVAD support, suggesting incomplete normalization of inflammatory signaling cascades during mechanical unloading.[89–92]

Immunohistochemical analysis of failing human heart samples before and after LVAD support did not reveal a significant difference in cardiac resident macrophage density determined by CD68 staining.[93, 94] While the total number of CD68 positive cardiac resident macrophages remains unchanged with LVAD support, growing lines of evidence suggests presence of macrophage phenotype switch with mechanical unloading. Gene expression studies of isolated cardiac macrophages have shown reduced expression of pro-fibrotic M2 macrophage genes including KLF-4, TGM2, and MRC1 and a trend towards reciprocal increase in pro-inflammatory M1 macrophage genes including IL-1β and TNF-α with mechanical unloading.[93] LVAD-induced changes in macrophage gene expression profile also includes a significant reduction in MMP2 gene transcription, which likely contributes to persistent myocardial fibrosis with mechanical unloading. Patients with improved left ventricular systolic function on LVAD support had lower absolute numbers and percentage of pro-inflammatory CCR2+ macrophages both at the time of LVAD implantation and at the time of explant.[94] The percentage of CCR2+ macrophages, but not CD68+ macrophage abundance, correlated with left ventricular systolic improvement following LVAD implantation. These observations suggest that functionally distinct subsets of cardiac macrophages play important roles in LVAD-induced reverse remodeling.

Impact of Mechanical Unloading on Failing Myocardial Transcriptome

Transcriptional profiling has been used extensively to gain insights into mechanisms of LVAD-induced reverse remodeling and to identify novel biomarkers of myocardial recovery. Early transcriptional profiling studies used hybridization-based approaches such as microarray which are limited by the probe content, while more recent studies used next-generation RNA-sequencing which allows for unbiased identification of splice variants as well as noncoding transcripts. Aside from the platform used, these studies also differ with regards to the etiology of HF, concomitant medical therapy, duration of LVAD support, statistical criteria used to detect differentially expressed transcripts, and whether or not “non-failing” control cardiac tissue samples have been included in the experimental design (Table 1). In the largest and the most comprehensive analysis to date, Margulies et al. reported that of 3088 transcripts dysregulated in heart failure, only 238 exhibited a statistically significant change in expression levels after LVAD support.[95] Moreover, HF genes which were significantly regulated with LVAD support were more likely to exhibit further deviation from the non-failing transcription levels (exacerbation or persistence) instead of returning towards normal levels (partial recovery, normalization, or overcorrection).

While only a small proportion of HF-dysregulated genes normalize with LVAD support, several mRNAs enriched in inflammatory (C/EBPβ, NFKBIA, CXCL12, CCL2, CD14) and oxidative stress pathways (MT1F, MT1X) were detected in at least 3 independent LVAD transcriptional studies, suggesting that mechanical unloading could have a unique gene signature irrespective of the changes in cardiac function.[96]

The recent advances in sequencing technology demonstrated that the majority of cellular transcriptome consists of RNAs transcribed from the non-coding region of the genome.[97] These include microRNAs (miRNAs) and long-non coding RNAs (lncRNAs), which have important regulatory and functional roles in the pathophysiology of HF. Matkovich et al. demonstrated that out of 28 “heart failure” miRNAs, which were significantly upregulated at least 2 fold in the failing human hearts, 20 (71.8%) showed full normalization or significant reduction in expression levels following LVAD support, suggesting that miRNAs could be more sensitive than mRNAs in relation to the functional status of the failing human heart.[98] These LVAD-responsive miRNAs included myomiRs (miR-1, miR-133, miR-499) and other miRNAs implicated in cardiomyocyte hypertrophy (miR-23a and miR-195), metabolism (miR-378), and fibrosis (miR-21 and miR-29).[98] In contrast, Ramani et al. demonstrated only 10 myocardial miRNAs out of 108 screened to be differentially expressed in LVAD patients, including miR-23a and miR-195 which were expressed at lower levels at the time of LVAD implantation in patients who recovered on LVAD support.[99] Akat et al. examined circulating levels of cardiac- and muscle-specific miRNAs including miR-1–1, miR-208-a, and miR-208-b, which were increased up to 140-fold in advanced HF patients and demonstrated a near complete normalization of expression following LVAD support, suggesting that circulating miRNAs could potentially serve as biomarkers of myocardial recovery.[100]

Yang and colleagues for the first time performed first sequencing-based transcriptional profiling of the failing human heart before and after LVAD support and provided comprehensive analysis of LVAD induced changes in mRNA, microRNA (miRNA), and long noncoding RNA (lncRNA) expression signatures in the failing human heart.[101] Their analysis suggested that of all transcripts examined, lncRNAs exhibited the highest level of improvement (defined as correction of expression level by at least 25%) with LVAD support including 8.1% and 9.8% of lncRNAs dysregulated in ICM and NICM, respectively. (Figure 4).[101] Only 4.4% vs 7.5% of miRNAs and 5.1% vs. 4.3% of mRNAs dysregulated in ICM vs. NICM, respectively, showed improvement in expression levels with LVAD support. Expression signature of lncRNAs, but not mRNAs or miRNAs, distinguished heart failure (HF) samples before and after LVAD in clustering and principal component analysis, suggesting that non-coding transcripts are more likely to improve with mechanical unloading compared to protein-coding transcripts. Nevertheless, confirming prior microarray studies, >90% of myocardial transcriptome including coding and non-coding elements remained persistently dysregulated by RNA sequencing following LVAD support.

The majority of the transcriptional studies performed to date on LVAD supported patients utilized RNA extracted from the myocardium and do not account for the complexity and heterogeneity of cell populations with potentially diverse origins in the failing human heart. Recent advances in low-input RNA sequencing allowed for definitions of cellular

transcriptomes at single-cell resolution scale, highlighting more than 20 cell subtypes within the human heart.[102, 103] Wang et al. performed single-cell RNA sequencing using cells isolated from two patients before and after LVAD support and showed that cell-specific transcriptional profiles obtained from an LVAD supported heart with improved cardiac function have increased similarity of cell-specific gene expression to profiles obtained from non-failing control hearts, which was most notable for the endothelial cell compartment.[104] In contrast, cell-specific transcriptional profiles obtained from the second LVAD patient without significant improvement of cardiac function on LVAD showed no changes in including cardiomyocyte, fibroblast, or endothelial cell specific gene expression profiles.

Impact of Mechanical Unloading on Myocardial Protein Composition

While transcriptional studies provided insight into LVAD-induced reverse remodeling, changes at the mRNA level do not always correlate with corresponding protein levels due to post-translational regulatory mechanisms. Towards this goal, several investigators used mass spectrometry technique to quantify proteins that change abundance following LVAD support.[47, 105] de Weger et al. identified 16 proteins (all 16 downregulated) which were differentially regulated in non-Ischemic failing human hearts and 50 proteins (38 downregulated, 12 upregulated) which were differentially regulated in ischemic failing human hearts with mechanical unloading. LVAD-induced changes in myocardia proteome included downregulation of several cytoskeletal proteins including desmin, vinculin, α-actin as well as upregulation of several metabolic enzymes including NADH dehydrogenase, pyruvate dehydrogenase, ATP synthase, and creatine kinase.[47] Using pathway enrichment analysis, Shahinian and colleagues demonstrated down-regulation of proteins mapping to extracellular matrix, TGF-β signaling, complement system, and cardiac peptide hormones as well as up-regulation of proteins mapping to innate immune system, metabolism, and protein synthesis following mechanical unloading.[105] Serine protease inhibitor α−1-antichymotrypsin (ACT) has been identified as a candidate protein that is consistently down-regulated in LVAD supported failing hearts by mass spectrometry and validated by immunosorbent assays.[47, 105] Further work suggested that LVAD support results in a significant reduction of stromal ACT staining as well as circulating ACT levels.[106] While implications of ACT for reverse remodeling are unknown, mast-cell derived serine protease Cathepsin G, which is an ACT target and activator of TGF-β signaling, is significantly downregulated following LVAD support.[107]

Impact of Mechanical Unloading on the Epigenetic Landscape of Failing Myocardium

Epigenetic mechanisms associated with the development of pathological cardiac hypertrophy include DNA methylation, histone modifications, and ATP-dependent chromatin remodeling. While changes in genome-wide myocardial DNA methylation has not been yet characterized, LVAD support was associated with a significant increase in the protein levels of repressive histone marks including H3K4me2, H3K4me3, H3K9me2, and H3K9me2.[108] These changes were accompanied by a significant upregulation of histone methylators including H3K9 methyltransferase and suppressor of variegation 3–

9 homologue 1 (SUV39H1) and a reciprocal downregulation of histone demethylators including H3K9 demethylase and jumonji domains (JMJD1A, JMJD2A, and JMJD2D) at the transcript level. Importantly, changes in histone methylation negatively correlated with changes in NPPA and NPPB gene expression in LVAD supported hearts. Class II histone deacetylases are signal responsive repressors of hypertrophy and transition to heart failure. Phosphorylated HDAC4 levels remained persistently elevated in the failing human heart following LVAD support which was associated with nuclear accumulation of MEF-2 signal.[63]

Animal Models of Reversible Cardiomyopathy

While examination of paired cardiac tissue before and after LVAD support provides a unique opportunity to study structural and functional changes induced by mechanical unloading at the cellular and molecular levels, animal models are necessary to gain mechanistic insights into biology of myocardial recovery. Pharmacological, surgical, and genetic strategies have been successfully employed to develop models of reversible cardiomyopathy. Pharmacological models include administration of pro-hypertrophic agonists (Angiotensin II or Isoproterenol) or inflammatory cytokine (Interleukin-β1) followed by drug withdrawal resulting in normalization of heart weight / body weight ratio and echocardiographic indices of LV systolic function.[109, 110] Surgical models of reversible cardiomyopathy include aortic banding-debanding[111–115], heterotopic cardiac transplantation[77, 116], and aorta-caval fistula reversal[117, 118]. Genetic models include tetracycline-regulated expression of transgene in the cardiomyocyte using either “tet-off” (Ro-1[78], antisense mRNA against the murine mineralocorticoid receptor [MR][119], TRAF2[79]) or “tet-on” approach (peroxisome proliferator-activated receptor γ coactivator-1α [PGC-1α][120]). Finally, inducible cre recombination strategy can be utilized for transient activation of target gene by tamoxifen administration (GαqQ209L[121]) followed by withdrawal resulting in reversible heart failure phenotype.

Myocardial gene expression profiling studies from animal models of reversible cardiomyopathy demonstrate an incomplete reversal of HF transcriptional program mirroring observations from genes expression profiling studies from LVAD patients.[79, 112, 115] Persistent dysregulation of the myocardial transcriptional profile in LVAD supported patients may in part explain low incidence of LVAD weaning to a degree sufficient to permit device explantation observed in the clinical registries.[122, 123] It is also plausible to hypothesize that signaling mechanisms responsible for recovery of the failing human heart could be distinct from those responsible for its development. However, functionally recovered mice hearts with persistently dysregulated myocardial transcriptome develop an exaggerated hypertrophic response in response to pressure-overload injury resulting in increased mortality, which suggests that persistent transcriptional dysregulation following LVAD implantation may represent a maladaptive response as well as a potential therapeutic target for achieving myocardial recovery in larger numbers of patients.[79]

Clinical aspects of myocardial reverse remodeling, remission and recovery

As studies of LVAD-induced *reverse remodeling* noted above began appearing in the literature, there were also anecdotal reports of normalized LV function.[27, 69, 124] This led to the concept that LV function of the end-stage failing heart could recover during LVAD support, fostering enthusiasm for use of LVADs for *bridge to recovery*. However, those early reports of LVAD explants were soon followed by reports of relapses of heart failure signs and symptoms. These observations eventually led to the proposed use of the term *remission*, defined as "…the normalization of the molecular, cellular, myocardial, and LV geometric changes that provoke cardiac remodeling that are insufficient to prevent the recurrence of heart failure in the face of normal and/or perturbed hemodynamic loading conditions…"[3] True *recovery* is considered to have occurred when an LVAD is explanted, the ventricular retains normal size and function and the patient does not experience clinical heart failure events despite withdrawal of medical therapies. Accordingly, *recovery* is a diagnosis that can only be made after a significant period of clinical observation following LVAD explant. Describing the effects of LVAD-associated improvements of ventricular function as *remission* (as opposed to *recovery*) is consistent with the observations detailed above that a vast majority of genes abnormally expressed in heart failure do not fully normalize during LVAD support (detailed above). In fact, some of the genetic, molecular and cellular characteristics described above that do not normalize during LVAD support may pose significant potentially non-modifiable impediments to achieving recovery.

Assessment and predicting sustainability of recovery/remission

Early studies showed low rates of remission and LVAD explants, with relatively high rates of heart failure relapses in those patients whose LVADs were explanted.[122–124] Nevertheless, several common factors have been identified in independent studies as being associated with a greater chance of successful LVAD explantation: younger age, non-ischemic etiology, shorter duration of heart failure, smaller LV size, lack of an implantable cardioverter-defibrillator and better renal function.[122, 123, 125] Although the overall rate of recovery sufficient for device explantation is less than 5% an additional 9% of LVAD population exhibit significant improvement in LV function (defined as LVEF >40%) on LVAD support termed as "partial recovery" and suggested that myocardial recovery is a clinical spectrum rather than a binary clinical phenomenon.[123] Interestingly, it has been noted that characteristics of patients who are likely to recovery on LVAD support are similar to the characteristics of patients likely to recover spontaneously even without LVAD support.[126] The implication of this observation is that the likelihood of a patient recovering is predetermined by the underlying pathophysiology (e.g., etiology and duration of heart failure), and the LVAD serves to ensure survival and potentially hasten the process through ventricular unloading, maintaining end organ function, reducing neurohormonal activation and permitting administration of pharmacologic agents (e.g., beta-blockers, ACE inhibitor or ARBs) which themselves are known to contribute to reverse remodeling. This concept underlies the potential benefits of intermediate-term use (weeks to months) of catheter-based, percutaneously deployable, full flow LVAD suitable for patients presenting with recent onset severe heart failure that can tide them through a period of vulnerability

for severe morbidities and mortality while permitting initiation of beneficial pharmacologic heart failure therapies.[127]

Efforts to enhance recovery

As implied above, use of pharmacologic therapies known to be beneficial in heart failure have been used in conjunction with LVADs to enhance the likelihood and extent of recovery. As such several investigators have systematically analyzed myocardial recovery in LVAD patients (Table 2). This concept was first explored in a prospective study of 15 patients who received "intensive medical therapy" with lisinopril, carvedilol, spironolactone, losartan and clenbuterol during support with an early generation pulsatile LVAD. Eleven of these patients exhibited sufficient recovery of ventricular function to permit LVAD explantation after an average of ~1-year support.[27, 128] There was an 88.9% freedom from heart failure events through 4 years of follow up and peak VO2 at 3 years averaged a remarkable 26 ml O2/kg/min. Similar results were obtained in a follow up study of 20 recipients of a continuous flow LVAD by the same authors. Twelve of these patients were explanted, with an 83.3% 3-year heart failure event-free survival. The recent, multicenter Remission from Stage D Heart Failure (RESTAGE-HF) study employed reported 40% success to meet explanation criteria at 18 months in 40 LVAD recipients with similar intensive drug regimen minus clenbuterol (i.e., lisinopril, carvedilol, spironolactone, losartan).[4] While these results are promising, it is important to recognize the limitations of the recovery literature, which include single arm studies without the control group, differences in pharmacological and device weaning protocols, and enrollment of patients who are more likely to recover (young age, non-ischemic etiology, shorter duration of HF) limiting generalizability to broader LVAD population. Cell therapy has been suggested as an adjuvant approach to promote myocardial recovery during LVAD support. In a multicenter randomized controlled clinical trial involving 159 patients with advanced heart failure, intramyocardial injection of allogeneic mesenchymal precursor cells during LVAD implantation did not significantly affect successful temporary weaning from device support or 1-year mortality.[129]

In summary, the current consensus is that a small percentage of the overall LVAD population achieves recovery of LV function to the point where LVAD explantation can be considered. Those most likely to recover are younger patients with non-ischemic cardiomyopathies and a relatively short duration of heart failure symptoms. Of patients fitting these characteristics, ~50% will experience improvement of LV function sufficient to permit LVAD explant. Of patients who meet specific criteria and are explanted, ~80% will experience long term freedom from the need for transplant or LVAD reinsertion.

Impediments to recovery

Potential importance of promoting reverse remodeling independent of remission and recovery—There are at least two potentially important interrelated reasons to promote reverse remodeling in LVAD patients even if they don't ultimately improve the rate of recovery: 1) improving LV contractility with the goal of improving exercise tolerance while on support and 2) the potential to induce right ventricular reverse remodeling to reduce RV failure and improve overall hemodynamic status.

It is well documented that exercise tolerance is limited in LVAD patients with peak VO_2 values typically ranging between 12 to 16 ml O2/kg/min during optimal levels of support.[124, 130, 131] Poor exercise tolerance has been attributed to the limited flow provided by LVADs at the speeds at which they are set for daily living; i.e., generally between 4 and 5 L/min. Even at higher speeds, current mean blood flows achievable by current LVADs are only 7 to 8 L/min. If total cardiac output is supplied only by the LVAD, this puts a very limited upper limit on oxygen delivery to the periphery, even at higher than usual speeds. Assuming peak exercise performance is tightly coupled with peak oxygen delivery, there are limited approaches to increasing exercise tolerance in LVAD patients. As reviewed previously, strategies can include:[132] 1) ensuring optimal hemoglobin levels; 2) enhancing blood flow distribution to exercising muscle by restoring more normal peripheral arterial vasodilatory responses; and, 3) reversing the switch of skeletal muscle from the fast to slow twitch phenotype, the latter being less efficient in oxygen utilization.

An alternative approach to improving oxygen delivery and exercise tolerance involves improving native LV and RV contractilities. A prior study showed that LVAD patients whose hearts are able to respond more appropriately to exercise with increased heart rates and contractility were better able to work in parallel with the LVAD, opening the aortic valve and contributing significantly to total cardiac output.[133] This study demonstrated that total cardiac output (the sum of LVAD and native LV output) could reach ~15 L/min in some patients, approximately half of which was from the LV and half of which was from the LVAD. Overall, exercise tolerance was progressively better the more a patient's heart was able to increase native output. Notably, one key indicator that proved increased LV contribution to total blood flow during exercise was the progressive increase of arterial pulse pressure.

SUMMARY AND CONCLUSIONS

In recent years LVADs have become a mainstay for treating advanced heart failure with outcomes mirroring short and midterm survival of heart transplantation. Furthermore, significant improvements in the adverse effect profile, with near elimination of device thrombosis and 50% reduction of the stroke rate have been reported with newer LVAD devices. The biological changes associated with LVAD support are complex and lead to significant research in the field with the hope of achieving myocardial recovery and increased rates of successful device explantations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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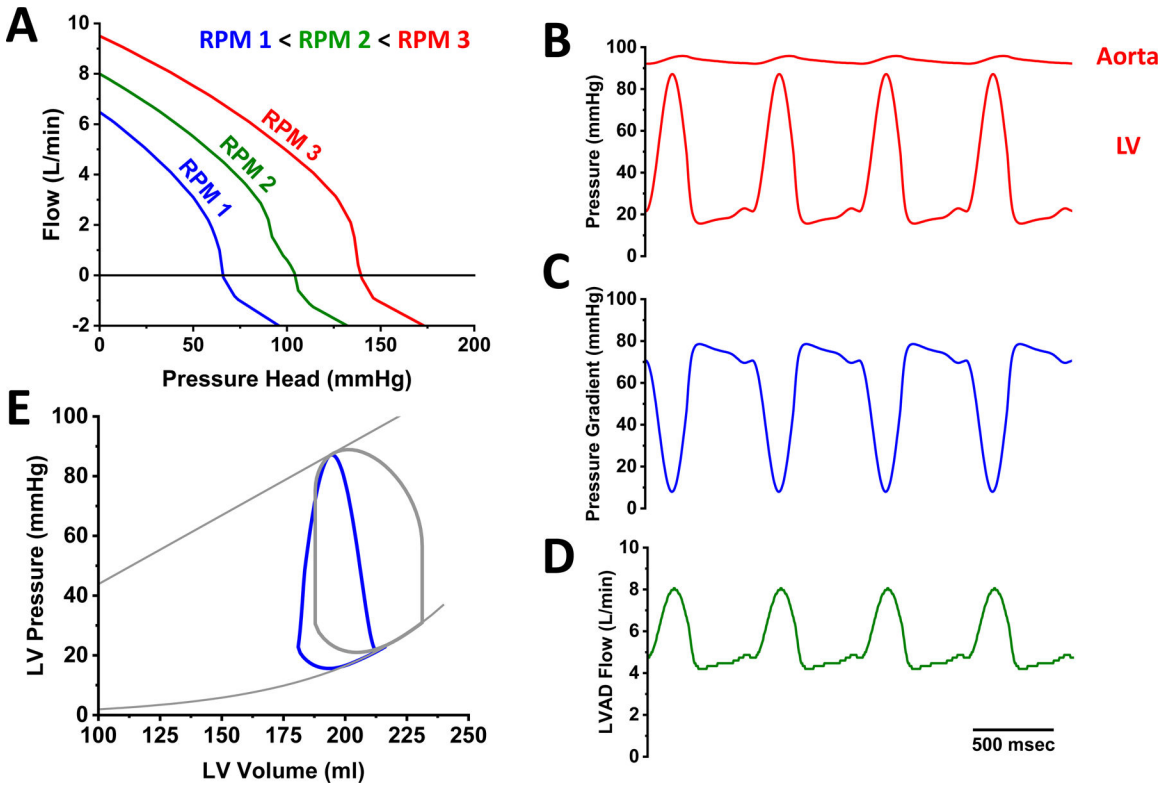

Figure 1.

Basic principles of the hemodynamics of continuous flow left ventricular assist device (LVAD) support. A. Each device is characterized by an RPM-dependent relationship between pressure gradient and flow. B. LVAD support increases aortic pressure and decreases LV pressure such that they can become uncoupled. As a result of the time-varying pressure gradient between aorta and LV (C) LVAD flow also varies over time (D). E. LVAD support leads to LV unloading characterized by leftward shift of the pressure-volume loop and loss of isovolumic phases.

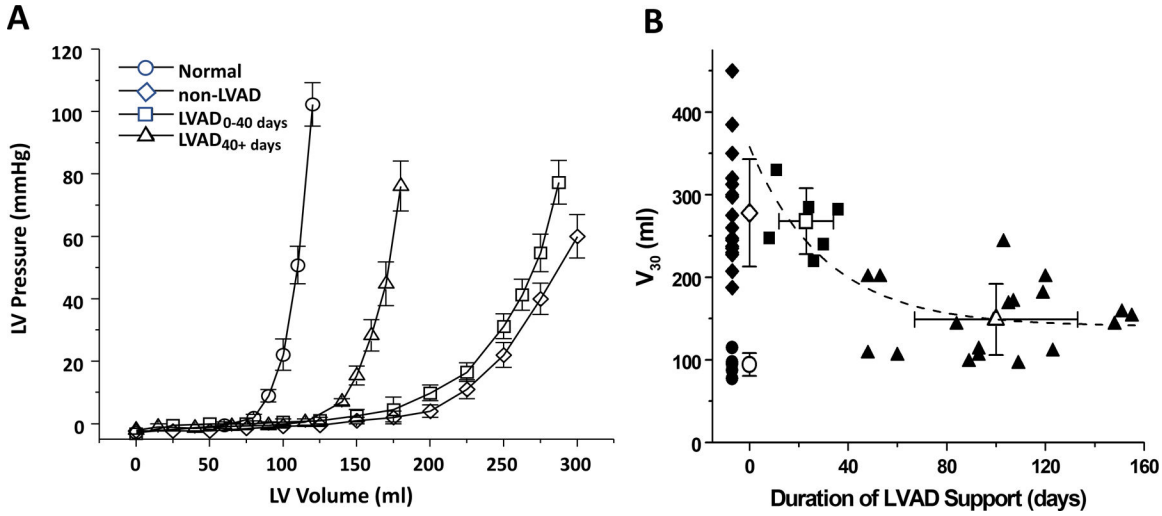

Figure 2.

A. Time-dependent LVAD-associated reverse structural remodeling as indexed by leftward shifts towards normal of the end-diastolic pressure-volume relationship. B. Volume at a filling pressure of 30 mmHg (V_{30}) as a function of duration of support in comparison to normal (open circles) and hearts that did not undergo LVAD support (diamonds); squares and triangles are data from patients supported by LVAD for 0–40 days and >40 days, respectively.[19]

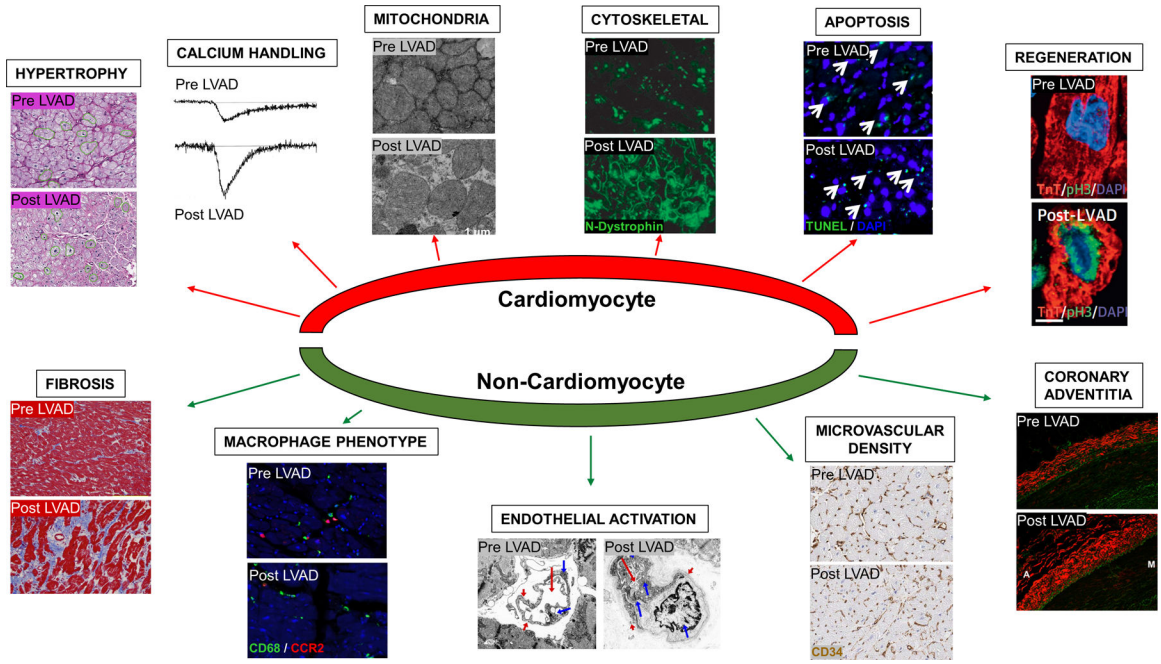

Figure 3.

Effects of Mechanical Unloading on Cardiomyocyte and Non-Cardiomyocyte Components of LV Remodeling. LVAD support is associated with regression of cardiomyocyte hypertrophy[29], improved calcium handling[134], improved mitochondrial ultrastructure[55], improved cytoskeletal organization[45], no change in cardiomyocyte apoptosis[63], improved cardiomyocyte regeneration[50], no change or increase in myocardial fibrosis, macrophage phenotype switch[94], endothelial cell activation[24], increased microvascular density[135], and increased fibrosis of the coronary adventitia[84].

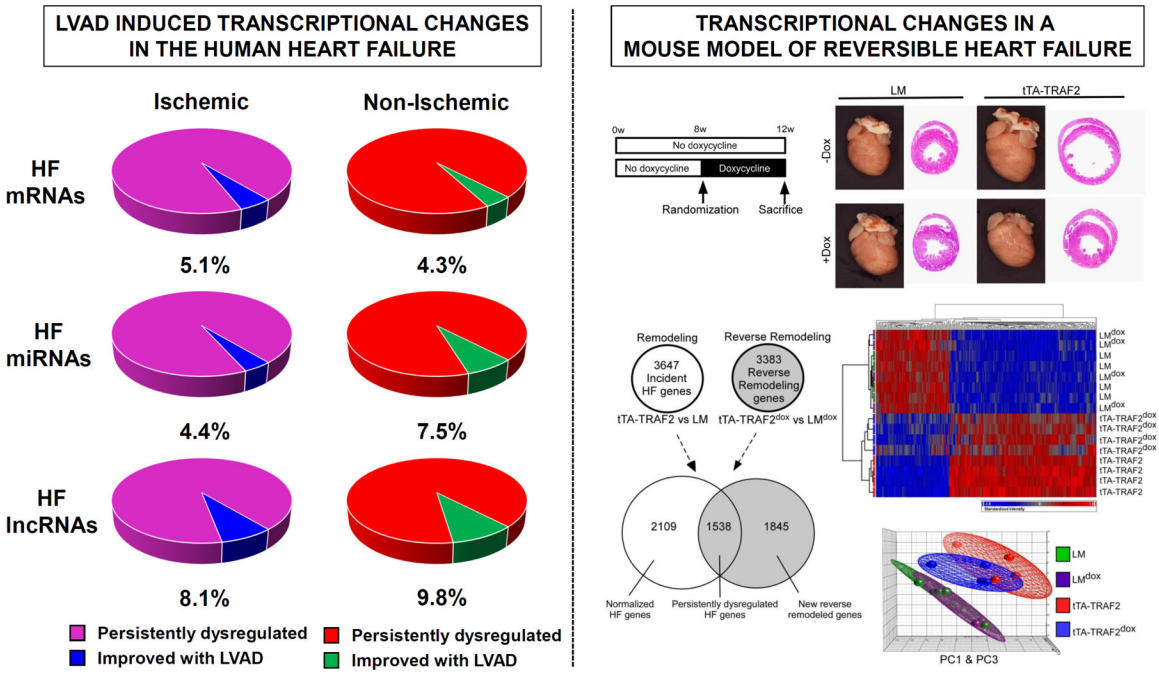

Figure 4.

A) Transcriptional Changes in Failing Human Hearts following Mechanical Unloading with LVAD Support demonstrating persistent dysregulation in >90% of coding and non-coding transcripts in Ischemic and Non-Ischemic Heart Failure (adopted from Yang et al.[101])

B) Transcriptional Changes in Mouse Model of Myocardial Recovery using conditional expression of TNF-associated factor 2 (TRAF2) demonstrating persistent dysregulation of HF transcriptional profile in the recovered mouse hearts (ttA-TRAF2 dox) by Venn-diagram, hierarchical clustering, and principal component analysis (Topkara et al.[79]).

Table 1.

LVAD Induced Changes in Myocardial Transcriptional Profile

Author	Platform	NF-pre-post	HF Etiology ICM / NICM	Paired tissue	LVAD flow	Tissue	Transcript	Major Findings
Blaxall et al - 2003[136]	Microarray	0 – 6 – 6	3 / 3	All	Pulsatile	Heart	mRNA	Significant enrichment of genes involving metabolic pathways
Chen Y et al - 2003[137]	Microarray	0 – 7 - 7	0 / 7	All	Pulsatile	Heart	mRNA	Upregulation of transcription genes and Downregulation of cytokine genes
Chen MM et al - 2003[138]	Microarray	0 – 11 – 11	4 / 7	All	Pulsatile	Heart	mRNA	Upregulation of Apelin signaling in endothelial compartment
Hall et al – 2004[30]	Microarray	0 – 19 - 19	8 / 11	All	Pulsatile	Heart	mRNA	Downregulation of GATA-4 Upregulation of genes involved in vascular organization
Margulies et al – 2005[95]	Microarray	14 – 157 - 28	NR	Some	Pulsatile	Heart	mRNA	Persistent dysregulation of HF transcriptome
Rodrigue et al – 2005[139]	Microarray	4 – 19 - 12	14 / 5	Some	Pulsatile	Heart	mRNA	Upregulation of sarcomeric and calcium handling genes
Hall et al – 2007[140]	Microarray	0 – 6 - 6	0 / 6	All	Pulsatile	Heart	mRNA	Upregulation of integrin signaling and downregulation of cAMP signaling genes
Matkovich et al – 2009[98]	RNA seq	6 – 13 - 4	7 / 10	None	NR	Heart	mRNA & miRNA	miRNA profile more reflective of LV function on LVAD support compared to mRNA profile
Ramani et al. - 2011[99]	PCR array	7 – 34 - 6	0 / 34	Some	Pulsatile	Heart	miRNA	miR-23a & miR-195 levels at LVAD implant predicts functional recovery on device support
Yang et al – 2014[101]	RNA seq	8 – 16 - 16	8 / 8	All	Continuous	Heart	mRNA & miRNA & lncRNA	Persistent dysregulation of HF transcriptome including mRNAs, miRNAs, and lncRNAs
Akat et al – 2014[100]	RNA seq	8 – 34 - 15	13 / 21	Some	NR	Heart & Blood	miRNA	Normalization of circulating myomiR levels with LVAD support
Wang et al – 2020[104]	sc-RNA seq	0 – 2 - 2	NR	All	Continuous	Heart	mRNA	Functional recovery linked to changes in cell-specific transcriptome

Table 2.

Clinical Studies Investigating LVAD-Induced Myocardial Recovery

Study – Year	Study Design	N	NICM	Age	LVAD	Support duration (months)	Cardiac Recovery (%)	Recurrent HF (%)
Columbia – 1998[124]	Retrospective	111	46%	36	Pulsatile	3	5 %	80% at 2yr
Texas Heart – 2003[141]	Prospective	16	75%	34	Pulsatile	7	56%	22% at 14m
Harefield – 2006[27]	Prospective	15	100%	36	Pulsatile	11	73%	11% at 4yr
LVAD WG – 2007[69]	Prospective	67	55%	50*	Pulsatile	4	9.0%	0.% at 6m
Berlin – 2008[142]	Prospective	188	100%	41	Pulsatile	4	18.6%	44% at 5yr
Harefield – 2011[128]	Prospective	20	100%	34	Continuous	10	60.0%	11% at 4yr
Montefiore – 2013[143]	Prospective	21	62%	50	Continuous	10	14.0%	0 % at 5yr
UNOS – 2015[122]	Registry	686	61%	40	Continuous	17	5 %	33% at 1yr
Utah – 2016[144]	Prospective	154	60%	56*	Continuous	6	14.7%	NR
INTERMACS – 2016[123]	Registry	13454	54%	46	Continuous	17	1.2%	NR
RE-STAGE – 2020[4]	Prospective	36	100%	35*	Continuous	12	48%	33% at 3yr

LVAD WG: LVAD Working Group. “Cardiac recovery” defined as LVAD explantation due to functional improvement except for the UTAH Study in which “Cardiac recovery” was defined as LVEF >40% in at least 2 consecutive turn-down echocardiograms. Age and duration of support provided for recovery cohort or *full study cohort.