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Left ventricular assist device-induced reverse remodeling: it's not just about myocardial recovery

Karolina K Marinescu, MD¹, Nir Uriel, MD, MSc², Douglas L Mann, MD³, and Daniel Burkhoff, MD, PhD^{4,*}

¹Assistant Professor, Department of Medicine, Division of Cardiology, Advanced Heart Failure, Rush University Medical Center, Chicago, IL

²Professor of Medicine, Department of Medicine, Division of Cardiology, University of Chicago, Chicago, IL

³Professor of Medicine, Department of Medicine, Division of Cardiology, Washington University School of Medicine/Barnes Jewish Hospital, St. Louis, MO

⁴Adjunct Associate Professor of Medicine, Department of Medicine, Division of Cardiology, Columbia University Medical Center/New York-Presbyterian Hospital, New York, NY

Abstract

Introduction—The abnormal structure, function and molecular makeup of dilated cardiomyopathic hearts can be partially normalized in patients supported by a left ventricular assist device (LVAD), a process called reverse remodeling. This leads to recovery of function in many patients, though the rate of full recovery is low and in many cases is temporary, leading to the concept of heart failure remission, rather than recovery.

Areas covered—We summarize data indicative of ventricular reverse remodeling, recovery and remission during LVAD support. These terms were used in searches performed in Pubmed. Duplication of topics covered in depth in prior review articles were avoided.

Expert Commentary—Although most patients undergoing mechanical circulatory support (MCS) show a significant degree of reverse remodeling, very few exhibit sufficiently improved function to justify device explantation, and many from whom LVADs have been explanted have relapsed back to the original heart failure phenotype. Future research has the potential to clarify the ideal combination of pharmacological, cell, gene, and mechanical therapies that would maximize recovery of function which has the potential to improve exercise tolerance of patients while on support, and to achieve a higher degree of myocardial recovery that is more likely to persist after device removal.

Keywords

Heart failure; Heart assist device; Myocardial remission; Extracellular matrix; Sympathetic activation; Inflammation; Micro-RNAs; Exercise tolerance

1. Introduction

Heart failure is a progressive disease that is initiated by an insult to the myocardium resulting in decreased cardiac output, decreased blood pressure and organ hypoperfusion. The body's natural response to such conditions involves activation of autonomic reflexes and stimulation of the renin-angiotensin aldosterone system (RAAS). Over time, the resulting mechanical and neurohormonal stresses on the heart lead to myocyte hypertrophy, progressive loss of myocyte number (apoptosis), further reductions of myocardial contractile strength and progressive dilation of the ventricle. There are profound effects on gene expression, protein expression and function, kinetics of intra- and extra-cellular signaling pathways, metabolic processes, extracellular matrix properties, global ventricular geometry and on electrophysiology at muscle and ventricular levels. Collectively, these changes constitute the phenomenon referred to as *ventricular remodeling* (1). Some of these affected processes have become targets for successful drug- and device-based therapies for heart failure therapies.

2. Reverse remodeling: a historical perspective

Until the mid-1990's, ventricular remodeling was thought to be largely irreversible, especially in patients considered to have *end-stage* disease. Earlier evidence suggested that the remodeling process could be blunted by early application of angiotensin converting enzyme (ACE) inhibitors in the setting of myocardial infarctions (2–4), but the concept that a severely dilated heart could revert to more normal size, shape and function was not present in the literature. Initial challenges to the irreversibility of LV remodeling were largely based on observations made in patients supported with left ventricular support devices (LVADs) (5). Studies of hearts bridged to transplant showed that LVAD support induced regression of cellular hypertrophy, and that the LV end-diastolic pressure-volume relationship (EDPVR) was shifted leftward, towards the normal volume range (Fig. 1A) (5). Such a shift of the EDPVR signifies a fundamental restoration of more normal cell sizes, fiber architecture and chamber geometry. Accordingly, these hearts were said to have exhibited a reversal of the remodeling process, a process now referred to as ventricular *reverse remodeling*.

These studies led the way to a new human tissue-based experimental paradigm for studying heart failure and its reversal through comparisons of characteristics of the heart and tissue obtained at the time of LVAD implant (with the heart in a state of severe dysfunction) to those of the heart and tissue, in many instances from the same patient, obtained at the time of heart transplant following the intervening period of LVAD support. This line of investigation was pursued vigorously and it is now known that *reverse remodeling* can be seen on molecular, cellular, extracellular and global levels in a majority of patients receiving LVAD support. Time-dependent improvements in hypertrophy, ventricular geometry, myocardial contractile function, calcium cycling, beta-adrenergic signaling, metabolism, myocyte death, sympathetic innervation, endothelial function, microvasculature structure and function have all been documented and reviewed in detail previously (5–10).

Along with the development of the different generations of LVADs, evidence also emerged that the degree of reverse remodeling depends on the degree of unloading provided by the

device. The originally introduced devices were pulsatile in nature and had the capacity to markedly unload the native LV because blood flowed from the LV into the device chamber under low pressure. In a sense, these pulsatile devices turned the LV into a low pressure atrium for the LVAD. The next generation of LVADs were continuous flow rotary pump devices which provided less pressure and volume unloading. It was shown that LV size and function and circulating levels of BNP and markers of extracellular matrix turnover were significantly more effectively normalized during support with pulsatile and continuous flow devices (11). More recently, studies performed in hearts of patients receiving partial support by a low flow continuous flow LVAD showed less reverse remodeling than those supported with a high flow device (Fig. 1B) (12).

Finally, since LVADs restore more normal blood pressure and flow to the periphery, secondary improvements of neurohormone and natriuretic peptides levels have also been documented, signifying a move towards resolution of the systemic effects of the heart failure state (13, 14). These factors have been shown to be important mechanisms in the mediation of many aspects of *reverse remodeling*.

3. Myocardial recovery and remission: a historical perspective

At the time when studies of the various aspects of LVAD-induced *reverse remodeling* were intensifying, anecdotal experiences of normalization of LV function to the point where LVADs could be explanted also began to appear (15–17). LV function in such patients were said to have *recovered*. These experiences, in combination with the growing understanding of the breadth and extent of reverse remodeling achievable during LVAD support, gave hope to the notion that studies of reverse remodeling would lead directly to new therapies for heart failure, possibly even to a cure. However, those early reports of LVAD explants were soon followed by reports of heart failure relapses. In some cases relapse occurred rapidly and with complete return of severe LV dysfunction and symptomatic heart failure (15). In other patients, the rate of decline of LV function was more gradual (16). This led us to propose the use of the term *remission*, which we 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. Thus, although myocardial remission may be associated with stabilization of the clinical course of heart failure as well as reversal of many aspects of the heart failure phenotype, it is not associated with freedom from future heart events” (9). In addition to LVAD-induced remission, heart failure remission has been observed with other therapies (18, 19). For example, some patients taking beta-blockers who have shown dramatic improvements in LV function have relapsed when the beta-blockers were discontinued (20).

The use of *remission* in favor of *recovery* is further supported by observations that a vast majority of abnormally expressed genes expressed in heart failure do not normalize during LVAD therapy (discussed further below). Nevertheless, it may be appropriate to designate an LVAD-explant patient as *recovered* if that patient remains free from heart failure symptoms, heart failure medications can be weaned and the heart retains normal size and function after a relatively long period of time; the exact duration required to declare recovery is thus far

not specified. However, most physicians who care for LVAD-explant patients maintain guideline recommended heart failure medical therapies for life, obviating the ability to truly test the degree of permanence of the recovered phenotype (18, 19).

4. Assessment and predicting sustainability of recovery/remission

In order to identify the presence of myocardial recovery, reversal of the phenotype of the failing heart must take place. Several approaches for clinical assessment of reverse remodeling and improved function have been employed, including exercise and/or dobutamine stress testing following reduction of the degree of mechanical support. Mancini *et al* described a protocol whereby exercise testing was combined with respiratory gas analysis with hemodynamic and echocardiographic measurements (16). Maybaum *et al* selected patients with EF >40% to undergo dobutamine stress echocardiography with hemodynamic monitoring. Here, increasing dobutamine doses were given while the patient was maintained on partial VAD support. In general the patients who maintain low filling pressures and increased LVEF during stress tests were considered potential candidates for device explantation (21).

Similarly, it has been shown that rest and stress hemodynamics performed at reduced VAD speeds in selected groups of patients could be utilized to identify those with potential myocardial recovery (16). Birks *et al* utilized a protocol where LV structure and function was assessed during serial reductions in VAD pump speed of HeartMate II to 6,000 revolutions per minute (RPMs) with two-dimensional echocardiography. This assessment was then followed by 6-minute walk test, as well as cardiopulmonary exercise testing; VAD explantation was considered if the following four criteria were met: “1) LV end-diastolic dimension (LVEDD) was less than 60 mm, LV end-systolic diameter (LVESD) was less than 50 mm, and ejection fraction (EF) was greater than 45 %; 2) LV end-diastolic pressure or pulmonary capillary wedge were less than 12 mm Hg; 3) the resting cardiac index was greater than 2,800 mL/min/m²; and 4) maximal oxygen consumption with exercise (mVO₂) was greater than 16 mL/ kg/min” (22).

Still, a significant number of patients that meet criteria for remission and undergo LVAD explantation do not sustain adequate cardiac function long term (16, 23). Thus, the optimal method for assessment of recovery is not known, and the issue of how to assess the likelihood of maintenance of good cardiac function remains unresolved.

5. Factors associated with recovery/remission

Several factors have been identified as being associated with a greater chance of leading patient care to LVAD explantation. A recent study evaluated UNOS registry data that included 594 patients receiving a HeartMate II and 92 patients with an HVAD, who were supported for an average of 500.4±325.3 days (24). It was observed that 5% of these patients were explanted in the setting of recovered LV function. Those more likely to recover were younger (40.1±14.5 vs. 53.4±11.6, p<0.001), female gender, had lower BMI (25.7±5.8 vs. 27.9±4.7, p=0.010) and lower serum Cr (1.0±0.4 vs 1.3±0.6, p=0.002). 91.2% of recovered patients were of non-ischemic cardiomyopathic etiology. Other incidental findings included

the fact that recovered patients had lower chances of having an ICD (44.1% vs. 79.0%, $p<0.001$) and lower cardiac output (3.8 ± 1.4 vs. 4.5 ± 1.5 L/min, $p=0.008$) at the time of LVAD implantation. As will be discussed further in the next section, patients having the characteristics of those more likely to recover during LVAD support are similar to the characteristics of patients more likely to recover even without LVAD support (25).

From a historical perspective, it is also noteworthy that results from one institution with experience from a large number of patients suggested that higher rates of recovery were observed in patients receiving a pulsatile rather than continuous flow LVADs (26). The reasons for this are not clear. The authors suggest that more normal pulsatility of pressure and flow in the arterial system as a contributing factor. Indeed, potential consequences of the lack of arterial pulsatility with continuous flow devices has been debated for almost a decade (27, 28). An alternate hypothesis relates to the fact that, as noted above, pulsatile devices provide more unloading and result in greater degrees of reverse remodeling and continuous flow devices. We favor this latter hypothesis because the experience with the low flow partial support devices (29) also noted above. With the low flow, partial support LVAD that was studied clinically, full arterial pulsatility was retained, the degree of reverse remodeling was less than is seen with full support continuous flow LVADs (Fig. 1B) and the rate of recovery/remission was equally low. Nevertheless, this topic deserves further consideration; while the degree of unloading may not be able to be increased, a certain degree of pulsatility can be introduced with continuous flow devices by pump control algorithms that vary pump rotational speed.

6. Incidence of LVAD-induced recovery/remission

With the exception of observations made by a small number of investigators, myocardial recovery occurs in a minority of the overall patient population undergoing mechanical circulatory support (MCS) (16). However, Drakos and Mehra correctly point out that until recently most centers have not evaluated patients for the degree of reverse remodeling and the extent of recovery, so the true incidence is likely unknown (30). In their review, the percent of recovered patients at 9 different centers ranged from 9% to 63% (Fig. 2). Additionally, when separated into those with intense adjuvant heart failure drug protocol (2 centers), and those without (7 centers), those with treatment plans that included intense medical therapy and surveillance had a higher rate of recovery (43.5% vs 22.4%) (30). However, these rates do not reflect the rate of recovery in the overall LVAD population; rather, these are rates among a highly selected group of patients with a higher probability of showing improved LV function during LVAD support. Taking this into account, the proportion of the overall LVAD population who recover or show indications of being potentially recoverable is small.

Further to this point, as noted above, patients more likely to recover during LVAD support are the younger cohort, with idiopathic cardiomyopathy, with a relatively short duration of symptoms (24). Interestingly, these characteristics overlap with those of patients more likely to recover with other forms of therapy, including beta-blockers and CRT; the so-called super responders” (18, 19, 25) (Fig. 3). For example, rates of recovery/remission are relatively high with peripartum cardiomyopathy or acute lymphocytic myocarditis, particularly in the

setting of aggressive neurohormonal blockade, even without MCS (25). These observations raise the possibility that in patients having characteristics of those likely to recover, LVADs serve as a tool to provide life-saving hemodynamic support during the early stage of an insult that causes severe heart failure and contributes to (or even accelerates) the process of reverse remodeling but that recoverability is pre-determined by the factors noted above (25).

7. Enhancing recovery: impediments and opportunities

Structural and functional changes indicative of reverse remodeling are dramatic, reproducible and common. However, relatively early in the course this research indications emerged that the reverse remodeled myocardium and heart have not truly returned to normal anatomy and physiology. Furthermore, some of the properties that do not normalize may pose significant potentially non-modifiable impediments to recovery.

7.1 Gene and micro RNA expression patterns

Using gene array analysis, Margulies *et al* identified 3088 transcripts that exhibited abnormal abundances in failing human myocardium (31). Of those, only 238 showed any consistent response to LVAD support. Of those 238 genes, 11% exhibited partial return towards normal, 5% showed full normalization and 2% showed overcorrection. The implication of these findings is that despite the normal appearance achieved with MCS at a macroscopic level, many abnormalities persist at genetic and molecular levels. It has been hypothesized that such persistent abnormalities may not only explain the low incidence of recovery, but also the incidence of remission following LVAD explant when the reverse-remodeled heart is re-exposed to normal hemodynamic stresses. The essence of these findings has been confirmed in several other studies of human myocardium (32–39).

Most recently, Topkara and colleagues (40) developed an murine model of heart failure based on conditional expression of TNF receptor-associated factor 2 (TRAF2), a proinflammatory transgene, which allowed detailed study of the genetic and functional changes during the development of heart failure, and its reversal following removal of the inflammatory stimulus in a highly controlled and reproducible setting. The conclusions from these studies were consistent with and significantly extended those obtained from the human gene array studies noted above. When the inflammatory stimulus is withdrawn for 4 weeks, there was complete normalization of LV structure and function, but only partial (~60%) normalization of the heart failure genotype (Fig. 4). Genes belonging to extracellular matrix, integrin/cytoskeletal, excitation-contraction coupling, metabolism and sarcomeric protein families were all among the persistently abnormally expressed genes. When these functionally recovered hearts were stressed by transaortic constriction, the mice showed exaggerated hypertrophic response and increased mortality compared to normal littermates. The longer the time period allowed following withdrawal the inflammatory stimulus, the greater the degree of genetic normalization, achieving 88% normalization after 8 weeks. Another key finding of this study was that a set of newly expressed unique genes were identified in the reverse-remodeled hearts, which were termed “reverse remodeling genes.” All of the findings in the experimental model were reproduced in comparisons of gene array analysis of pre- and post-LVAD supported human myocardium. Whether the “reverse

remodeling genes” or the persistently abnormally expressed genes contribute to the low incidence of recovery and to the incidence of relapse after LVAD explant is unknown.

To the degree that full normalization of the genotype is required for myocardial recovery, these findings and those obtained in the clinical studies cited above suggest a certain irreversibility of the heart failure state that may pose a significant, fundamental impediment to recovery for which there is currently no known means of overcoming. However, new information related to the role of micro RNAs in heart failure and during LVAD support might have an impact.

Changes in micro RNA expression observed in heart failure and during LVAD support have been the topic of recent studies (41, 42). Since micro RNAs appear and are stable in the blood stream, some studies have explored pre-LVAD micro RNA levels as a marker for the potential to recover during LVAD support (43). Other studies have examined their role in the reverse remodeling process (44–46). Since micro RNAs regulate gene expression on a posttranscriptional level and influence expression of gene networks, they may have therapeutic potential to influence the persistently abnormal gene programs noted above during reverse remodeling process (41, 42).

It is also possible that epigenetic changes may be responsible for the persistently abnormal gene expression that is observed in reverse remodeled hearts. Further to this point, the consistent profile of gene expression changes in explanted failing hearts, as well as the persistent expression of genes following LVAD support suggests that changes in the epigenome may “lock” certain genes into an on or off position (47). In human heart failure DNA methylation differences were present in promoters of upregulated genes but not downregulated genes. Thus, distinct epigenomic patterns exist in important DNA elements of the cardiac genome in human end-stage heart failure (48). Although this has not clearly been linked to any genes that are known to be critical for reverse LV remodeling, changes in methylation showed a predicted correlation to differential expression of several angiogenesis genes. Given that the epigenome can be modulated pharmacologically, it opens the possibility that some of the persistent gene regulation that has been observed in failing human hearts can be manipulated. However, to date there is no clear proof, so this remains hypothetical and such research is in its infancy (49).

7.2 Extracellular matrix

Other equally important non-normalized properties, which may be more readily modifiable during MCS. LVAD-associated changes in the extracellular matrix (ECM) are important examples. Studies of ECM were initially mixed as to whether total collagen content was increased or decreased during LVAD support (see reference (8) for detailed summary of this controversy). It was soon discovered that concomitant use of ACE-inhibitors had a major impact; total collagen and cross-linked collagen increased in LVAD patients not taking an ACE-inhibitors while both decreased back towards normal in those taking an ACE-inhibitor (50). Notably, this was the first demonstration of an LVAD-mediated biological process modified by a drug. This led to a concept of the interrelations between mechanical load, regulation of tissue hormone levels (specifically angiotensin II), enzymatic regulation of ECM turnover and how this process could be regulated by drug intervention (Fig. 5) (8).

More recent, detailed studies have started to explore regulation of ECM turnover in LVAD supported hearts, its impact on extracellular cytokines and signaling proteins and their influence on myocyte properties (51, 52). In addition to abnormalities at the protein level, studies have similarly shown interesting changes in patterns of ECM-related gene expression during LVAD support (33). However, in light of data summarized above regarding ACE-inhibitors, one factor often overlooked is the role of background medical therapy in patients supported with mechanical circulatory devices. It is crucial to note that the conclusions from such studies will be confounded, as we are/on is unable to separate effects of unloading from that of drug therapy.

Finally, regardless of the direction of change, the time course of matrix protein changes was much slower than that of all other properties investigated (with a half-life of approximately 90 days for ECM proteins compared with a half-life of 30 days for regression of cellular hypertrophy and leftward shifting of the EDPVR) (10)); this observation may have implications for the expected time course of recovery and why some patient exhibit recovery only after a year or more of support (30).

Since the ECM plays many roles in the heart, significant questions remain unanswered with regard to recovery. Even with normalization of collagen content, whether the structure and detailed composition of the matrix and its relationship to cardiomyocytes are also becoming normalized is as yet unknown. Encouraging results were obtained from isolated muscle strips showing that changes in myocardial stiffness paralleled changes in the quantities of cross-linked collagen (53). However, clinical observations made in some patients following LVAD explant who showed rapid (within days) re-dilation (15) of the LV (which is normally prevented by the ECM) suggested lack of reestablishment of normal matrix structural functionality. Accordingly, this observation may suggest that therapies that prevent heart dilation (such as a ventricular constraint device (54)) might have a role in preventing this aspect of relapse. Most recently an FDA-approved biologic ECM construct synthesized from decellularized porcine small intestinal submucosa (CorMatrix Cardiovascular Inc. CA, USA) (55) that is rich in collagen, glycosaminoglycans and growth factors that stimulates ECM production and increases the myofibroblast and cardiomyocyte numbers (56, 57) has been studied in conjunction with LVAD support. Preliminary data suggests that this combination has the potential to enhance cardiac function and promote myocardial recovery (58). Other, pharmacologic based approaches to reconstructing the extracellular matrix in terms of structure, mechanical function, and providing a normal biochemical milieu, may also be feasible.

The important message, however, is that there are many conceivable approaches to address persistent abnormalities of the ECM that are logical targets for improving the rate of recovery and its permanence.

7.3 Right ventricle

Right heart failure is a significant clinical problem both short and long term and is the cause for a large proportion of repeat hospitalizations after LVAD implantation (59, 60). In addition, RV dysfunction has been considered an impediment to recovery in some patients and may contribute to relapse of heart failure after LVAD explantation. Importantly, there are

no established strategies to facilitate RV recovery. One untested hypothesis is that the use of optimal guideline directed medical therapies for left heart failure, believed to promote reverse remodeling and recovery (i.e., beta-blockers, ACE-inhibitors or ARBs, mineralocorticoid inhibitors and diuretics), may exert such beneficial effects on RV myocardial and chamber properties during LVAD support. However, there are no guideline recommendations for the use of these drugs during LVAD support. Accordingly, their use varies significantly between institutions: they are used routinely to maximal recommended doses in some sites while in other sites their use is largely limited to treating symptoms and achieving blood pressure control. While use of these drugs is a key part of the so called “Harefield protocol” for recovery (17), the impact on RV function has not been reported.

It is also noteworthy that the beneficial effects of LVAD support on the LV only partially extended to the RV (61). Reverse remodeling of chamber and myocardial properties that are governed by reduction of ventricular preloading (e.g., reverse remodeling of the ventricle, many of the changes in the ECM, improvement in the expression of certain genes) are not improved in the RV during LVAD support. While LVADs can reduce RV afterload, they don’t reduce RV preload; frequently, RV preload is increased. On the other hand, properties that are governed by normalization of circulating neurohormones (e.g., restoration of myocardial beta adrenergic responsiveness) can be improved in the RV as well as the LV.

Other factors potentially contributing to RV dysfunction include the impact of LVAD-induced leftward shifting of the interventricular septum, RV volume overloading due to too high LVAD flow, excessive RV afterload (i.e., increased pulmonary vascular resistance) and total body fluid overload. It has been proposed that these issues can be partially dealt with by more detailed hemodynamic-echocardiographic “ramp studies” to optimize RPMs and diuretic doses (62). It would be interesting to test whether this approach can also enhance the likelihood of myocardial recovery.

7.4 Persistent sympathetic activation

While many abnormalities of the neurohormonal axis present in the heart failure state are improved during LVAD support (13), at least one study has reported a significant persistence of sympathetic activation in patients with continuous flow devices (63). When compared to patients supported with pulsatile VADs, patients with continuous flow VADs who have very little arterial pulsatility showed exaggerated increases in sympathetic nerve activity in response to 60° head-up tilt testing. The authors speculated that this sympathetic activation was due to baroreceptor unloading with the loss of pulsatility, and that this persistent elevated nerve activity may inhibit myocardial recovery and contribute to end-organ dysfunction. It was suggested that strategies to induce arterial pulsatility may be necessary to improve outcomes. Interestingly, current devices incorporate RPM control algorithms that induce some degree of arterial pulsatility. Whether these algorithms provide a sufficient degree of arterial pulsatility and can reduce sympathetic activity have not been tested.

7.5 Persistent inflammatory state during LVAD support

A series of recent studies have examined changes in levels of inflammatory markers during long-term LVAD support (64–66). Consistent with observations reviewed above, Grosman-

Rimon *et al* observed significant *reverse remodeling* as evidenced by reductions in LV size, and trends towards improved LV ejection fraction. They observed reductions in BNP levels, an indicator of reduced myocardial stress. However, levels of a multitude of inflammatory markers, including monocyte chemoattractant protein-1, interferon γ -induced protein, and C-reactive protein were significantly greater than normal through 9 months of follow-up. In addition, levels of serum interleukin-8, tumor necrosis factor- α , macrophage inflammatory protein- β and macrophage-derived chemokine were higher than normal and continued to increase during the course of LVAD support. The implications of a persistent inflammatory response as it relates to reverse remodeling have not been determined. Whether this persistent inflammatory state reflects a systemic foreign body response, a response to ongoing damage to blood elements caused by the pump (hemo-incompatibility) or some other factor is unknown. Nevertheless, this observation is potentially important as it serves as an indicator that on a whole body level, LVAD support does not restore true normal conditions.

8. Importance of promoting reverse remodeling independent of remission

There are at least two potentially important interrelated reasons to institute therapies to promote reverse remodeling in LVAD patients (especially in destination therapy) 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 (67–70). In older LVAD patients, who are more likely to be implanted for destination therapy, peak VO₂ values typically range from 12 to 16 ml O₂/kg/min, approximately 50% of predicted values. This low exercise tolerance is largely attributed to the fact that at maximum recommended speeds, mean blood flows generated by currently available LVADs reach only 7,000 or 8,000 mL/min. If total cardiac output is supplied only by the LVAD, this puts an upper limit on oxygen delivery to the periphery. Assuming new higher flow LVADs will not be available, and assuming exercise tolerance is linked with peak oxygen delivery there are limited approaches to increasing exercise tolerance at fixed flows. Ensuring optimal hemoglobin levels may be impactful. For example, an increase of hemoglobin concentration from 10 to 13 g/dL increases oxygen delivery by ~250 ml/min at a flow of 7,000 mL/min. For a 70 kg person, and assuming O₂ extraction rates of 50%, this translates to a potential increase in peak VO₂ of almost 2 mlO₂/kg/min. Restoration of more normal peripheral responses to exercise can also be helpful. Arterial vasodilation in the muscular beds with reductions of systemic vascular resistance (SVR) is a fundamental normal response to exercise. Although exercise-induced reductions in SVR on a whole appears only mildly blunted in heart failure (71), vasodilation of the vascular beds of the muscle is significantly reduced (72). This can be overcome to a certain extent by exercise training and by vasodilator drugs such as ACE-inhibitors (72). In addition, although muscle of exercising heart failure patients extracts more oxygen from the blood, switching of skeletal muscle types (from fast to slow twitch) and abnormalities of muscle metabolism render them less efficient in oxygen utilization; contribute significantly to exercise intolerance.

However, a potentially more plausible means of increasing blood flow, oxygen delivery and exercise tolerance, is to restore native LV contractility and, more specifically, to restore myocardial beta-adrenergic responsiveness so that LV contractility and heart rate can increase appropriately during exercise. With increased contractility and pressure-generating capacity, the LV can overcome aortic pressures and eject, thus adding native ejection to LVAD flow, increasing total cardiac output. Even in cases when the LV is already ejecting under resting conditions, the amount of LV ejection increases with increasing LV contractility. Unlike LVAD flow, LV outflow is linearly dependent on heart rate, so the faster an ejecting LV can beat, the greater the output from the native heart. Indeed, it has been shown in one study that during graded exercise, total cardiac output was able to reach 15,000 mL/min, of which approximately half was from the LV and half was from the LVAD (Fig 6A) (69). Another indicator of increased LV contribution to total blood flow in these patients was the progressive increase of arterial pulse pressure (Fig. 6B). Finally, it was of interest to note that, as discussed above, overall exercise-induced vasodilation was intact as well (Fig. 6C). On the whole, exercise tolerance was significantly greater in patients able to increase the contribution of the heart to the total blood flow.

As discussed in detail above, the potential to induce reverse remodeling of the RV may impact significantly on overall hemodynamics at rest and improve the likelihood of recovery in some patients. However, improved RV function may also have benefits to enhance exercise tolerance; improved RV function improves ability to fill LV for better LVAD flow.

Thus, for these two reasons alone, there are theoretical motivations to pursue therapies that enhance myocardial reverse remodeling and recovery, even if the degree of recovery is not sufficient to permit explantation of the LVAD. Currently, as detailed above, the only therapies that have the potential to promote remodeling in LVAD patients are neurohormonal antagonists and diuretic therapies. ACE-inhibitor use appears to lead to greater reductions in LV size and decreased myocardial fibrosis during LVAD support. The effects of beta-blockers and mineralocorticoid antagonists have not been specifically studied. The original Harefield protocol for enhancing recovery included these drugs (at high doses) in addition to clenbuteral; studies of that protocol and derivatives thereof have focused on the ability to explant devices. Unfortunately, their impact on exercise tolerance and RV function have not been specifically studied in a randomized fashion.

9. Summary and Conclusions

In summary, *reverse remodeling* is not synonymous with *recovery*. *Remission* may be a more appropriate term to apply to patients with normalized LV size and function in whom LVADs can be successfully removed. Reverse remodeling is necessary but not sufficient for remission; however, it remains an important surrogate marker for a partial return towards the normal non-pathological condition. While almost all hearts exhibit reverse remodeling during LVAD support only a small percentage of the overall LVAD population truly show remission. Specific subgroups of patients appear more likely to exhibit remission during LVAD support to the point where LVADs can be explanted. These subgroups are typically comprised of younger, female patients whose heart failure is of non-ischemic origin and whose duration of symptoms is relatively short. It has been revealed over the past decade

that despite appearances of normalized structure and function at the whole heart level, the failed myocardium does not really normalize during LVAD support. Persistent changes at molecular and cellular levels may explain the low rates of remission and the occurrence of relapses once LVAD support is withdrawn. Although speculative, it is also quite likely that these observations are also quite pertinent to our understanding of why heart failure with reduced ejection fraction patients with a partial normalization of LV ejection fraction on medical therapy will ultimately redevelop heart failure over time. Deeper understanding of these persistent abnormalities may lead to new therapeutic approaches to improve the rate and permanence of remission.

Initial interest in reverse remodeling focused on its link with recovery. However, we propose that there are other potential clinical benefits of promoting reverse remodeling and improved cardiac function, especially in the setting of destination therapy, where survival rates are improving and durations of support are increasing. Since mean flow rates provided by current LVADs are limited, improved exercise tolerance and quality of life may depend on the ability of the left ventricle to provide the extra needed cardiac output during relatively short bursts of activity. Similarly, promotion of recovery of RV function may have several benefits, including reducing heart failure related admissions and improving exercise tolerance.

The time course of innovation in LVAD device technology is relatively slow, often taking 2–3 years for introduction of incremental improvements, and as much as a decade for introduction of a new device into the clinic. The most recent introductions into clinical trial, including HeartMate 3 and MVAD (73, 74) have the same flow capacities as the prior generation of devices, and may ultimately show improved hemocompatibility and lower adverse event rates. This has the potential to expand the acceptance of the use of LVADs for destination therapy. Improvement of the rate, extent and permanence of the reverse remodeling-remission-recovery sequence may be considered the next frontier in the evolution of LVAD therapy. Research over the past decade has identified several potential targets addressable by either drugs or devices that may help achieve this goal.

10. Expert Commentary

Treatment goals in the care of patients undergoing left ventricular assist device (LVAD) support differs depending on whether the implant is intended of a bridge to transplant (BTT) or as destination therapy (DT) without the possibility of transplant. With BTT, the goal generally focuses on minimizing adverse events until the time of donor heart availability. Goals during DT therapy also focus on minimization of adverse effects but also more broadly include providing the highest possible quality of life to patients that may be supported for long periods of time. It has been known for more than 25 years that dilated hearts supported by an LVAD reduce their size towards normal and show improved function, a phenomenon known as reverse remodeling. Observations that some BTT and DT patients have exhibited marked degrees of reverse remodeling and improved ventricular function during LVAD support to the point where devices have been explanted, the concept of bridge to recovery (BTR) has received significant attention. However, although most patients show a significant degree of reverse structural remodeling, very few exhibit sufficiently improved

function to justify device explantation. Furthermore, many patients from whom LVADs have been explanted have relapsed back to the original heart failure phenotype. While some studies have tested strategies to enhance the extent, rate and permanence of recovery, none has proved successful. The most recent studies exploring the changes in gene and protein expression in heart failure and their further changes during reversal back towards normal indicate that although a reverse remodeled heart may appear normal, many molecular abnormalities persist and many newly expressed “reverse remodeling” genes appear whose functional significance is unknown.

Future research has the potential to clarify the mechanisms that regulate changes in gene program expression during the development of heart failure and during recovery. The ultimate goal of ongoing research is development of means of controlling these mechanisms in order to normalize myocardial function as much as possible at every stage of the disease. Ideally, this could be achieved through pharmacological means. Gene and cell therapies, though more complex from developmental, regulatory and implementation perspectives, also have great potential. Alternatively, or in combination, certain types of device-based therapies used in conjunction with LVADs may offer means of improving the extent of recovery of LV function and maintaining it when LVAD support is withdrawn.

Regarding this last point, one interesting concept relates to means by which the small size of the reverse remodeled ventricle can be retained after withdrawal of LVAD support and the ventricular wall is re-exposed to normal forces; it is postulated that the extracellular matrix plays an important role in this process. Yet, it is known that the extracellular matrix take the longest time to remodel and reverse remodel and whether a truly normal extracellular matrix can be achieved is currently unknown. Prior work with extra-cardiac constraint devices, which failed to prove useful when applied to the already dilated heart, may have a role in maintaining normal left ventricular size following withdrawal of LVAD support.

Independent of the ability to achieve higher rates of remission, efforts to improve the extent of reverse remodeling is important because of its implications for improved quality of life and exercise tolerance for LVAD-supported patients. Improve native LV and RV function may be one way of reducing recurrent heart failure hospitalizations and improving exercise tolerance of LVAD patients; stronger native heart function translates to improved overall cardiovascular performance. This is because overall cardiovascular properties (including total cardiac output, pulmonary capillary pressures and blood pressure) can be improved if the native heart can make a contribution, especially during short bursts of exercise.

Overall, research aimed at understanding the molecular changes that occur during the development of heart failure and during its reversal have the potential to lead to new therapies for the benefit not only of patients undergoing LVAD support, but the general population of heart failure patients.

11. Five-year view

Progress in the understanding the factors that underlie the process of reverse ventricular remodeling has been slow. Even slower has been an understanding of how to optimize the

conditions to achieve maximal recovery of ventricular function during LVAD support. In the absence of a fundamental breakthrough in understanding, efforts at the clinical level are likely to focus on identification of clinical characteristics that render a patient more likely to recover LV function during LVAD support and optimizing the use of currently available pharmacological therapies to achieve facilitate the process. As success of this strategy is reported by the limited number of investigators currently pursuing this line of investigation are reported, we will see a proliferation of sites working heart to promote reverse remodeling and remission to the point where LVADs can be explanted.

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Key Issues

- Reverse remodeling is the process whereby abnormalities of ventricular structure and function and abnormalities of myocardial cellular, molecular, genetic and extracellular matrix revert back towards normal.
- Reverse remodeling can occur spontaneously, or during therapies such as beta-blocker administration, cardiac resynchronization therapy and during left ventricular assist device (LVAD) therapy.
- Among heart failure therapies, the greatest degree of reverse remodeling is seen with LVAD therapy.
- The degree of reverse remodeling seen with LVADs is sometimes associated with improvement in LV function to the degree that the therapy can be withdrawn.
- Although previously referred to as recovery, observed relapses of heart failure following withdrawal of LVAD support have indicated use of the term “remission” is more appropriate than “recovery.”
- Studies at the molecular level support this shift in terminology in that the reverse remodeled heart has a high percentage of abnormally expressed genes and a high number of newly expressed “reverse remodeling” genes, the functional consequences of which are unknown.
- Observed persistent abnormalities during LVAD-induced reverse remodeling are potential targets to improve the rate, extent and permanence of remission of the heart failure state.
- Such understanding may ultimately lead to new therapies for the larger population of heart failure patients not undergoing LVAD support.
- Efforts to improve the extent of reverse remodeling can be important, independent of the rate of remission, because improved intrinsic LV and RV function has the potential to reduce occurrences of heart failure exacerbations and improve exercise tolerance during LVAD support.

Fig. 1A

Fig. 1B

Figure 1.

A. End-diastolic pressure-volume relations (EDPVRs) of ex-vivo hearts explanted at the time of heart transplant. “CHF” are patients with severe heart failure transplanted without LVAD support. “LVAD” are patients with severe heart failure who were transplanted after a prolonged period of LVAD support. “Normal” are normal donor hearts not suitable for heart transplantation. Data from Levin et al (5). Reproduced with permission from Levin HR, Oz MC, Chen JM, Packer MP, Rose EA, Burkhoff D. Reversal of chronic ventricular dilation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. *Circulation* 1995; 91:2717.

B. Ex-vivo EDPVRs from hearts transplanted without any support, those supported by a full support axial flow pump and those supported with a partial support LVAD that provides less ventricular unloading. Data from Jacobs et al (12). Reprinted from Klotz S, Burkhoff D, Garrelids IM, Boomsma F, Danser AH. The impact of left ventricular assist device-induced left ventricular unloading on the myocardial renin-angiotensin-aldosterone system: therapeutic consequences? *Eur Heart J* 2009. with permission from Elsevier.

Figure 2.

Rates of recovery at different institutions according to whether or not adjuvant medical therapy is used during LVAD support with the goal of optimizing reverse remodeling and increasing the percentage of patients who can potentially be explanted. Data from Drakos and Mehra (30). Reprinted from Drakos SG, Mehra MR. Clinical myocardial recovery during long-term mechanical support in advanced heart failure: Insights into moving the field forward. *J Heart Lung Transplant* 2016; 35:413–20., with permission from Elsevier.

Figure 3.

Rates of spontaneously improved LV function as a function of underlying etiology. Data from Giverts and Mann (25). Reproduced from Givertz MM, Mann DL. Epidemiology and natural history of recovery of left ventricular function in recent onset dilated cardiomyopathies. *Curr Heart Fail Rep* 2013; 10:32, with permission of Springer.

Figure 4.

Numbers of genes with abnormal abundances observed in the heart failure state and during the reverse remodeling in an experimental model of heart failure induced by inflammation. This study revealed a number of abnormally expressed genes that normalize during recovery from heart failure, that are persistently abnormal during recovery, and genes that are newly, abnormally expressed during recovery. See text for further details. Data from Topkara et al (40). Republished with permission of The American Society for Clinical Investigation. JCI Insight. 2016;1(4):e86038. doi:10.1172/jci.insight.86038

Figure 5.

A scheme by which mechanical and neurohormonal factors interact to modulate extracellular matrix metabolism that can help explain why, during LVAD support, extracellular matrix increases in some patients and decreases in other patients. Reprinted from Klotz S, Danser JAH, Burkhoff D. Impact of left ventricular assist device (LVAD) support on the cardiac reverse remodeling process. *Prog Biophys Mol Biol* 2008. with permission from Elsevier.

Figure 6.

Hemodynamic changes during exercise in LVAD patients. Patients with better intrinsic LV function can exercise more. See text for details. Reproduced with permission from Martina J, Jonge N, Rutten M, et al. Exercise hemodynamics during extended continuous flow left ventricular assist device support: the response of systemic cardiovascular parameters and pump performance. *Artif Organs* 2013; 37:754–62.