Bridge to Recovery
Understanding the Disconnect Between Clinical and Biological Outcomes

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Left ventricular (LV) assist devices (LVADs) are increasingly used in everyday clinical practice either as a bridge for end-stage heart failure (HF) patients to heart transplantation or as a permanent (destination) therapy.1,2 Yet, there is still significant uncertainty about the consequences of this intervention both at the level of the detailed myocardial biology (ie, biological outcomes) and at the functional cardiovascular response of the patient at the organ level (ie, clinical outcomes).

The LVAD patient population presents a series of significant advantages as far as research is concerned. First, LVAD therapy offers the ability to acquire paired human myocardial tissue at LVAD implantation and again on LVAD removal. The ability to obtain human tissue and the possibility for its serial examination before and after any therapeutic investigational therapy combined with LVADs provide an important opportunity for in-depth study of the changes in the structure and function of the diseased human heart caused by the specific investigational therapy. Second, this population represents a relatively safe investigational platform because the hemodynamic support provided by VADs makes these patients significantly less vulnerable to any arrhythmic3 or hemodynamic adverse events potentially associated with new aggressive investigational therapies. Third, the volumes of potential study subjects for these investigations (ie, patients who receive LVADs) are rapidly increasing; because of a lack of donor organs and incremental progress in device design and durability, the number of advanced HF patients with LVADs has been continuously increasing.1,2 These 3 research advantages create an ideal setting for various new HF therapies to test their potential efficacy in LVAD patients. Fourth, this population offers an opportunity to investigate the effects of the LVAD-induced removal of excess mechanical load, which drives the vicious cycle of myocardial remodeling and eventually leads to the clinical HF syndrome.4 Increasing evidence suggests that a significant degree of improvement in myocardial structure and function can be observed after LVAD-induced mechanical unloading,5 to the point that some of these advanced HF patients can eventually be weaned from mechanical support and achieve sustained myocardial recovery.6,7

These important research advantages may transform this LVAD patient population into a precious translational research vehicle for investigating new antiremodeling and regenerative therapies for HF. However, for these promises to be fulfilled, we must first establish the baseline and better understand the fundamental impact of LVAD-induced unloading on the failing human heart.

LVAD Bridge to Recovery: Clinical Outcomes
Witnessing a chronically sick, almost moribund, end-stage HF patient achieve sustained myocardial recovery after LVAD weaning is one of the most fascinating and rewarding experiences in the contemporary treatment of heart disease (Figure 1). The main results of key clinical outcome studies investigating LVAD bridge to recovery are summarized in Table 1.8–20 Except for 3 recent studies from Berlin,21 Harefield,12 and Vancouver,14 the majority of the devices used in the bridge-to-recovery studies have so far included first-generation, pulsatile-flow LVADs. As shown in Table 1, the most effective approach aiming at recovery of myocardial function reported so far is the Harefield protocol, which tested mechanical unloading combined with aggressive antiremodeling drug therapy and the β-2 agonist clenbuterol in nonischemic cardiomyopathy patients.11–13,22 The Harefield protocol was also tested in the Harefield Recovery Protocol Study (HARPS) multicenter study.23 Of 13 patients, only 1 met explantation criteria, with the authors attributing their inability to reproduce the recovery rates of prior Harefield protocol reports potentially to differences in the patient characteristics of the population studied or modifications of the Harefield protocol done in the HARPS study.23 Reproducibility of the Harefield protocol results in larger patient cohorts and in a randomized fashion is of great importance. Similarly, as evident from Table 1, the success of LVAD weaning and of achieving sustained myocardial recovery varied significantly across the reported studies. This variability may have been caused by a variety of factors such as...
1) nonstandardized heart function monitoring during LVAD support, 2) differences in medical therapy added to LVAD therapy, 3) variable duration of LVAD unloading, 4) divergences in LVAD weaning criteria, and 5) diversity of the populations studied in their propensity for recovery (type of HF, extent of pre-LVAD cardiac remodeling). These limitations were especially prominent in the multicenter LVAD trials focused on bridge-to-transplantation or destination therapy, which, for this reason, are not included in Table 1.24 As we discuss later, the wide range of results described in Table 1 might have contributed to the observed disconnect between clinical and biological outcomes of LVAD studies.

Several studies described significant beneficial effects of LVAD unloading on specific parameters of cardiovascular function: LV and left atrial geometry and function, volume and pressure unloading, systemic hemodynamics, cardiopulmonary gas exchange, and cardiac output. These effects were associated with improvements in clinical outcomes, such as survival, hospitalization rates, and functional status.

Table 1. Left Ventricular Assist Device Bridge-to-Recovery Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Adjuvant Drug Therapy Protocol</th>
<th>Monitoring Heart Function Protocol</th>
<th>Unloading Duration, mo</th>
<th>Recovery,* n (%)</th>
<th>Freedom From HF Recurrence, %/Follow-Up (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US LVAD Working Group 2007</td>
<td>P</td>
<td>67</td>
<td>Not standardized</td>
<td>Yes</td>
<td>4.5</td>
<td>6 (9)</td>
<td>100/6 mo</td>
</tr>
<tr>
<td>Berlin 2008 and 2011</td>
<td>R</td>
<td>188</td>
<td>Not standardized</td>
<td>Yes</td>
<td>4</td>
<td>35 (19)</td>
<td>74 and 66/3 and 5 y, respectively</td>
</tr>
<tr>
<td>Harefield 2006</td>
<td>P</td>
<td>15</td>
<td>Yes</td>
<td>Yes</td>
<td>11</td>
<td>11 (73)</td>
<td>100 and 89/1 and 4 y, respectively</td>
</tr>
<tr>
<td>Harefield 2011</td>
<td>P</td>
<td>20</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
<td>12 (60)</td>
<td>83/3 y</td>
</tr>
<tr>
<td>University of Athens–Harefield 2007</td>
<td>P</td>
<td>8</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
<td>4 (50)</td>
<td>100/2 y</td>
</tr>
<tr>
<td>Vancouver 2011</td>
<td>P</td>
<td>17</td>
<td>Not standardized</td>
<td>Yes</td>
<td>7</td>
<td>4 (23)</td>
<td>100/2 y</td>
</tr>
<tr>
<td>Gothenburg 2007</td>
<td>P</td>
<td>18</td>
<td>Not standardized</td>
<td>Yes</td>
<td>7</td>
<td>3 (17)</td>
<td>33/8 y</td>
</tr>
<tr>
<td>Pittsburgh 2003</td>
<td>R</td>
<td>18</td>
<td>Not standardized</td>
<td>Yes</td>
<td>8</td>
<td>6 (33)</td>
<td>67/1 y</td>
</tr>
<tr>
<td>Osaka 2005</td>
<td>R</td>
<td>11</td>
<td>Not standardized</td>
<td>NA</td>
<td>15</td>
<td>5 (45)</td>
<td>100/8–29 mo</td>
</tr>
<tr>
<td>Pittsburgh 2010</td>
<td>R</td>
<td>102</td>
<td>N/A</td>
<td>NA</td>
<td>5</td>
<td>14 (14)</td>
<td>71/5 y</td>
</tr>
<tr>
<td>Multicenter 2002</td>
<td>R</td>
<td>271</td>
<td>N/A</td>
<td>NA</td>
<td>2</td>
<td>22 (8)</td>
<td>77/3 y</td>
</tr>
<tr>
<td>Columbia 1998</td>
<td>R</td>
<td>111</td>
<td>N/A</td>
<td>NA</td>
<td>6</td>
<td>5 (4.5)</td>
<td>20/15 mo</td>
</tr>
</tbody>
</table>

HF indicates heart failure; LVAD, left ventricular assist device; P, prospective; R, retrospective; and NA, not applicable.

*Defined as LVAD explantation as a result of functional myocardial recovery.
monary function, and exercise capacity.\textsuperscript{25–33} As reviewed in detail elsewhere,\textsuperscript{34} the impact of LVAD therapy on the arrhythmogenicity of the heart is controversial, with data from a recent small prospective study showing a significant decrease in premature ventricular contractions and ventricular couplets but no change in the incidence of nonsustained or sustained ventricular tachycardia.\textsuperscript{35} In terms of the cardiovascular functional effects of pulsatile- versus continuous-flow LVADs, several clinical studies that directly addressed this issue are summarized in Figure 2. It seems that pulsatile-flow LVADs might have some advantages over continuous-flow devices, which may be further translated to more favorable outcomes in terms of bridge to recovery.\textsuperscript{21} However, this issue warrants further investigation and remains to be proven in a properly designed prospective study. Moreover, with pulsatile-flow LVADs, the device ejection is not generally coordinated with ventricular contraction, and this device-heart dyssynchrony may paradoxically increase afterload. Continuous-flow LVADs are not subject to such dyssynchrony, and whether this theoretical advantage translates to clinical benefits warrants further investigation. Other potential advantages of continuous-flow devices include increased pump durability,\textsuperscript{1} which allows longer recovery time if needed, and the greater ability to modify the degree of unloading over time.

LVAD Bridge to Recovery: Biological Outcomes

Parameters of cardiac remodeling that have been shown to be favorably altered—improved or normalized—during LVAD unloading are summarized in Table 2. These effects are described briefly in this section.

Cardiac Hypertrophy- Atrophy

Pulsatile LVAD unloading has repeatedly been shown to induce the regression of cardiac myocyte hypertrophy: cell length, width, and thickness.\textsuperscript{22,39} In terms of the exact mechanisms governing hypertrophy regression during pulsatile-flow LVAD support, reviewed in detail elsewhere,\textsuperscript{26} ongoing investigations have been examining the roles of several complex pathways, including cyclooxygenase-2–induced Akt phosphorylation, mitogen-activated protein kinase/Erk, and Akt kinase/glycogen synthase kinase 3β. Whether the primary stimulus for the regression of hypertrophy is related directly to mechanical unloading/stretch or to circulating systemic factors needs to be investigated further.

Animal models of prolonged unloading of nonfailing, nonhypertrophic myocardium by means of heterotopic transplantation,\textsuperscript{40} LVAD,\textsuperscript{41} or severing of the chordae tendinae of the mitral papillary muscle\textsuperscript{42} suggested that mechanical unloading could lead to cardiac myocyte atrophy. Whether this

Table 2. Cardiac Remodeling Parameters Favorably Altered With Left Ventricular Assist Device Unloading

<table>
<thead>
<tr>
<th>Myocyte biology changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophy</td>
</tr>
<tr>
<td>Contractile dysfunction</td>
</tr>
<tr>
<td>Calcium cycling</td>
</tr>
<tr>
<td>Cytoskeletal proteins (sarcomeric, nonsarcomeric, membrane)</td>
</tr>
<tr>
<td>β-Adrenergic signaling</td>
</tr>
<tr>
<td>Metabolism and bioenergetics</td>
</tr>
<tr>
<td>Myocardial changes</td>
</tr>
<tr>
<td>Myocyte death (apoptosis, autophagy, stress)</td>
</tr>
<tr>
<td>Endothelium and microvasculature</td>
</tr>
<tr>
<td>Sympathetic innervation</td>
</tr>
<tr>
<td>Circulating systemic markers</td>
</tr>
<tr>
<td>Neurohormones</td>
</tr>
<tr>
<td>Natriuretic peptides</td>
</tr>
<tr>
<td>Cytokines</td>
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</tbody>
</table>
phenomenon applies exclusively to unloaded nonfailing and nonhypertrophic myocardium or also to hypertrophic and failing myocardium is controversial.\textsuperscript{43,44} In 2 human HF studies, unloading by means of pulsatile-flow LVAD support decreased cardiac myocyte size but not to levels below the respective of normal donor cardiac myocytes.\textsuperscript{45,46} In the latter study, light microscopy findings complemented by ultrastructural and metabolic data did not identify any evidence suggesting cardiac myocyte atrophy or degeneration during pulsatile-flow LVAD support.\textsuperscript{46} These data are in agreement with echocardiographic data in pulsatile-flow LVAD patients.\textsuperscript{8} However, whether prolonged mechanical unloading with the currently used continuous-flow LVADs affects the basic protein degradation pathways and/or fetal gene program overexpression implicated in cardiac hypertrophy and atrophic remodeling\textsuperscript{43,47,48} remains to be investigated.

**Contractile Dysfunction, Calcium Handling, and Cytoskeletal Proteins**

The myocyte contractile defects observed in failing hearts were shown to be reversed after pulsatile-flow LVAD unloading, showing improved shortening and relaxation in isolated myocytes and isolated strips of ventricular tissue.\textsuperscript{6,49} These interesting effects on contractile dysfunction can be partially explained by pulsatile-flow LVAD studies demonstrating significant improvements in Ca\textsuperscript{2+} handling such as faster sarcomemmal Ca\textsuperscript{2+} entry and shorter action potential durations, higher sarcoplasmic reticulum Ca\textsuperscript{2+} content, improved abundance of sarcoplasmic/endoplasmic reticulum calcium ATPase, decreased abundance of Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger, and beneficial changes in L-type calcium channel and ryanodine receptor function.\textsuperscript{6,7,50,51} The aforementioned LVAD-induced benefits in myocardial contractility have been associated with favorable changes in cytoskeletal proteins: sarcromeric and nonsarcomeric proteins and the membrane-associated integrin pathway known to play an important role in mechanotransduction by mediating stretch signals from the extracellular matrix.\textsuperscript{52–56}

**β-Adrenergic Signaling and Sympathetic Innervation**

Pulsatile LVAD unloading has been shown to induce improvements in β-adrenergic receptor density, location and distribution pattern, contractile response to β-adrenergic stimuli, and adenyl cyclase activity.\textsuperscript{6,7,49} In a recent investigation using iodine 123-meta iodobenzylguanidine scintigraphy, it was shown that pulsatile-flow LVAD unloading resulted in improvements in sympathetic innervation in the failing heart accompanied by clinical, functional, and hemodynamic improvements.\textsuperscript{57}

**Metabolism and Bioenergetics**

Pulsatile LVAD support has been shown to be associated with improved respiratory capacity and increased nitric oxide–dependent control of mitochondria respiration.\textsuperscript{58,59} Furthermore, cardiolipin, a lipid component of the mitochondrial membrane important for ATP formation and substrate transport, has been shown to normalize after pulsatile-flow LVAD unloading.\textsuperscript{60} These changes, along with post-LVAD alterations in the expression of several metabolism-related genes and proteins,\textsuperscript{49,51,61} require further investigation to elucidate their role within the broader metabolic changes occurring during cardiac remodeling.\textsuperscript{62}

**Cell Death and Stress**

Markers of autophagy have been shown to be downregulated after LVAD unloading of failing hearts.\textsuperscript{63} Several studies demonstrating changes compatible with reduced apoptosis during LVAD unloading were recently reviewed in detail by Soppa et al.\textsuperscript{49} These favorable changes in myocyte attrition are complemented by data suggesting that pulsatile-flow LVAD unloading reduces myocardial stress, as indicated by the reductions of the stress proteins metallothionein and heme oxygenase-I.\textsuperscript{64,65}

**Endothelium and Microvasculature**

Pulsatile-flow LVAD support was associated with changes in the expression of genes involved in the regulation of vascular organization and migration.\textsuperscript{66} In addition, animal data showed that mechanical unloading by means of heterotopic transplantation increased microvascular density.\textsuperscript{67} In agreement with these experimental findings, a recent human study showed that microvascular density was decreased in the failing human hearts compared with normal donors and that pulsatile-flow LVAD unloading induced a significant increase in the microvascular density toward normalization.\textsuperscript{46} The same study provided immunohistochemical and ultrastructural evidence of endothelial cell activation that is consistent with the observed increase in microvascular density.\textsuperscript{46}

**Natriuretic Peptides, Cytokines, and Neurohormones**

Pulsatile LVAD unloading has been associated with decreased levels of atrial and brain natriuretic peptides and tumor necrosis factor-α both in serum and in myocardial tissue.\textsuperscript{8,68,69} The changes in the levels of other key neurohormones implicated in the progression of HF syndrome appear to be more complex. Specifically, the circulating levels of epinephrine, norepinephrine, renin, angiotensin II, and arginine vasopressin have been shown to decrease during LVAD unloading.\textsuperscript{70} However, as discussed below, the effects on the myocardial tissue levels of these neurohormones are not uniform.

**Extracellular Matrix**

Investigations of the effect of LVAD unloading on extracellular matrix have shown conflicting results; a few studies reported decreased fibrosis, whereas most other investigations found a significant increase in fibrosis.\textsuperscript{26,34,49} The explanation for the contradictory observations is not clear, with some attributing the inconsistent results to differences in the background medications or the applied methodology.\textsuperscript{26,49} This controversial issue was recently addressed with the use of advanced image analysis techniques in whole-field digital microscopy, an approach that reduces observer bias, markedly increases the amount of myocardial tissue analyzed, and permits comprehensive endocardium-to-epicardium evalu-
It was found that myocardial tissue from HF patients undergoing LVAD implantation, compared with normal myocardium, had increased interstitial and total fibrosis. The interstitial and total collagen content further increased after pulsatile-flow LVAD unloading in these patients. Recent findings on the effects of pulsatile-flow LVAD unloading on the myocardial tissue levels of neurohormones of the renin-angiotensin-aldosterone axis and matrix metalloproteinases support the above results. However, whether the observed increase in fibrosis is a manifestation of further progression of this aspect of cardiac remodeling that pulsatile-flow LVAD unloading failed to reverse or is a direct result of pulsatile-flow LVAD unloading actively inducing an increase in fibrosis warrants further investigation.

Gene Expression, MicroRNAs, and Proteomic Profiling

Studies in LVAD patients investigated mRNA, microRNA, and protein expression profiling. We hope that future investigations using these technologies will consistently include in their study design the collection of functional myocardial recovery data and thus increase their potential to provide mechanistic insights.

Why Do We Observe a Disconnect Between Clinical and Biological Outcomes?

Any attempt to associate in a systematic and logical way the key LVAD-induced biological effects with their expected corresponding clinical outcomes would be challenging. It could be argued that the reported beneficial LVAD-induced biological outcomes (Table 2) should have more consistently led to better clinical outcomes in terms of functional myocardial recovery (Table 1). The anticipated “sequential pattern” of biology findings defining clinical functional response does not appear to always be clear or consistent (Tables 1 and 2). Therefore, we wonder why we observe these discrepancies:

1. Structure Function Correlation: A Critical Starting Point That Has Yet to be Defined (see p 234)
2. Major Limitations in Study Design (see p 235)
3. Biological Signature of Myocardial Recovery: Still in Search (see p 236)

Structure-Function Correlation: A Critical Starting Point That Has Yet to be Defined

One possible reason for the observed disconnect between the clinical and biological outcomes is the attempt to correlate findings across separate clinical and biological studies rather than focusing this effort on investigations using the same structured and well-controlled approach. Specifically, as we have previously reviewed in detail, in most of the reported LVAD tissue/biological outcomes studies, no functional myocardial recovery data were collected; vice versa, most of the clinical outcomes/bridge-to-recovery studies (Table 1) were lacking a comprehensive structural or molecular investigational arm. As a consequence, we cannot distinguish between structural, cellular, and molecular changes that occur in all LVAD patients regardless of possible induced myocardial recovery and changes that occur exclusively in patients in whom LVAD unloading induced myocardial functional recovery (target 1 in Figure 3). These biological changes unique to LVAD patients who achieved functional recovery might help us identify mechanisms of reverse remodeling that lead to myocardial recovery. Examination of tissue from both patients with evidence of various degrees of LVAD-induced myocardial functional recovery (ie, responders) and LVAD patients without functional myocardial improvement (ie, nonresponders) is critical. This type of study becomes the springboard for further in-depth investigational steps through future ani-
nal and human studies that will determine causality and provide mechanistic insights.

In fact, the ability offered by LVAD studies to correlate human tissue to functional data is something rare in clinical medicine. This type of tight association between structure and function is achievable in animal models; however, it is very unusual to achieve this level of understanding in human investigational models. From that perspective, the LVAD patient population offers an important opportunity for performing in-depth structure-function investigations that will, we hope, lead to clarification of some of the observed discrepancies between LVAD clinical and biological outcomes. The current absence of such in-depth structure-function investigations makes any attempt to connect the biological and clinical outcomes very difficult. In essence, at least a degree of the observed disconnect between clinical and biological outcomes is a result of these missing data.

**Major Limitations in Study Design**

The aforementioned disconnect between clinical and biological outcomes may also be a consequence of a series of major limitations that are confounding many of the reported studies. As analyzed in the following sections, these specific limitations may have led to an inaccurate description, and thus poor understanding of both the clinical and biological effects of LVAD unloading. Thus, attempts to understand the potential associations or connections between the reported clinical and biological outcomes might be hampered by several problems in the design of these studies. In essence, we may be trying to connect 2 locations on the map (ie, biological and clinical outcomes), but the coordinates of these 2 locations have not been well defined.

**Issues Limiting the Reported LVAD Biological Outcomes**

**Confounding Effects of Concurrent Drug Therapy**

Various medications known to affect the function and structure of the failing human heart (β-blockers, renin-angiotensin axis inhibitors, aldosterone antagonists) have been routinely used in previous studies in patients with LVADs, but no standardization or randomization of their use was attempted. In most LVAD tissue studies, no information on concurrent antiremodeling drug therapy was reported.34 In fact, systemic blood pressure increases in many LVAD patients, and consequently, these patients are often treated with high doses of these medications. This is an important confounder because, in the studies reported so far, the drug-induced effects on cardiac remodeling cannot be separated from the effects of mechanical unloading alone.

**Propensity for Reversal of Cardiac Remodeling**

The patient populations studied so far differ in their potential for reversal of cardiac remodeling; factors such as specific HF cause and duration of HF symptoms have been reported to play significant role in this propensity for recovery.10,12,24 Both of these factors varied significantly among the reported clinical and biological studies, making comparisons or associations between their findings problematic.

**Variable Duration of LVAD Support**

Clinical and experimental studies demonstrated that the duration of mechanical unloading significantly affects the changes in the remodeling of the failing heart.8,25,44,53,82,83 Therefore, it might be misleading to either claim or negate associations between biological and clinical outcomes studies that had different durations of LVAD unloading. Even within a single study, more often than not, LVAD support duration varied considerably between patients.

**LVAD Era Change**

The great majority of biological outcomes reported in the literature were derived from studies involving pulsatile-flow LVADs. However, because of mainly engineering reasons, newer second-generation, nonpulsatile, continuous-flow LVADs are now being used almost exclusively for long-term support. Compared with pulsatile-flow LVADs, these newer devices produce a qualitatively different type of unloading (Figure 2). Given that clinical outcomes related to myocardial recovery originating from continuous-flow LVADs have now started to be reported,12,14,21 it is necessary for the corresponding biological outcomes also to be updated. Pulsatile LVAD era biological outcomes and their presumed associations or dissociations with clinical outcomes cannot be taken for granted in the continuous-flow era.

**Deficiencies in Acquisition and Analysis of Human Myocardial Tissue**

1. The baseline human myocardial tissue is obtained from the LV apex at the time of LVAD implantation, and this sample might not reliably represent the global LV remodeling changes.84

2. In most studies, the post-LVAD unloading myocardial tissue sample has also been obtained from the apical region with the purpose of being comparable with the pre-LVAD sample. However, this standard approach may be confounded by myocardial tissue changes induced by foreign-body inflammatory reactions triggered by the LVAD inflow cannula placed at the apex. An approach proposed to circumvent this problem is the collection of the post-LVAD sample from an area 1.5 to 2 cm distant from the LVAD inflow cannula and use of morphological or other criteria to rule out the presence of reactive inflammatory response in the studied myocardium.46 Future studies need to control for potential LV regional differences by comparing post-LVAD unloading tissue samples from the apical and other areas of the LV.

3. The confounding effect of endocardial versus epicardial sampling has not been well controlled in previous LVAD studies. This is a potentially important confounder because it has been described that basic structural remodeling features such as fibrosis differ significantly between epicardium and endocardium.84 There are methodologies that can be used to prevent such variability resulting from sampling.46

4. Many prior studies lacked prospectively designed protocols for myocardial tissue acquisition, processing, and preservation. In-depth investigation at the structural, ultrastructural, and molecular levels is not possible if the retrospective study design consists of only snap-freezing of myocardial tissue in the operating room during LVAD surgery, as was frequently done in the past.34
Reference Trap
Relative values and ratios should be used with caution in the assessment of the biological effects of LVADs. For example, hypertrophy regression is universally seen after LVAD unloading, and the decrease in cardiomyocyte size affects other morphometric measurements that are based on the relative quantification of other myocardial components (e.g., fibrosis). When ratios are used, no significant changes in the structures of interest can be detected when both the nominator and the reference parameter (denominator) show changes of the same size and direction. This problem, called in stereology the reference trap, has been reviewed in detail by Baba and Wohlschlaeger.26 One approach proposed to circumvent this problem is to estimate the heart volume with magnetic resonance or computed tomography imaging and to extrapolate the absolute volume from the volume fraction of the measured parameter.26

Issues Limiting the Reported LVAD Clinical Outcomes
Most of the above-described limitations of the biological outcomes also apply to LVAD clinical outcomes studies: concurrent antiremodeling medical therapy, variable propensity for reversal of cardiac remodeling, variable duration of LVAD unloading, and differences between pulsatile and nonpulsatile unloading. In addition to those factors, the reported clinical outcomes are also limited by the following challenges.

Challenges in Monitoring the Unloaded Heart
There was no standardization across reported studies of protocols to monitor the functional status of the heart serially and reliably during mechanical unloading. This is an important limitation of many studies (Table 1). Preferably, these protocols should include studies done with full LVAD support and with prolonged minimal LVAD support (the so-called turn-down or off-pump studies) to allow the assessment of the native cardiac function under renewed pressure and volume load.85–89 The complexity of this issue is reviewed in a separate article in this Advances in Mechanical Circulatory Support series.

Undefined LVAD Weaning Criteria
There is neither robust clinical evidence nor expert consensus that would delineate criteria of likely sustained recovery after LVAD explantation. In the published bridge-to-recovery studies (Table 1), the LVAD explantation criteria used (echocardiographic, hemodynamic, cardiopulmonary/exercise capacity) varied significantly. As a result, no consistent conclusions can be made on outcomes such as frequency or sustainability of myocardial recovery after LVAD implantation.

Biological Signature of Myocardial Recovery: Still in Search
While grappling to understand the potential associations or disconnects between the reported LVAD-induced clinical and biological outcomes, we should take into account that, despite the enormous progress in the understanding of HF pathophysiology during the last 2 decades, important pieces of information are still missing. As reviewed in detail by Mann and Bristow,78 our current hemodynamic, cardiorenal, and neurohormonal model systems are necessary but not sufficient to explain all aspects of the HF syndrome. Most important, they fail to adequately explain forward disease progression.78 Similarly, the reverse process of myocardial improvement or recovery resulting from the use of currently approved medical or device HF therapies is also incompletely understood. The issue is perhaps complicated by the fact that reversal of key features of cardiac remodeling such as hypertrophy regression is governed by distinct pathways that are different from those implicated in forward remodeling and HF syndrome progression.90

Furthermore, reverse cardiac remodeling and sustained clinical myocardial recovery are not necessarily synonymous;91–92 as shown by several published LVAD studies, the partial or sometimes nearly complete reversal of the HF phenotype at the structural, cellular, or molecular level (i.e., reverse cardiac remodeling) is not always followed by a similar degree of sustained clinical myocardial recovery at the organ level.34,91,92 Future studies need to focus specifically on advancing our understanding of these phenomena. The realization of this important need highlights the unique opportunity of current investigations of LVAD-induced unloading to elucidate the incompletely understood relationship between reverse remodeling and myocardial recovery. Importantly, this process can identify potential new therapeutic targets in HF. Given that a large part of prior research, in both HF and cardiovascular disease in general, has focused on predicting adverse outcomes, we maybe now also need to focus on determining methods to better understand, predict, and enhance myocardial recovery. In conclusion, it should probably have been anticipated that attempts at systematically correlating specific LVAD-induced structural or molecular alterations with specific favorable post-LVAD functional myocardial responses would lead to an inevitable degree of disconnect between these biological and clinical outcomes insofar as the specific biological signature of myocardial recovery of the failing heart is still not very well defined.34,91,92

Roadmap to Connect and Improve LVAD-Induced Clinical and Biological Outcomes: Future Directions
It is obvious from the analysis above that many important issues remain to be elucidated.

The impact of the cause of HF on the potential for myocardial recovery is not well understood (target 2 in Figure 3). Direct comparisons between ischemic and nonischemic patients were performed in only a few LVAD studies.8,24,46,60,66,73 The likely candidates for reverse remodeling induced by LVAD unloading are usually patients with nonischemic cardiomyopathy of different types: idiopathic, hypertensive, peripartum, familial, alcoholic, etc. However, ischemic cardiomyopathy patients who have suffered myocardial infarction and have large areas of noninfarcted myocardium that remodeled over the years could also be considered candidates.13 This latter concept deserves further investigation and could combine the excision of scarred myocardium, through the use of LV reconstruction techniques (e.g., Dor operation), with
LVAD unloading. It can be argued that with this approach the initial insult that triggered the cascade of cardiac remodeling progression—ie, the post–myocardial infarction scar—has been eliminated. In contrast, in most nonischemic cardiomyopathy cases, the initial insult that caused progressive ventricular remodeling and HF often remains undetermined, most likely persists despite an initially successful reversal of the process by mechanical unloading, and might recur and cause further progression of HF after the termination of LVAD support. This might explain why long-term freedom from recurrent HF in the largest bridge-to-recovery series in nonischemic cardiomyopathy patients was 74% and 66% at 3 and 5 years, respectively.

The importance of the duration of HF on the prospect of cardiac reverse remodeling also deserves further study. Data from 2 series of LVAD patients who were successfully bridged to sustained recovery have identified duration of HF history (ie, time from HF symptoms onset) as an important predictor of favorable response. In terms of cardiac remodeling course, the time from the initial insult that triggered the HF syndrome, rather than the time from symptom onset, would be an even more meaningful target (target 3 in Figure 3). However, we need to acknowledge that this target may be too hard to identify. The initial insult can often be determined in ischemic cardiomyopathy patients, but this may be difficult in nonischemic patients. Even in ischemic cardiomyopathy, other factors such as ischemia induced by nonculprit lesions and repetitive stunning add to the complexity. Insofar as the HF history duration can be viewed as a surrogate of potential irreversibility of chronic remodeling, it may be argued that a more direct research target would be the identification of a degree of pre-LVAD structural or molecular remodeling beyond which there is “no return.” Indeed, Bruckner et al have reported that patients with worse hypertrophy and a higher degree of fibrosis at baseline (ie, the time of LVAD implantation) were much less likely to show recovery of LV systolic function during LVAD unloading. More research needs to be done to determine what extent of the pre-LVAD myocardial remodeling changes preclude unloading-induced reversibility and thus provide useful guidance for LVAD bridge-to-recovery patient selection (target 4 in Figure 3).

Another important issue is recognition of the specific type of mechanical unloading that best promotes reverse remodeling (target 5 in Figure 3). Various LVADs have been used in the experimental and clinical arenas during the last half-century: pulsatile, nonpulsatile/continuous flow, and counterpulsatile. As a result of favorable engineering characteristics that were translated to better morbidity and mortality outcomes, the clinical field has recently shifted from pulsatile- to continuous-flow LVADs. The key known effects of pulsatile- and continuous-flow LVADs specifically on cardiovascular functional parameters are summarized in Figure 2. Whether these devices also have different effects on the biological outcomes, we definitely need to learn more. Consequently, whether the prospects of LVAD-induced reverse remodeling are better served by pulsatile, nonpulsatile, or counterpulsation devices and by full or partial unloading is unknown.

Future studies should target specific VAD properties that best promote reverse remodeling.

The potential impact of the following important issues also needs to be clarified: the concept of targeted adjuvant therapies/disease-modifying medications (introduced by Sir Magdi H. Yacoub), the optimal duration of mechanical unloading, and the development of advanced protocols to monitor the unloaded myocardium during LVAD support (targets 6–8 in Figure 3). These latter protocols could include hemodynamic evaluations, exercise testing protocols, conventional imaging techniques (echocardiography, nuclear imaging, computed tomography), or molecular imaging. As pointed out in the previous section, these protocols need to address the challenging issue of testing the cardiac performance under both decreased and increased loading conditions. These monitoring protocols should also carefully evaluate the short-term and long-term impact of LVAD support on the right ventricle (RV). Some investigations have shown evidence of improved RV structure and function after LVAD support. This can be attributed both to the normalization of the neurohormonal milieu and to the reduction in LV filling pressures, resulting in decreased RV afterload. However, Klotz et al found that biventricular VAD support resulted in significant reverse structural and functional remodeling of both the RV and the LV, whereas RV reverse remodeling was not found during LVAD support alone. The authors concluded that the lesser degree of volume unloading provided to the RV during LVAD support may not be sufficient to result in significant reverse structural and functional remodeling of the RV. Along the same lines, a recently published study showed that pre-LVAD RV dysfunction seen on intensive medical therapy that included inotropes and diuretics persisted after 3 months of LVAD unloading. More research is warranted to elucidate the impact of chronic LVAD support on the RV.

Future Investigational Platforms: Bridge-to-Recovery and Bridge-to-Transplantation Study Design

Both the bridge-to-transplantation and bridge-to-recovery investigational settings offer important research advantages and, by addressing most of the research targets outlined in Figure 3, can help advance the field. It is absolutely necessary that both types of investigations include in their study design a comprehensive heart function monitoring protocol (such as serial echocardiographic studies) to allow structure-function correlation.

The bridge-to-transplantation investigational setting offers 2 important advantages. First, it offers access to paired myocardial tissue specimens of large quantity from both recovery responders and nonresponders (given that both functional responders and nonresponders will be transplanted per the clinical bridge-to-transplantation protocol). On the contrary, bridge-to-recovery studies offer scarce, often minute amounts of human myocardial tissue at the post-LVAD time point, and this only from recovery responders on LVAD explantation. Nonresponders either remain on LVAD as destination therapy and do not offer paired myocardial tissue or enter the transplantation list after the end of the bridge-to-recovery study. Access to adequate quantities of paired...
human tissue from both myocardial recovery respondents and nonresponders is of great importance in that it allows investigational approaches that can examine differences between LVAD-induced biological changes that are associated with recovery and changes that occur in LVAD patients regardless of the functional response (target 1 in Figure 3). The second advantage of adequately powered, large-scale bridge-to-transplantation studies is the opportunity to study the impact of the duration of LVAD unloading on cardiac remodeling. The patients are transplanted at different times since LVAD implantation and the tissue specimens can thus be grouped by duration of unloading (target 8 in Figure 3).

Bridge-to-recovery studies also present unique advantages. They can lead to the identification of clinical and biological markers of sustained (post-LVAD explantation) myocardial functional recovery. The identification of markers of myocardial recovery will help to establish reliable LVAD explantation criteria (target 9 in Figure 3). Furthermore, myocardial recovery after LVAD unloading is not an all-or-nothing phenomenon. Prior LVAD studies have shown that although only a relatively small proportion of end-stage HF patients had complete normalization of heart function, a much larger proportion showed significant improvement (“partial recovery”) to a degree similar to that of stable HF outpatients.8 LVAD explantation for partial recovery warrants further study in future bridge-to-recovery investigations. Bridge-to-recovery studies should also test surgical techniques of LVAD explantation that would minimize iatrogenic myocardial damage and enhance the sustainability of the achieved myocardial recovery.

Conclusions
Increasing clinical use of LVADs presents a key opportunity for in-depth investigations of the biology of the failing human heart. Through an effort to better define and connect the biological and clinical outcomes in this unique patient population, we may eventually identify new therapeutic strategies that augment myocardial recovery and regeneration.

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None.

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