

# Clinical myocardial recovery in advanced heart failure with long term left ventricular assist device support



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## KEYWORDS:

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Left ventricular assist-device (LVAD) implantation is a life-saving therapy for patients with advanced heart failure (HF). With chronic unloading and circulatory support, LVAD-supported hearts often show significant reverse remodeling at the structural, cellular and molecular level. However, translation of these changes into meaningful cardiac recovery allowing LVAD explant is lagging. Part of the reason for this discrepancy is lack of anticipation and hence promotion and evaluation for recovery post LVAD implant. There is additional uncertainty about the long-term course of HF following LVAD explant. In selected patients, however, guided by the etiology of HF, duration of disease and other clinical factors, significant functional improvement and LVAD explantation with long-term freedom from recurrent HF events has been demonstrated to be feasible in a reproducible manner. The identified predictors of myocardial recovery suggest that the elective therapeutic use of potentially less invasive VADs for reversal of HF earlier in the disease process is a future goal that warrants further investigation. Hence, it is prudent to develop and implement tools to predict HF reversibility prior to LVAD implant, optimize unloading-promoted recovery with guideline directed medical therapy and monitor for myocardial improvement. This review article summarizes the clinical aspects of myocardial recovery and together with its companion review article focused on the biological aspects of recovery, they aim to provide a useful framework for clinicians and investigators.

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Left ventricular assist devices (LVAD) improve clinical outcomes in patients with advanced heart failure (HF) with reduced ejection fraction (HFrEF) who are refractory to

guideline-directed medical therapy (GDMT). In some patients, the hemodynamic unloading provided by an LVAD enables reverse structural remodeling to such a degree that a sustained improvement in myocardial function is noted.<sup>1,2</sup> This has allowed us to gain significant additional insights into the biology of HF.<sup>3-6</sup>

Although using durable LVAD support as a bridge to recovery (BTR) is a highly desirable strategy, only few

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LVAD centers currently have implemented a systematic approach to test for myocardial improvement after LVAD implantation. The incidence of significant myocardial improvement with durable LVAD should be distinguished from device explantation rates. (Table 1)<sup>7</sup> Specifically, the real-world LVAD explantation rate in 1% to 2%, as indicated in the US and European multicenter registries, while the incidence of substantial myocardial improvement was found in the same registries to be about 10 times higher.<sup>3, 8-11</sup> The main reasons patients with substantial myocardial improvement do not proceed to LVAD explantation include: (1) uncertainty regarding short- and long-term outcomes after LVAD explantation, along with the perceived benefit-risk ratio for each patient, (2) physician comfort, center experience and lack of randomized clinical trials in the field confound the LVAD explantation decision, (3) patients and providers often choose the “gold-standard” heart transplant over the “investigational” device explantation.<sup>12-15</sup>

In earlier years, the strategy to promote unloading using optimal LVAD settings, combined with GDMT and regular testing to assess for cardiac recovery resulted in a 70% explant rate in a prospective study with the Heartmate XVE pulsatile LVAD and 60% using the Heartmate II continuous flow LVAD.<sup>1,16,17</sup> More recently, the prospective, multicenter RESTAGE-HF (Remission from Stage D Heart Failure) study demonstrated that optimized LVAD mechanical hemodynamic unloading, coupled with GDMT and regular echocardiograms improved the incidence of LVAD explantation in a preselected patient population compared to historical controls.<sup>18</sup> (Table 1) Patients weaned from LVADs were at a comparable risk for death in comparison with those who underwent cardiac transplant.<sup>19,20</sup> Perhaps more importantly, explanted patients have significantly improved cardiac and functional capacity than patients who remain on LVAD support, often achieving peak O<sub>2</sub> consumption within the ranges of healthy controls.<sup>21</sup>

The use of LVAD support as BTR gives rise to 5 major challenges in the field: (1) pre-implantation prediction of cardiac recovery during mechanical ventricular unloading, (2) promotion of myocardial recovery while on LVAD support, (3) assessment of myocardial improvement after LVAD implantation, (4) decision-making to proceed with LVAD explantation versus ongoing support and/or cardiac transplant, and (5) long term follow-up and management after discontinuing LVAD support. (Figure 1) In this review, we will cover clinical aspects of contemporary LVAD therapy which, in synergy with medical therapy, results in ventricular unloading, reverse remodeling, myocardial remission and recovery.<sup>5,22</sup>

## Pre- LVAD implantation prediction of cardiac recovery

HF is a progressive disorder that is characterized by compensatory mechanisms designed to reduce wall stress,

sustain LV function, and maintain cardiac output<sup>23</sup>; however, these systems become overwhelmed leading to symptomatic HF.<sup>24</sup> Clinical factors associated with myocardial recovery include several features suggesting patients are earlier in this disease progression: a short HF duration (<5 years),<sup>9,25,26</sup> non-ischemic cardiomyopathy (NICM),<sup>27</sup> younger age <50,<sup>16,25,28</sup> normal or mildly impaired renal function (<1.2 mg/dl), and not-large left ventricular end diastolic diameter (LVEDD) (<6.5 cm).<sup>9,10,27</sup> Of patients fitting these characteristics, nearly half will experience improvement of LV function sufficient to permit LVAD explant, with long-term freedom from the need for transplant or LVAD reinsertion.<sup>5</sup> The duration of HF, more so than the LV size, appears to be a key clinical factor in predicting the likelihood of recovery as well as long-term post weaning cardiac stability. In fact, the mean LVEDD for 35 patients weaned off of LVAD support was  $74 \pm 1.2$  cm, with a mean duration of HF of  $4 \pm 0.6$  years.<sup>29</sup>

*Etiology of HF and its impact on recovery:* There is a greater chance of recovery in patients with an underlying diagnosis of transitory or reversible myocardial disease.<sup>9</sup> When specific HF etiologies were investigated, the greatest rates of myocardial recovery were observed in patients with myocarditis (7.7%), postpartum cardiomyopathy (4.4%), and adriamycin-induced dilated cardiomyopathy (4.1%).<sup>8</sup> Given the heterogenous genetic architecture of dilated cardiomyopathy (DCM) and varying potential of reverse cardiac remodeling,<sup>30</sup> genetic counseling and testing for DCM genes is recommended for all patients with a NICM and prior to termination of device support. Improvement in LVEF has also been reported in 5% of advanced ischemic cardiomyopathy patients post LVAD, and can be a reasonable strategy in select, revascularized patients without large myocardial infarcts.<sup>31</sup>

*Clinical Prediction Scores:* The clinical characteristics of patients with a high potential for recovery can be combined into a prediction score which is a helpful decision aid at the time of LVAD implantation. The INTERMACS Cardiac Recovery Score (I-CARS) predicts recovery with a modest area under the curve of 0.58 (95% CI: 0.56-0.6) and in unselected INTERMACS patients, a higher score is associated with 29% probability of myocardial recovery (Table 2).<sup>9</sup> When validated in a BTR patient population, the I-CARS score demonstrated a good performance in discriminating cardiac recovery (AUC: 0.94; 95% CI: 0.91-0.98).<sup>9</sup> Similarly, the INTERMACS recovery risk model associated young age, non-ischemic etiology, shorter duration of HF and a not very dilated LV size associated with myocardial recovery.<sup>10</sup>

*Role of Bridge-to-Recovery LVAD Indication:* Clinical intent at time of LVAD implantation is an important predictor of myocardial recovery as it creates a deliberate framework for clinical management. In an analysis of the INTERMACS registry, when patients are implanted with a LVAD as BTR, the incidence of recovery is 11% compared to 1% in the general LVAD population.<sup>9</sup> In fact, centers that have implemented protocols for systematic evaluation of myocardial function after LVAD implant have seen greater rates of myocardial

**Table 1** Studies Evaluating Myocardial Improvement Following LVAD Support

Study (Year, Center)	n	LVAD type	HF etiology	Duration of LVAD support (average, in months)	% patients with significant improvement in cardiac function (LVEF>40%) <sup>a</sup>	LVAD support discontinuation (explant or decommissioning)	Follow-up & Outcomes of explanted pts (cause of death)
2006, Harefield (15)	15	HM XVE	NICM: 100%	11	73%	11 (73%)	-Follow up: 4 years -1 died within 24 hours post explant (intractable arrhythmia). -1 died 27 months post-explant (malignancy). -1 had heart transplant 33 months post-explant. -Freedom from HF: 100% (1 year), 88.9% (4 year)
2007, US LVAD Working Group (11)	67	HM XVE (59) Novacor (5) DeBakey (1) BiVAD (2)	NICM: 55% ICM: 45%	4.4	NICM: 13.5% ICM: 3.3%	6 (9%)	- Follow-up: 6 months - Freedom from HF: 100%
2008 Berlin (26)	188	Novacor (27) TCI (3) Berlin heart (5)	NICM: 100%	4.3	43%	35 (18.6%)	-Follow up: >5 years -16 with HF recurrence post-explant (9 occurred in 1 year) -7 died (5 from extracardiac causes, 2 died waiting for transplant) -Survival without transplant: 76.2% (5 year), 70.7% (10 year)
2011, Harefield (16)	20	HM II	NICM: 100%	9	60%	12 (60%)	-Follow up: 3 years -1 died on day 6 post-explant (failure to wean from CPB, sepsis). -1 died on day 26 post-explant (VF arrest). -1 required 7 day RVAD support post explant. -30 day and 3 year survival: 83.3%
2011 Berlin (56)	90	-Pulsatile LVAD (33) -CF-LVAD (12) -BiVAD (2)	NICM: 45%	4.9	52%	47 (52%)	-Median follow up: 5.7 years (0.1-14.8) -17 with HF recurrence within 5 years (9 occurred in 1 <sup>st</sup> year) -14 died (9 from non-cardiac causes) -Transplant-free survival: 68.9% (5 year), 61.6% (10 year)
2013, Montefiore (44)	21	HM II	NICM: 62% ICM: 38%	9	NICM: 23% ICM: 0%	3 (14%)	- Median follow-up: 4 years - No recurrence of HF
2016, Utah Cardiac Recovery Program (UCAR) (31)	154	CF-LVAD	NICM: 60% ICM: 40%	6	NICM: 21% ICM: 5%	N/A	N/A
2016, INTERMACS (9)	13,454	CF-LVAD	ICM: 46% NICM: 54%	11.4	9.8%	163 (1.2%)	N/A

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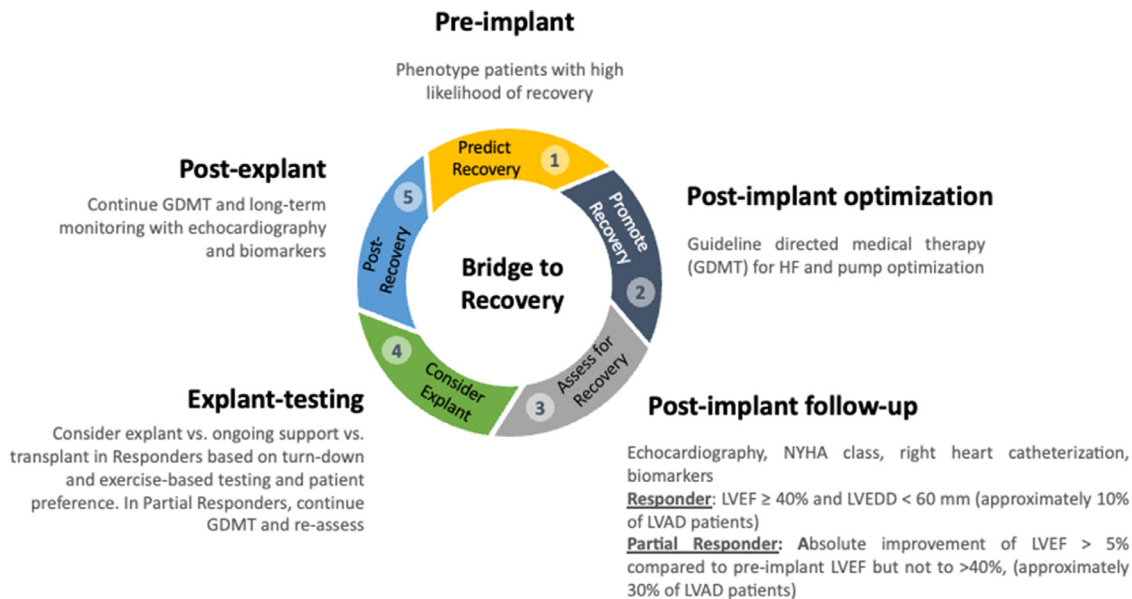
**Table 1** (Continued)

Study (Year, Center)	n	LVAD type	HF etiology	Duration of LVAD support (average, in months)	% patients with significant improvement in cardiac function (LVEF>40%) <sup>a</sup>	LVAD support discontinuation (explant or decommissioning)	Follow-up & Outcomes of explanted pts (cause of death)
2020, EUROMACS (8)	45	HM II (14) HVAD (11) HM3 (2) Unknown (1)	NICM: 49%	13	100% <sup>b</sup>	45 (outcomes only in 28)	-Follow up: 26 months (0.3-73) -2 had HF recurrence -1 required LVAD reimplant -1 died on day 302 (sepsis) -Freedom from death, LVAD reimplant, HF, transplant at 2 years: 88%
2020, RESTAGE-HF (Multicenter US) (18)	40	HM II	NICM: 100%	18	50% (of those who received protocol)	19 (47%)	-Follow up: 3 years -7 died at 1.1 (0.04-2.8) year post-explant -4 had transplant -9 remained on LVAD -Survival free from LVAD re-implant or transplant: 90% (1 year), 77.1% (3 year)
2021, UTAH-INOVA (7)	358	HM II (203) HVAD (132) Jarvik (18) VentraAssist (3) Lavecort (1)	NICM: 65% ICM: 35%	12	41%	N/A	N/A
2021 INOVA-Newcastle (46)	515	HVAD (11) HM II (6)	NICM: 100%	28.7	N/A	17 (5.6%)	Follow up: 3 years - 1 patient required a transplant - 3 patients died due to device infections

Abbreviation: BiVAD, biventricular assist device; CF-LVAD, continuous flow LVAD; HMXVE, HeartMate; HF, heart failure; HM II, HeartMate II; HVAD, Heart Ware Assist Device; ICM, ischemic cardiomyopathy; LVAD, left ventricular assist device; NICM, non-ischemic cardiomyopathy; RESTAGE, Remission from Stage D Heart Failure.

<sup>a</sup>The percentage of patients with a significant improvement in LVEF post LVAD implant is approximately 10 times higher than the LVAD explantation rates due to reasons discussed in the text.

<sup>b</sup>Pre-selected patient population for LVEF improvement.



**Figure 1** Clinical considerations in using LVAD as bridge to recovery. GDMT, guideline directed medical therapy; LVAD, left ventricular assist device; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

improvement compared to the general LVAD patient population.<sup>32</sup>

**Biomarkers and Imaging:** Baseline myocardial and systemic inflammatory burden inversely correlates with cardiac improvement following LVAD support. A circulating 2–cytokine model (i.e., low levels of circulating interferon gamma and tumor necrosis factor alpha) predicting significant reverse remodeling was identified, warranting further investigation as a practical preintervention tool in identifying patients prone to LVAD–mediated cardiac improvement and device weaning.<sup>33</sup> After LVAD implantation there is a reversal of HF biomarkers including N-terminal pro-B-type natriuretic peptide (NT-proBNP), growth differentiation factor-15 (GDF-15) and ST2.<sup>34</sup>

HF and LVAD therapy alter normal ventricular chamber geometry and torsional forces.<sup>35</sup> Reverse remodeling with LVAD support is associated with reductions in LV size, volume, and an improvement in myocardial function. Early data suggests that use of dobutamine stress echocardiography<sup>36</sup> and speckle tracking to assess LV torsion can potentially identify pre-LVAD patients with a high degree of subsequent myocardial reverse remodeling.<sup>37</sup>

## Promoting myocardial recovery with a LVAD

Successful LVAD management and elimination of HF symptoms is predicated on optimal unloading of the left ventricle, with concomitant use of GDMT. Our approach to promoting reverse cardiac remodeling and myocardial recovery is outlined in Figure 2.

**Optimal LV unloading:** Traditionally, transthoracic echocardiography (TTE) has been used to adjust LVAD speed to achieve proper unloading. Patients in RESTAGE-HF trial underwent echocardiographic speed optimization either before discharge from pump implantation or at the

first follow-up appointment to reduce the LVEDD to  $<$ 60 mm and the severity of mitral regurgitation (MR) to less than moderate.<sup>18</sup> Hemodynamic ramp testing with right heart catheterization, although invasive, is effective in guiding patient management to achieve more normal hemodynamics.<sup>38–40</sup> The goal of a hemodynamic ramp study is to demonstrate a pump speed that allows for, (1) normal pulmonary capillary wedge pressure (PCWP)  $<$ 18 mm Hg, (2) central venous pressure  $<$ 12 mm Hg, (3) cardiac index  $>$ 2.2 L/min per m<sup>2</sup>. A concomitantly performed TTE would aim for trace or mild MR, an LV size (LVEDD)  $<$ 60 mm, neutral interventricular septum, minimal or no aortic regurgitation, and intermittent aortic valve opening. Titration of pump speed has also allowed permitted patients to tolerate greater levels of GDMT.<sup>18</sup>

**Guideline Directed Medical therapy (GDMT):** LVAD-mediated mechanical unloading is caused primarily by the reductions in wall stress which drives the vicious cycle of adverse remodeling and HF progression.<sup>41,42</sup> In a prospective LVAD study, clinical and histopathological evidence indicated that adjuvant HF pharmacological therapy was associated with additional favorable effects on the structure and function of the unloaded myocardium that extended beyond the beneficial effects attributed to LVAD-induced unloading alone.<sup>43</sup> LVAD induced unloading of the LV should be combined with early use of state-of-the-art GDMT to promote reverse remodeling in all patients implanted as BTR. Although RESTAGE-HF used the traditional neurohormonal blockade therapies (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers), beta blockers and mineralocorticoid receptor antagonists; the scope of GDMT in HFrEF has expanded significantly in recent years.<sup>44</sup> The role of angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), ivabradine and soluble

**Table 2** Intermacs Cardiac Recovery Score (I-CARS)

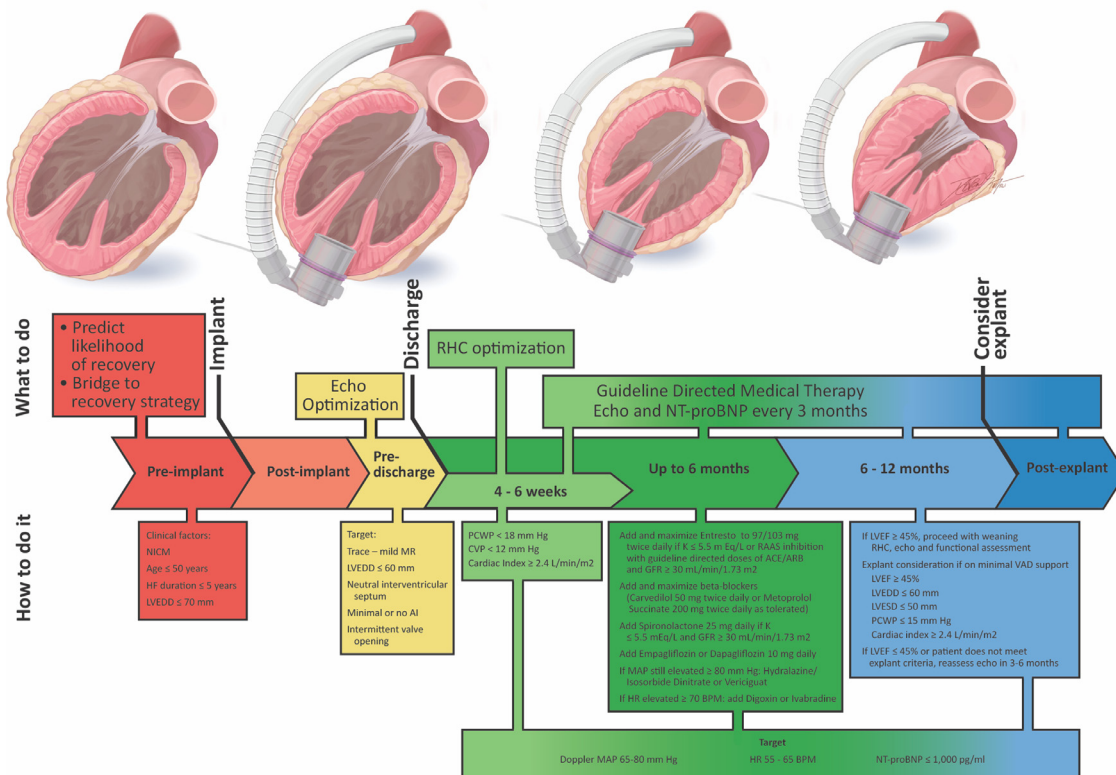
Clinical Characteristic	Incidence Rate of Recovery v pts without characteristic (events/100-pts-yrs)	OR (95% CI)	Score
Nonischemic Cardiomyopathy	1.6 vs 0.3	4.7 (3.1-7.1)	3
Implanted ICD	2.9 vs 0.5	3.7 (2.6-5.2)	2
Age <50 years	2.2 vs 0.5	1.9 (1.4-2.7)	1
Time from Diagnosis <2 years	2.7 vs 0.5	2.2 (1.5-3.1)	1
Creatinine ≤1.2 mg/dl	1.4 vs 0.5	2.0 (1.4-2.7)	1
LVEDD <6.5 cm	1.6 vs 0.7	1.8 (1.3-2.5)	1
Total Score Range			0-9

Abbreviations: ICD, Implantable Cardioverter Defibrillator; LVEDD, left ventricular end diastolic diameter. Low probability group (0-3 points), an intermediate probability group (4-6), and a high probability group (7-9).

guanylate cyclase stimulator therapies is now well established in patients with HFrEF.<sup>45</sup> Similar to patients with HFrEF, GDMT in LVAD patients implanted as BTR should be titrated to a mean arterial pressure >65 mm Hg and a heart rate of 55-65 beats per minute, as long as the patient is asymptomatic, with adequate renal function and electrolytes within the normal range.<sup>18</sup> (Figure 2) For patients in atrial fibrillation or atrial flutter cardioversion and/or ablation to eliminate the atrial arrhythmia to support the reverse remodeling process should be considered.

*Time course of reverse remodeling on LVAD support:* In as much as cardiac failure does not follow a single,

unique trajectory, there exist multiple paths for its reversal: both in terms of degree and rapidity. Depending on the etiology, patients may have an improvement in LV function shortly following implant (usually over 6 months), or over an extended course of time.<sup>12,18</sup> In RESTAGE-HF(18), both LVEF and LVEDD showed evidence of improvement within 6 weeks following pump speed optimization and then continued to improve throughout the ensuing 18 months of follow-up.<sup>18</sup> Two recent analyses have suggested that patients can continue to exhibit reverse cardiac remodeling beyond 2 years of device support.<sup>10,46</sup>



**Figure 2** Clinical recommendations to promote myocardial recovery post LVAD implantation, ranging from pre-implant to explant. ACE, angiotensin converting enzyme inhibitor; AI, aortic insufficiency; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BPM, beats per minute; CPET, cardiopulmonary exercise test; CVP, central venous pressure; GFR, glomerular filtration rate; HF, heart failure; HR, heart rate; K, potassium; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; MAP, mean arterial pressure; MR, mitral regurgitation; NICM, non-ischemic cardiomyopathy; PCWP, pulmonary capillary wedge pressure; RAAS, renin-angiotensin antagonist system; RHC, right heart catheterization.

## Assessing for myocardial recovery during LVAD support

Evidence of cardiac improvement can be seen during routine echocardiography performed after LVAD implantation. Objective findings of structural and functional remodeling include: a reduction in LVEDD, improvement in ventricular function (LVEF), reduction in MR severity and regular opening of the aortic valve. Formal recovery testing is performed while observing the response of the native heart while the degree of LVAD support is down regulated. Other centers have been more aggressive with turn-down studies that including pump stoppage and/or endovascular occlusion of the outflow graft to mimic native heart support.<sup>47</sup>

It is critical to note that reverse remodeling is not a binary phenomenon but a continuum<sup>7</sup>:

- Responder: defined as patients achieving an LVEF of  $\geq 40\%$  and an LVEDD  $\leq 6.0$  cm
- Partial responder: defined as improvement of LVEF  $> 5\%$  compared to pre-implant LVEF but not  $> 40\%$ , independent of changes in LVEDD
- Non-responder: defined as a patient with no demonstrable improvement in LVEF, independent of changes in LVEDD

Recovery assessment protocols published to date have utilized various combinations of functional capacity measurement, imaging studies, and biomarkers to determine candidacy for LVAD explant or “decommissioning.”

*Functional capacity, hemodynamics and exercise testing:* It is recommended that recovery assessment may also be done during exercise to evaluate for cardiovascular reserve, as data at rest can be within the normal ranges.<sup>48</sup> Cardiopulmonary exercise test (CPET), has been used as a component of the recovery assessment protocol.<sup>16,49,50</sup> Most studies demonstrate an improvement in the NYHA functional class, but the peak  $O_2$  consumption ( $pVO_2$ ) after LVAD implantation remains impaired.<sup>51</sup> Because exercise capacity is impacted by extracardiac factors, a low  $pVO_2$  on its own should not preclude consideration for LVAD weaning.<sup>49,52</sup> In fact, peak  $VO_2 > 16$  mL/kg/min was an optional pump explant criterion in the RESTAGE-HF trial.<sup>18</sup> Other CPET parameters such as anaerobic threshold, aerobic efficiency, ventilatory efficiency ( $V_E/VCO_2$  slope), and presence of periodic breathing or exercise oscillatory ventilation have been incorporated to assess for recovery.<sup>49</sup>

While assessing hemodynamics for recovery, an off-pump trial should be done under full anticoagulation and combined with TTE based measurements of LVEF and LV geometry. Normalization of LV size and geometry, with an LVEF  $\geq 45\%$  and resting PCWP  $< 15$  mm Hg with a concomitant cardiac index  $> 2.4$  liters/min/m<sup>2</sup> on minimal LVAD support settings is associated with successful explant and freedom from recurrent HF.<sup>29,53</sup> Exercise testing can be combined with hemodynamics to generate a comprehensive view of a patient’s myocardial reserve and candidacy for LVAD removal. A flat slope of  $\leq 2$  mmHg/L

min for the PCWP/CO ratio during exercise can be used to determine candidacy for pump explant.<sup>49,54</sup>

*Imaging modalities and biomarkers:* TTE is the most commonly used imaging modality to assess for normalization of LV size and geometry post LVAD. In RESTAGE-HF, TTE parameters for pump explant eligibility included LVEDD  $< 60$  mm, left ventricular end-systolic diameter  $< 50$  mm and LVEF  $> 45\%$ .<sup>18</sup> Although an LVEDD between 55 and 60 mm can be considered borderline normal in patients with a body surface area  $\geq 1.8$  m<sup>2</sup>, an LVEDD  $> 55$  mm was associated with post explant recurrence of HF within 3 years.<sup>29</sup> Also, the RESTAGE-HF protocol specified pump speed optimization to achieve mitral regurgitation less than grade 2, while other studies required all valvular regurgitation (aortic, tricuspid, pulmonic) to be less than grade 2.<sup>29,49</sup> “Normal” criteria for right ventricular structure and function included outflow tract diameter  $< 35$  mm, right ventricular short and/or long axis ratio  $< 0.6$ <sup>19</sup> right ventricular ejection fraction  $> 40\%$ ,<sup>49</sup> or more vaguely, “good” right ventricular function.<sup>55</sup> Additional information on ventricular function can be obtained by tissue Doppler imaging and assessment of regional wall thickness, which also help assess the risk of HF recurrence.<sup>56</sup> Hence, a LVEF  $\geq 45\%$  is a reliable criterion for LVAD explantation only in patients with other criteria for normalization of LV size and geometry.

There are sparse data that compares biomarker levels in recovered versus non-recovered LVAD patients. Examples of biomarkers studied in LVAD patients include markers of myocardial stretch (BNP or NT-proBNP),<sup>34,57</sup> neurohormones,<sup>58</sup> mediators of inflammatory and fibrotic responses (CRP, sST2, TNF $\alpha$ , IFN $\gamma$ , IL6),<sup>34,59,60</sup> and microRNAs.<sup>61,62</sup>

## Decision making to proceed with LVAD explantation

As with the decision to implant an LVAD, the process of shared decision making with the patient and their caregivers needs to be an integral part of LVAD explantation. This discussion should include a thorough review of the concept of recovery in terms that the patient can understand so as to align medical care, set expectations for life post explantation, and reduce any decision regret. Each patient should be provided detailed information on treatment options and associated outcomes so that patients can weigh the potential benefits and harms on their own intrapersonal scale. This discussion should be initiated at the time of the BTR implant and reviewed on an ongoing basis during follow-up and testing for recovery.

Despite the utility of the diagnostic studies described above, there are no standard best practices for LVAD explantation. Decisions regarding surgical strategies for explantation start at the time of LVAD implant by appropriately addressing valvular lesions and preparing the mediastinum for potential re-entry.<sup>63</sup> Historically, LVAD removal was performed through a midline sternotomy with complete extirpation of the device and outflow graft. However, redo-

sternotomy and explantation can place a patient at risk for other morbidities that might jeopardize a recovering myocardium, including blood transfusions and direct cardiac injury.

Multiple techniques have been described to facilitate VAD removal without requiring extensive surgical repair of the ventricle. Even through a mini-thoracotomy, the apical defect can be fixed directly with an aneurysmorrhaphy-type repair. Specially designed apical plugs can be inserted into the sewing rings of the pump without the use of cardiopulmonary bypass.<sup>64</sup> Recently, there has been growing enthusiasm for less invasive techniques where the LVAD is decommissioned or deactivated. Small subxiphoid or anterior thoracotomy incisions can be used to ligate the outflow graft with concomitant transection of the driveline at the exit site.<sup>65,66</sup> Nonsurgical approaches have also included the percutaneous occlusion of the outflow graft with an intravascular occlusion device.<sup>67,68</sup> Finally, some have advocated simply dividing the driveline and leaving the entire pump in situ, ultimately allowing the pump to fully develop a contained thrombus. The benefit of less invasive techniques needs to be weighed against the risk infection related to leaving parts of the LVAD inside the body.

### Long term clinical management and follow-up after discontinuing LVAD therapy

When managed appropriately, a significant percentage of LVAD explanted patients can achieve cardiac and physical functional capacity that is within the normal range of healthy controls.<sup>21</sup> In fact, the long-term survival rates after weaning from VADs appeared to be similar or even better than those expected after primary transplantation.<sup>20,26</sup> For the 45 patients undergoing LVAD explant in the EUROMACS registry, median follow-up after explantation was 26 months (range 0.3–73 months), and 82% of the patients were NYHA Class I or II.<sup>8</sup> In RESTAGE, post-explantation survival free from LVAD or transplantation was 90% at 1 year and 77% at 2 and 3 years.<sup>18</sup>

*Risk factors for recurrent HF:* Duration of HF, both pre-explant and off-pump LVEF impact the likelihood of recurrent HF following LVAD weaning.<sup>26</sup> A reduced regional wall thickness in patients with pre-explant EF between 45% and 50% was found to be highly predictive for HF recurrence within the first 3 years after LVAD explantation.<sup>56</sup> Similarly, a pre-explant LVEF reduction of more than 10% after attaining a maximum value was found to be a risk factor for HF recurrence for patients with pre-explant LVEF <50%.<sup>56</sup> Off-pump LVEF <45% showed an 88% predictive value for HF recurrence during the first 3 years after LVAD removal, and values <40% appear to consistently predict early recurrence of HF.<sup>53</sup>

*Need for long-term follow-up and continuation of medical therapy:* Post explant, maintaining patients on optimal GDMT is essential to prevent adverse remodeling and recurrent HF.<sup>69</sup> These patients should be followed

systematically in HF clinics with subjective assessments and objective screening for recurrence of HF. Serial monitoring of left ventricular structure and function and natriuretic peptides at 3 month intervals for the first year after LVAD weaning, every 6 months for the second year and yearly thereafter is recommended. Alternative strategies to assess for volume overload including implantable hemodynamic monitors are under investigation. Finally, it is critical that patients and other providers be counseled that recurrent HF is likely in >50% of patients with discontinuation of medical therapy as previously demonstrated in a non-LVAD HF population.<sup>69</sup>

*Anticoagulation in those undergoing explantation:* In the EUROMACS data, regardless of antithrombotic strategy (aspirin vs. warfarin) or whether the inflow cannula remained in situ after explantation or was removed, no strokes were reported in the patients during follow-up.

### Myocardial recovery in pediatric patient population

No prospective studies focusing on recovery have been conducted in children and published data is limited to single center studies.<sup>70-72</sup> While it is reasonable to follow adult guidelines in larger children on continuous flow LVADs, procedures to identify candidates for recovery and explantation of the device differ in para-corporeal pulsatile flow-LVADs.

Explantation rates from durable devices range from 2% to >70%.<sup>70-76</sup> Improvement can be expected to occur during the first 12-16 weeks, and the majority of explantations had been reported to occur within the first 3 months after implant.<sup>70,71,75,77</sup> GDMT is widely accepted to promote recovery. Since exercise testing is not feasible in most children, TTE is the main tool for assessment.<sup>70</sup> In para-corporeal pulsatile flow LVAD's, complete explantation is the rule, however clamping of the tip of the apical cannula is possible. Decommissioning and subsequent explantation after years has been described in children on continuous flow LVADs.<sup>78,79</sup> As with adults, life-long follow-up in children post explant is necessary, and lifelong medical treatment is critical.<sup>70</sup>

*Future Directions—*With the expanding HF population, the elective therapeutic use of LVADs for reversal of HF in its earlier stages and myocardial recovery is a future goal. Well-conducted, multicenter, randomized controlled trials of the BTR strategy in target patient populations (both adult and pediatrics) is needed to enhance our understanding and develop best practices of myocardial improvement with LVAD support. These trials should be appropriately powered to test whether a BTR strategy at the time of LVAD implant influences the incidence of recovery with mechanical unloading. A combination of clinical and biological studies for patients undergoing LVAD implantation by collecting histological and/or biological and clinical data before LVAD implantation, during LVAD support and after explantation are ongoing. Importantly, the field needs to invest in 'less-invasive' LVADs as BTR that can be placed



percutaneously, can support a patient for longer duration (weeks to months) and would not require the LV apex to be cored out. This will allow us meaningful insights into the pathophysiology of myocardial recovery and potentially preclude many patients with acute, severe HF refractory to GDMT from undergoing LVAD or heart transplantation. Machine learning based models may provide additional insights into prediction of myocardial recovery with LVAD resulting in pump explant.<sup>80</sup>

**Summary:** Myocardial recovery and remission from HF is a much-preferred outcome over cardiac transplantation and long-term LVAD support. A significant number of LVAD explanted patients can achieve cardiac and functional capacity similar to healthy controls. Yet, LVAD recovery remains under-evaluated and under-promoted. Every patient undergoing an LVAD implant, especially younger patients with a NICM of a short duration deserve a chance to be managed with intent to recover and promote the longevity of their native heart for as long as possible. Optimal unloading of the LV, combined with state-of-the-art GDMT should be facilitated in all patients. Cardiac transplantation should be reserved for those patients with no evidence of meaningful myocardial recovery, which may further optimize the allocation of this limited resource.

## Author contributions

All listed authors have contributed significantly to the design, writing and review of this manuscript and approved the final draft.

## Disclosure statement

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