Ventricular assist device–promoted recovery and technical aspects of explant

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Feature Editor Note—*Promoting left ventricular recovery after durable left ventricular assist device (LVAD) implantation remains a Holy Grail. Currently, less than 2% of patients exhibit signs of recovery after LVAD implantation, and even fewer tolerate device explantation without recurrence of heart failure. In this issue of the* Journal*, Drs Faerber and Doenst describe what we can do clinically to promote recovery, including how guideline-directed medical therapy may facilitate structural remodeling of the unloaded heart. Identifying recovery in the presence of ventricular unloading also presents a challenge, and the authors describe weaning protocols for various devices. Current evidence suggests that there are clinical predictors of recovery, including younger age, nonischemic etiology, smaller left ventricular size, and shorter duration from diagnosis of heart failure, and these can be used to help draw our focus toward patients who are more likely to tolerate device weaning and explantation. In those patients, preparing for device explantation requires early surgical planning, often at the time of LVAD implantation, including correction of valvular lesions that will be hemodynamically significant in the absence of LVAD support.*

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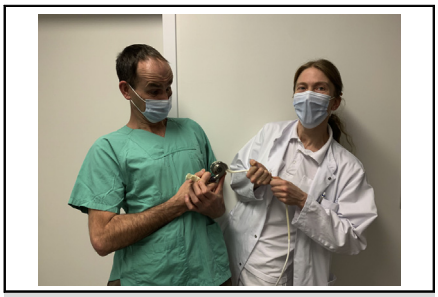

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CENTRAL MESSAGE

Ventricular assist device (VAD)-induced myocardial recovery is possible but rare. Keys to success are patient selection, surgical strategy, and specialized expertise for VAD weaning and explantation.

See Commentaries on pages 189 and 191.

Ventricular assist devices (VADs) represent an essential treatment option for patients with end-stage heart failure, often without an alternative.[1] VADs reduce symptoms of heart failure and improve survival as well as quality of life.[2,3] Currently, continuous-flow left ventricular assist devices (LVADs) represent the most common form of VAD therapy and therefore standard of care.[4,5]

VADs are currently implanted as bridge to transplantation (BTT) or destination therapy (DT).[1] However, limitations apply for both strategies, including driveline infections, device-related neurologic events, bleeding complications, and device malfunction. Although heart transplantation still delivers best long-term results, even this treatment option is far from curing the initial disease.[6] A mean survival of 11 to 13 years may not be sufficient for a young heart transplant recipient, and the need for lifelong immunosuppression carries a whole basket of new problems (including infection, rejection, and increased rates of cancer).[6]

In this treatment dilemma, observations of cardiac functional recovery on mechanical unloading raise hope for a third treatment alternative, one not requiring constant mechanical support or transplantation. Several approaches promoting functional cardiac recovery with potential VAD explantation have been investigated.[7] However, the initial hope and excitement of this bridge to recovery (BTR) strategy was blunted by observations that BTR reflects a rare indication (1%-2%) and actual VAD explantations are uncommon (<2%).[8-10] Enthusiasm was further dampened when recurrence of heart failure after initially successful weaning was reported.[10]

Yet, some centers focused on the weaning and explantation of VADs.[7,11-13] They reported exceptionally high survival and low rates of heart failure recurrence in selected patients.[7,11,12,14-16] They suggest that the proportion of patients on BTR might be underestimated and the potential of VAD-associated myocardial recovery

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has not yet been fully exploited. The implementation of these findings into broad clinical practice, considering the aforementioned sobering experiences,[4,5] requires investigation of the underlying recovery mechanisms. In addition, focused interest on weaning protocols and explantation algorithms may then allow a growing number of patients to benefit from BTR.

We here briefly summarize our current mechanistic understanding of VAD-promoted cardiac recovery and review device weaning aspects and the technical details of discontinuing mechanical support.

CARDIAC RECOVERY: DEFINITIONS AND POTENTIAL PATHOMECHANISMS

Mechanical unloading with VADs may lead to reversal of structural changes (reverse remodeling) and improvement of contractile function.[17] Functional recovery of failing hearts and the principles of unloading have long been in the focus of research,[18,19] not necessarily requiring the presence of a VAD. Injury to the heart is usually followed by loss of damaged cardiomyocytes, which are replaced with fibrotic scar tissue. Thus, treatment strategies at the cellular and molecular level aim at reversing this remodeling process and address principles that result in regeneration or repopulation of cardiomyocytes, using stem cells, growth factors, mircoRNAs, cellular reprogramming, tissue engineering, etc (reviewed in detail by Hashimoto and colleagues[20]). Among all heart failure therapies, the greatest degree of reverse remodeling has been seen with VADs.[21] Figure 1 schematically illustrates the plethora of mechanisms involved in VAD-induced cardiac recovery. A detailed description has been subject of several reviews.[17,22-24] In addition to strictly cardiac effects, it has been shown that VAD support decreases inflammation-mediated myocardial injury by reducing the level of plasma cytokines and production of autoantibodies against cardiac proteins level.[24] Furthermore, it has been shown that VAD support itself can downregulate the pathologically upregulated renin–angiotensin–aldosterone and sympathetic nervous systems.[23] Continuing guideline-directed medical therapy (GDMT) for heart failure should therefore be complimentary to the specific effects of mechanical unloading. Indeed, risk reduction for stroke, pump thrombosis, and gastrointestinal bleeding from arteriovenous malformation have been described by renin–angiotensin–aldosterone inhibition on LVAD.[23]

Currently, the relevance of the individually suggested recovery mechanisms is not clear. An interplay of many mechanisms was suggested to cause both remodeling and its reversal with or without VAD support.[19,25] It is similarly difficult to distinguish between spontaneous recovery and treatment effects because heart failure causes are heterogeneous and most patients are already treated with GDMT. In patients with VAD, classic assessment of recovery (ie, increases in ejection fraction, etc) is specifically challenging because mechanical assistance substantially alters loading conditions. In addition, predicting longevity of recovery

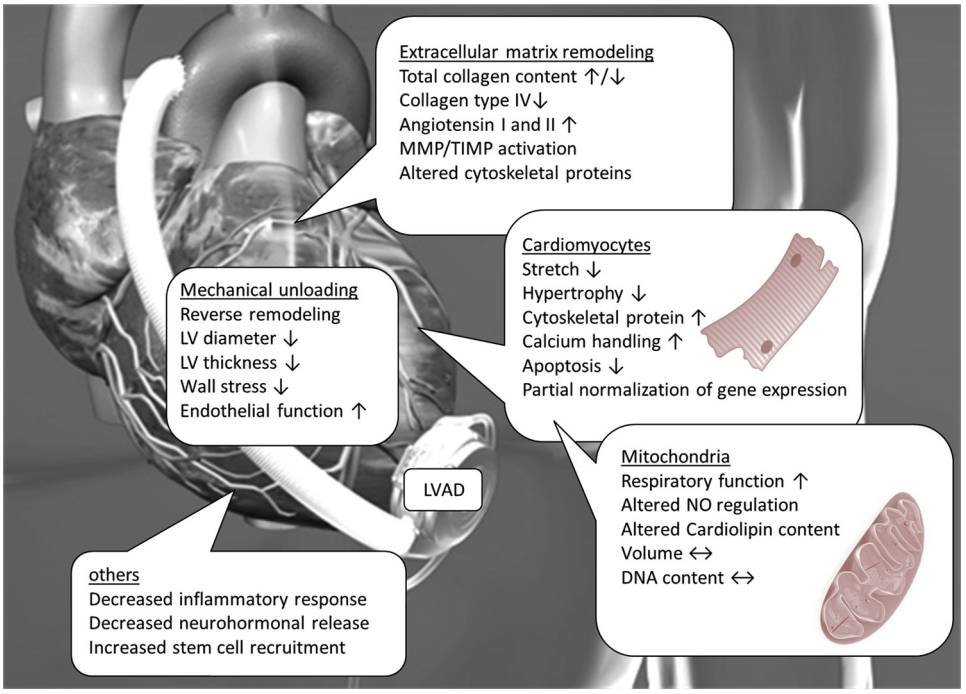

FIGURE 1. Mechanisms of ventricular assist device–promoted functional cardiac recovery. Modified after Miyagawa and colleaegues[17] and Gallo and colleagues.[22] *MMP/TIMP*, Metalloproteinases; *LV*, left ventricle; *LVAD*, left ventricular assist device; *NO*, nitric oxide.

remains a sophisticated task. In daily practice, the observed effects of mechanical unloading rarely translate into sustained improvements of ventricular function to the degree that VAD therapy can be withdrawn.[8,9,12] Severe heart failure with or without the need for renewed mechanical assistance occurs in a substantial fraction of patients after presumed recovery on VADs.[10] Therefore, it has been argued that the term "remission" may be more appropriate than "recovery."[10,19,26] Unfortunately, a clear-cut differentiation between myocardial "remission" and "recovery" is clinically not possible.[19,26] A working group of the National, Heart, Lung, and Blood Institute recently defined the term cardiac recovery for use in daily practice as "a reversal of the pathologic state of the myocardium with significant improvement in cardiac structure and function sufficient to achieve a sustained remission from recurrent heart failure events."[25] However, none of these terms are able to reflect the risk of relapse into overt heart failure or describe the underlying mechanism of recovery. Thus, attempts to discern these mechanisms must address patient-related factors influencing the potential for VAD-induced recovery.

PATIENT-RELATED FACTORS AFFECTING VAD-MEDIATED FUNCTIONAL RECOVERY

Table 1 shows a summary of patient-related criteria that have been identified to affect VAD-mediated myocardial recovery. Age and etiology of cardiomyopathy affect recovery potential most. Weaning in patients older than 50 years or ischemic heart disease are poor predictors of recovery. Similarly, longer history of heart failure before VAD implantation and longer duration of VAD support also reduce recovery potential. The same can be seen for renal function and ejection fraction. Some reports suggest that VADs with pulsatile flow may have a greater potential for recovery, but these findings likely suffer from substantial biases (eg, inferior durability, more adverse events with the "old" pulsatile systems).[21,24,42]

Wever-Pinzon and colleagues[27] developed a score consisting of 6 clinical factors based on the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) database, predicting individual probability of cardiac recovery. The INTERMACS Cardiac Recovery Score (I-CARS) expects cardiac recovery if patient age is older than 50 years, etiology is nonischemic, time from diagnosis of heart failure is less than 2 years, left ventricular end-diastolic diameter is <6.5 cm, and creatinine serum levels are ≤1.2 mg/dL (see also Table 1). They demonstrated that once a patient is identified as recovery candidate, the incidence of cardiac recovery increased 9-fold. Thus, this score may help in directing patient selection for VAD-discontinuation.

TABLE 1. Factors associated with VAD-promoted functional recovery

Basic patient and VAD-related data	Predictive data for positive outcome
Patient age[7,11,12,14,27-29]	<50 y, no linear correlation
Etiology of cardiac disease[7,16,27,29-31]	Nonischemic cardiomyopathies (DCM) or acute pathologies (myocarditis, peripartum heart failure, noncoronary postcardiotomy heart failure)
Duration of HF before VAD support[4,5,16,29,32]	Heart failure history <5 y before VAD implantation
Duration of VAD support[11,17,33,34]	VAD implantation (<6 mo)
VAD type[32,35-40]	Pulsatile flow
Echocardiography[16,29,41]	Higher pre-explant LVEF (≥45%) lower pre-explant LVEDD (<6.0 cm)
Creatinine serum level[27]	≤1.2 mg/dL

VAD, Ventricular assist device; *DCM*, dilative cardiomyopathy; *HF*, heart failure; *LVEF*, left ventricular ejection fraction; *LVEDD*, left ventricular end-diastolic diameter.

THERAPEUTIC STRATEGIES TO SUPPORT FUNCTIONAL RECOVERY ON VAD

Therapeutic strategies aimed at inducing cardiac recovery range from the development of specific heart failure medication protocols, to application of stem cells, to device selection, and the management of concomitant cardiac pathologies (specifically valve dysfunction).

Birks and coworkers[7,14,28] have shown that continuation and optimization of GDMT enhance reverse remodeling and myocardial recovery in patients with VADs. This "Harefield" drug protocol resulted in LVAD explantation rates of 40% to 73% in a selected, young patient population (age ~35 years, nonischemic etiology) with remarkable survival rates and sustained myocardial recovery.[7,14,28] It consisted of an initial high dose of angiotensin-converting enzyme inhibitor, unselective β-blocker, aldosterone antagonist, angiotensin II antagonist, and digitoxin. In a second phase, the investigators added the β2-agonist clenbuterol hoping to induce physiologic cardiac hypertrophy once signs of atrophy are visible with unloading through VAD support.[43,44] Other investigators questioned the therapeutic benefit of clenbuterol,[45] a drug that is also not available on the US market. A US-led trial then assessed the role of GDMT (practically the first phase of the "Harefield drug protocol").[14] The RESTAGE-HF trial (REmission From STAGE D Heart Failure) included 40 highly selected patients with a HeartMate II device from 6 different centers (practically all fulfilling the predictive criteria listed in Table 1). Survival free from mechanical support/heart transplantation at 1 year after LVAD explantation was achieved in 40% of patients. Although it is not clear whether recovery was due to patient, device, or medication selection (there was no control group differing in these points), the results confirm that some patients may be successfully

weaned from LVAD and may sustain their own cardiac pump function, if treated by specialized experts.[11-14]

The aforementioned approach using stem cell therapy for cardiac regeneration was tested in patients with LVADs by several studies, including a prospective randomized trial (159 patients were randomized to an intramyocardial injection of mesenchymal precursor cells or sham at the time of LVAD-implantation).[46,47] Unfortunately, the authors failed to show a relevant effect. Currently, several clinical trials are ongoing assessing different delivery and application techniques using combined stem cell/tissue-engineering approaches.[47]

One aspect that can be addressed at the time of device implantation is the management of concomitant cardiac pathologies. Many patients with LVADs either present with additional (mostly mitral and tricuspid) or develop (mostly aortic) valve pathologies during VAD implantation or ongoing support.[48,49] These additional valve pathologies affect VAD therapy in 2 ways. First, they may affect hemodynamic benefit of VAD support. Second, they may affect hemodynamic performance after VAD removal. It is the general notion that relevant aortic regurgitation may not be present for VAD implantation, that severe mitral regurgitation may be left untreated for the unloading effect of the VAD, and that at least severe tricuspid regurgitation should also be addressed during VAD implantation.[4,5] This notion gains a different perspective once a BTR strategy is pursued.[50] Thus, addressing valve dysfunction during VAD implantation may be performed more liberally than under BTT or DT strategies.[49] For instance, current recommendations do not support concomitant mitral valve surgery for severe regurgitation,[49] which would certainly change if future explantation is planned. Similarly, addressing the tricuspid valve is controversially discussed even for BTT or DT conditions. Based on our experience, concomitant tricuspid valve repair did not increase surgical risk but reduced the incidence of right heart failure.[51] In general, valve function should be optimal if explantation is the goal. Even percutaneous valve interventions may be valuable treatment options before explant. However, they are not always suitable for the individual valve pathology and their durability is also unclear. For instance, there is no readily applicable (or approved) device to treat pure aortic valve regurgitation, which occurs in 15% to 52% of patients on LVAD support.[5,49] Therefore, heart transplantation or aortic valve replacement remain as current practice. Irrespective of the chosen treatment strategy, sufficient and reliable valve function is important to give a "realistic" assessment of cardiac function before LVAD withdrawal.

WEANING PROTOCOLS AND EXPLANTATION CRITERIA

As mentioned previously, predicting VAD-induced recovery is difficult. It has been suggested to treat all patients with VAD and nonischemic cardiomyopathy as potential BTR candidates,[5,12] but assessing native heart function during VAD support and predicting long-term fate of recovery after VAD explantation is complex. Defining weaning conditions and protocols is perhaps the most challenging part. The use of BNP or isolated exercise testing has been suggested to guide these efforts[12,13,52]; however, both readouts have shown only limited prognostic value.[12,14]

Standardization of screening protocols are recommended to increase the pool of patients who are BTR.[11,12,14,32] Although several groups have published their experience with VAD weaning, no universal weaning protocol exists. Since the mechanisms of heart failure and recovery are heterogeneous and not yet fully understood, current work is bound to be experience-based. Thus, VAD centers have developed their own therapeutic strategies for their patients with VAD.

We addressed the "Harefield drug protocol" previously. In addition, weaning efforts were reported from groups in New York (Formica and colleagues[13]), Houston (Frazier and colleagues[12]) and Berlin (Potapov and colleagues[11,32,53]). They all apply GDMT and optimize unloading through the VAD. In case functional recovery is evident on echocardiogram, all groups perform hemodynamic assessment at rest and under various stress conditions at reduced pump speed settings. A period of "zero net flow" is assessed in all centers by running the "low operating mode" (eg, HVAD 1800-2200 rpm, HeartMate 3 3000-4300 rpm, HeartMate II 6000 rpm). In addition, the Berlin group also includes measurements with the pump fully stopped while the outflow graft is occluded with a balloon.[11,32,53] We adopted the Berlin protocol but chose not to occlude the outflow graft with a balloon for fear of shearing off emboli from the neointima usually present inside the Dacron outflow graft. However, there is general consensus on the explantation criteria, which include the following key parameters: on echocardiography, left ventricular end-diastolic diameter <6.0 cm, left ventricular ejection fraction ≥45%; for right heart catheterization, cardiac index >2.6 L/min/m^2, mean wedge pressure <16 mm Hg, and mean atrial pressure <10 mm Hg measured at different pump speed settings, at rest, and exercise.[11-14]

TECHNICAL ASPECTS OF EXPLANTATION

Once the decision for VAD explantation is made, technical aspects move into focus. Figure 2 shows published strategies for discontinuation of mechanical ventricular support.[13,54,55,57] VADs can be explanted by either full removal of the pump with or without in- and outflow graft (Figure 2, *A* and *B*) or by deactivation and leaving different degrees of device material in the patient (decommissioning, Figure 2, *C-E*). If complete device removal is required (mainly due to device infection or thromboembolic events), the entire system can be explanted via full redo sternotomy

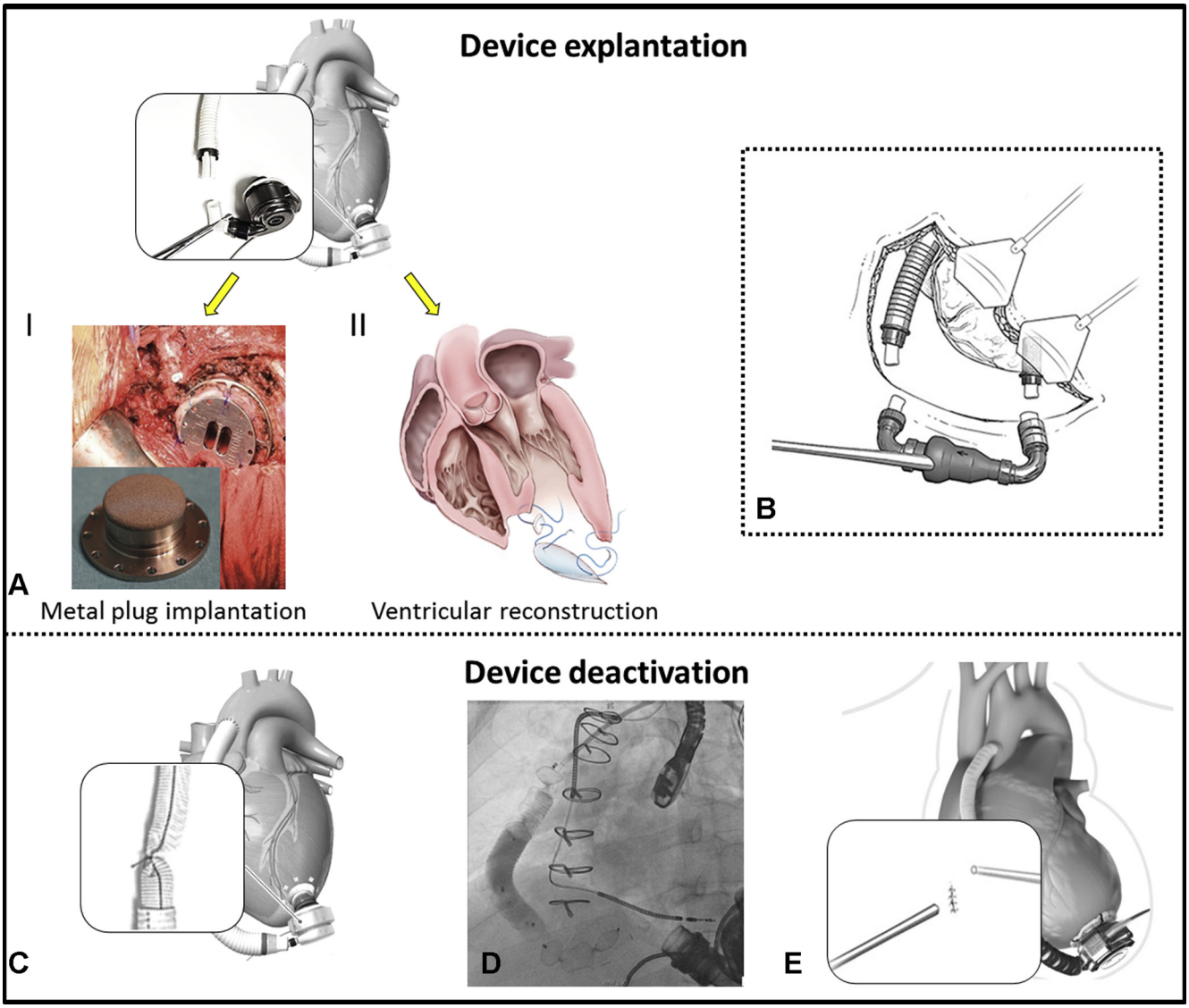

FIGURE 2. Schematic illustration of VAD-explantation techniques. Modified after Hanke and colleagues,[54] Albulushi and colleagues,[55] and Baldwin and colleagues.[56] A, Complete device explant. I, Apical cannula site can be closed with a custom-made metal plug or II, ventricular patch reconstruction. B, Incomplete pump explant leaving in- and outflow graft cannula. Device deactivation blocking the blood flow by C, outflow graft ligation, D, AMPLATZER Vascular plug implantation and, E, driveline transection.

or subcostal access with or without additional secondary incisions (partial sternotomy or thoracotomy). Several options for apical closure of the left ventricle have been described (usually requiring cardiopulmonary bypass). We and others have occluded the apex with a custom-made plug and preservation of the sewing ring (Figure 2, *A*, I).[54,58] This technique potentially allows VAD removal off-pump and also facilitates VAD-reimplantation, if needed. Schmitto and colleagues[57] describe a ventriculoplasty technique with complete removal of the sewing ring (Figure 2, *A*, II). LVAD decommissioning has emerged as a valuable alternative, avoiding invasive reoperation with the known complications of complex redo surgery.[10] With this technique, the deactivated device is left in place and the blood flow though the pump is interrupted. This can be achieved by outflow graft ligation through a small thoracotomy or subcostal incision (Figure 2, *C*)[59] or percutaneously by placing an AMPLATZER Vascular Plug II in the outflow graft (Figure 2, *D*).[55] Outflow graft occlusion may also occur spontaneously in case of full pump thrombosis (Figure 2, *E*).[56] In all of these conditions, the driveline is cut at the exit site (Figure 2, *C-E*).

Patients with LVAD require continuous anticoagulation, which may change after explant or decommissioning. There is no consensus regarding the anticoagulation regimen under these conditions. Temporary anticoagulation[54,58,59]

and dual- and single-antiplatelet therapy have been described.[52,60] It appears that the need for medical therapy in general (ie, including anticoagulation or antiplatelet therapy) is best tailored to the individual patient.[10]

CONCLUSIONS

VAD-induced myocardial recovery is a possible but rare scenario in the treatment of patients with terminal heart failure. Patient characteristics, surgical strategy, and specialized expertise for weaning and explantation of VADs determine the perspective and success of a BTR strategy. While the main difficulty for weaning lies in the assessment of native cardiac function under VAD support and the prediction of stability of recovery, there appears to be consensus that standardized screening protocols increase the chance for patient recovery. Despite these efforts, potential relapse of heart failure and our current inability to predict which patient sustainably benefits remain major challenges for future research.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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