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Review

Evaluation of Cardiac Recovery in Ventricular Assist Device Recipients: Particularities, Reliability, and Practical Challenges

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ABSTRACT

In carefully selected patients with ventricular assist devices (VADs), good long-term results after device weaning and explantation can be achieved when reverse remodelling and improvement of native cardiac function occur. Monitoring of cardiac size, geometry, and function after initial VAD implantation is necessary to identify such patients. Formal guidelines for recovery assessment in patients with VADs do not exist, and protocols for recovery assessment and criteria for device weaning and explantation vary among centres. Barriers to evaluation of cardiac recovery include technical problems in obtaining echo images in patients with VADs, time restrictions for necessary VAD reductions/interruptions during assessment, and regurgitant flow patterns that occur with interruption of continuous flow VADs. The few larger studies addressing cardiac recovery after VAD implantation employed varied study designs, limiting interpretation. Current clinical practice is guided largely by local practice patterns, case reports, and small case series, and the available body of research—consisting mostly of expert opinions—has not been systematically addressed. This summary reviews evidence and expert opinion on VAD-promoted cardiac recovery assessment, its reliability, and associated challenges.

RÉSUMÉ

Chez les patients soigneusement sélectionnés, porteurs d'un dispositif d'assistance ventriculaire (DAV), on peut s'attendre à obtenir de bons résultats à long terme après le sevrage et l'explantation lorsque surviennent le remodelage inverse et l'amélioration de la fonction cardiaque native. Le monitorage de la taille, de la géométrie et de la fonction cardiaque après l'implantation initiale du DAV est nécessaire pour identifier ces patients. Il n'existe pas de lignes directrices formelles sur l'évaluation du rétablissement des patients porteurs d'un DAV, mais on observe que les protocoles d'évaluation et les critères du rétablissement pour le sevrage et l'explantation du dispositif varient selon les centres. Parmi les obstacles à l'évaluation du rétablissement cardiaque, on retrouve les problèmes techniques dans l'obtention des images échocardiographiques chez les patients porteurs d'un DAV, les restrictions de temps pour les réductions/interruptions nécessaires du DAV durant l'évaluation, et les profils du débit de régurgitation qui surviennent lors de l'interruption des DAV à débit continu. Quelques études plus vastes qui portent sur le rétablissement cardiaque après l'implantation d'un DAV n'ont pas de plan d'étude comparable. La pratique clinique actuelle est en grande partie orientée par les schémas de pratique locale, les observations et les petites séries de cas, mais le corpus de recherche disponible, qui est principalement composé de l'opinion d'experts, n'a pas été abordé de manière systématique. Ce résumé passe en revue les données probantes et l'opinion d'experts sur l'évaluation du rétablissement cardiaque favorisé par le DAV, sa fiabilité et les enjeux qui y sont associés.

Ventricular assist device (VAD) implantation has become a commonplace bridge-to-transplantation or destination therapy option for drug-refractory end-stage heart failure (HF). For some patients, left-ventricular, biventricular, and isolated right-ventricular assist devices (LVADs, BiVADs, and RVADs, respectively) can also become a bridge to recovery. Although cardiac remodelling in chronic HF has often been considered to be unidirectional and irreversible, there are an increasing number of reports of successful weaning from LVADs not only for acute (ie, postcardiotomy and viral myocarditis-related HF) but also for chronic HF (especially of nonischemic origin, more rarely also of ischemic origin).[1-7] Thus, VADs can provide the basic preconditions for the possible regression even of chronic cardiac alterations.[2,5,8]

As a bridge-to-recovery VAD setting might be underused at present, further development of diagnostic tools for VAD-related cardiac recovery could assist to recognize candidates and noncandidates for VAD explantation. There is much to

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be done here because the few larger studies on cardiac recovery assessment in VAD recipients do not have comparable study designs. Clinical practice is still shaped largely by local practice patterns, case reports, and small case series, and the available body of research, consisting mostly of expert opinions, has not been systematically addressed.

This review summarizes the evidence and expert opinion related to the assessment of VAD-promoted cardiac recovery (for article selection methods see the Supplementary Material). Special attention is given to the reliability of recovery assessment and the particular challenges posed by the unusual conditions under which that assessment takes place. The review aims to provide a theoretical and practical basis for clinicians and researchers engaged in this timely and demanding topic.

Unloading-Promoted Cardiac Recovery

VAD-promoted myocardial recovery includes multilevel reversal of structural and functional alterations, which can induce remission of cardiac disorders or, more rarely, complete cardiac recovery.[9] Long-term postweaning freedom from recurrence of HF was documented for patients who have recovered from acute forms of HF and also for partially or completely recovered patients with preimplant chronic cardiomyopathy (CCM).[2,10]

With few studies on reverse remodelling/functional improvement in weanable VAD recipients—as well as varying etiology, severity, and pharmacological treatment of HF—not all mechanisms involved in the potential weaning/explantation process are fully understood. Although at cellular and sub-cellular levels, there is a high incidence of significant reversal of disorders relating to the HF phenotype, usually this reverse remodelling is incomplete.[8,11,12] It is still unknown which of the various cellular and subcellular changes that occur during reversal of the HF phenotype are most important and/or necessary for restoration and long-term preservation of ventricular structure and function.[9,13] At present, assessment of remission/recovery in VAD recipients and weaning decision making are still based on evaluations of cardiac morphology and function on organ level by echocardiography (ECHO) and right-heart catheterization (RHC).[10,14,15] In weaned patients with normalization of cardiac function, it is clinically impossible, as long as the postexplant ECHO and RHC parameters remain normal, to differentiate between recovery and remission.[9] Pre-explant prediction of postweaning cardiac stability, essential for weaning decisions, is particularly challenging.

Recovery Assessment in LVAD Recipients

Tools for recovery assessment

ECHO and RHC are the mainstays of recovery assessment and weaning decision making in LVAD recipients. A concept of the 4-stage approach to weaning, based mainly on ECHO and RHC measurements, which was applied by the Berlin group, is illustrated in Figure 1. Native cardiac remission/recovery assessment in LVAD recipients is challenging because all essential measurements require short-term interruptions of LVAD support.

Echocardiography. ECHO is the primary imaging modality for the selection of weaning candidates, and, together with RHC, it is also mandatory for weaning decisions.

Selection of weaning candidates. Serial transthoracic echocardiography (TTE) screening with normal LVAD function is necessary for selection of potential weaning candidates (patients with significant LV reverse remodelling and functional improvement). In clinically stable LVAD recipients, screening can be started after 2 to 4 weeks.[16] Potential weaning candidates are those with sinus rhythm, normal LV end-diastolic diameter (LVEDD), improvement of LV wall motion, no or $\leq$ grade 1 mitral and/or aortic valve (AV) regurgitation, no right ventricular (RV) dilation and no or $\leq$ grade 2 tricuspid regurgitation (TR) during full LVAD support (Fig. 1).[2,9,14,15] A progressive increase in the duration and frequency of AV openings during unchanged pump rate also indicates improvement of LV contractile function.[5,6,17-19] In potential weaning candidates, it is useful—before assessing the heart during complete interruption of LVAD support—to perform stepwise pump rate reductions under TTE monitoring to verify whether complete unloading interruption trials are possible and also safe.[2,14,15,20] If such pump rate reductions provoke symptoms (dizziness, sweating, etc) and/or significant cardiac arrhythmias, or if the LVEDD increases beyond the normal range, and/or the right side of the heart shows morphological and functional instability (increasing TR, RV dilation with reduced output), the patient is not a weaning candidate, and unloading interruption trials are not yet indicated (Fig. 1).

ECHO examination of weaning candidates. Challenges with ECHO examination. ECHO assessment of recovery is mostly based on data obtained at rest during repeated short-term interruptions of LV unloading (off-pump or pump turn-down to zero unloading trials).[2,5,14,15,21-28] Even under optimal anticoagulation, the duration of LVAD support interruptions should be limited to $\leq$ 15 minutes.[2,14,15] This time restriction results in several challenges with regard to ECHO data collection and their interpretation. A major challenge is the prediction of postexplant long-term cardiac stability based on data collected during only short interruptions of LVAD support.

Pulsatile LVADs allow optimal ECHO assessment of the native heart during complete pump-stops (real off-pump trials). To prevent blood stagnation, stopped devices should be allowed to pump at least once a minute, or 3 bursts of pneumatic hand pumping should be intercalated every 15 to 60 seconds.[1,2,15,16,21,22] These necessary procedures can affect the validity of ECHO measurements and therefore pose major challenges for investigators.

Continuous flow (CF) pumps, when completely stopped, allow retrograde flow into the LV, which induces a misleading LVEDD increase (volume overload) plus reduction of the diastolic arterial pressure (PA_d). By reducing the LV afterload, PA_d reduction can generate overestimation of LV systolic function.[2,17] The retrograde flow into the LV represents a serious problem for the prediction of cardiac stability after LVAD explantation. For such pumps, rotor-speed reduction (turn-down trials) to values resulting in $\pm$ zero flow in 1 cardiac cycle is therefore better than complete

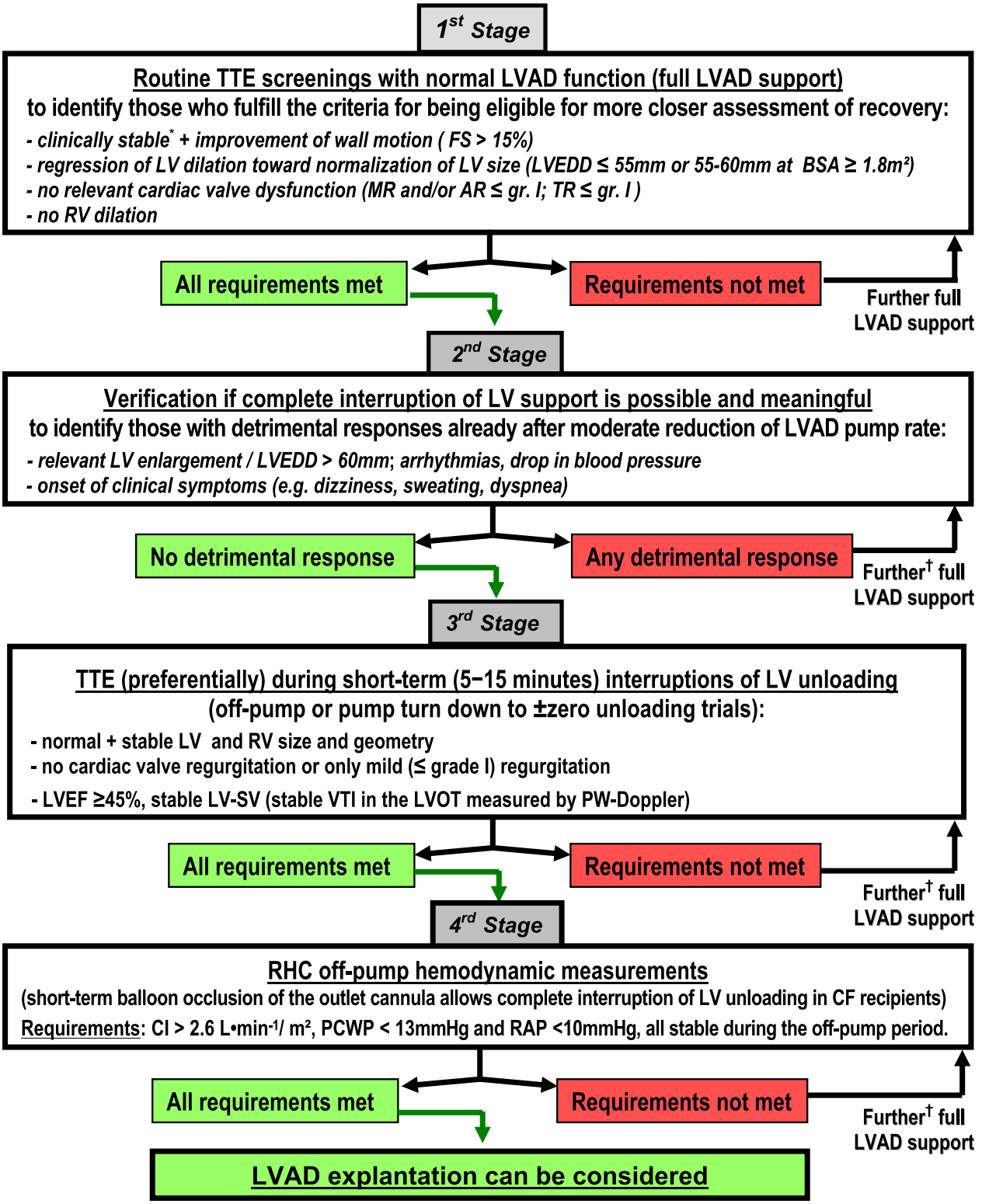

Figure 1. Proposed steps for assessment of LVAD-promoted reversal of HF-inducing cardiac alterations and selection of weaning candidates. AR, aortic regurgitation; BSA, body surface area; CF, continuous-flow; CI, cardiac index; FS, fractional shortening; HF, heart failure; LV, left ventricle; LVAD, left ventricular assist device; LVEDD, LV end-diastolic diameter; MR, mitral regurgitation; PCWP, pulmonary capillary wedge pressure; PW, pulsed-wave; RAP, right atrial pressure; RHC, right heart catheterization; RV, right ventricle; SV, stroke volume; TR, tricuspid regurgitation; VTI, velocity-time integral. * Including adequate renal, hepatic, neurologic, and pulmonary function. † Re-evaluation after 2 to 4 weeks.

pump-stop.[2,5,14,15,17,23,24] The optimal pump speed to achieve "zero net flow" varies depending on the type of pump (eg, 4000 to 6000 rpm for HeartMate 2 [HeartMate, Abbott, Abbott Park, Illinois], 3000 to 4300 rpm for HeartMate 3, and 1800 to 2200 rpm for the HeartWare HVAD[HeartWare, Medtronic, Framingham, Massachusetts]).[15,20,25] Doppler measurements of forward and reverse velocity time, integral at the inflow cannula, allow adjustment of pump speed until zero net flow is reached.[20,25-28]

After months of ongoing unloading, even short periods of physiological loading induced by interruptions of the LVAD support can present serious challenges for a possibly incompletely recovered LV. Experimental studies showed that after unloading-promoted restoration of LV structure and function, recovered hearts are initially vulnerable to hemodynamic stress and that this vulnerability diminishes only over time.[29] Hence, it is reasonable to avoid any potential myocardial exhaustion that might interfere with the possibly still ongoing recovery not only before but also early after VAD explantation (Fig. 2). Therefore, patients who were electively weaned from long-term VADs by the Berlin group underwent recovery assessment exclusively at rest.[14,24,28,30] Despite the lack of information about inotropic reserves and cardiac adaptation to stress, the weaning results obtained in Berlin were not worse than those reported by groups that additionally used dobutamine stress echocardiography (DSE) and/or exercise testing for recovery assessment.[14,15,20,24,31-34]

Supine bicycle exercise stress echocardiography (ESE) and off-pump DSE can provide useful information on ventricular adaptation to physical stress and can be helpful for weaning decision making.[15,33,34] In HeartMate 2 LVAD recipients who remained symptom free at rest during a 15-minute pump reduction to 6000 rpm, the Harefield group also used a 6-minute walk test with and without pump rate reduction, followed by repeated ECHO measurements, to determine the LV response to exercise (inotropic reserve).[27] Possible myocardial overstressing by DSE and ESE with negative impact on the myocardial recovery cannot be excluded.[10] Further studies are therefore required to establish both the real benefits and the possibly harmful side effects of DSE and ESE for the assessment of LVAD-promoted cardiac recovery.

During an off-pump or pump turn-down trial, it is preferable to perform the ECHO assessment step-by-step in the course of repeated short term (~5minutes) unloading interruptions, which are safer for the patient than 1 or 2 longer (15- to 20-minute) interruptions.[24] The optimal duration of LVAD interruptions for the evaluation of the stability of cardiac recovery is not defined.[5,10] Nonetheless, 15- to 20-minute complete interruption of LVAD support in the operating room (without external interference on myocardial inotropy or ventricular preload and afterload) is mandatory for the final ECHO evaluation concerning the decision in favour of or against LVAD explantation.[14,21,28]

A particular challenge for the ECHO assessment of LV function may arise in the presence of low systemic AP_d, which often occurs during CF pump turn-down trials.[22,35] In such cases, the reduced LV afterload can misleadingly increase the off-pump left ventricular ejection fraction (LVEF). Thus, even in patients with pre-explant LVEF $\geq$ 45%, an off-pump AP_d $\leq$ 50 mm Hg is a risk factor for postweaning recurrence of HF.[35]

Complete pump-stop or pump turn-down to $\pm$ zero flow is not indicated (risky) in patients with histories of stroke/transient ischemic attack, in those with hemolysis or difficulties in anticoagulation therapy, and especially when pump thrombosis is suspected (even in the absence of LVAD-related mechanical problems).[5]

ECHO measurements for assessment of cardiac improvement. ECHO assessment of recovery during off-pump/pump turn-down trials should be as comprehensive as possible and should include the use of tissue-Doppler imaging (TDI) and speckle–tracking-derived strain echocardiography (STE).[5,14,24,36] Table 1 shows the most useful ECHO measurements for the assessment of cardiac improvement. Doppler examinations can be hampered by LVAD-induced artefacts. The HeartWare LVAD impeller often generates color and spectral Doppler artefacts that impair or prevent Doppler assessment of the inflow cannula and/or the evaluation of 1 or more cardiac valves.[17,37]

TDI and STE provide important information on native cardiac remission.[14,21,24] Advantages of STE are its ability to differentiate between active and passive movement of ventricular wall segments, the angle independency of measurements, and the possibility to quantify intraventricular asynchrony and dyssynergy plus evaluating components of myocardial contractile function (such as longitudinal myocardial shortening) that cannot be visually assessed.[38,39] A limitation of STE is its dependence on image quality. Figures 2 and 3 show the usefulness of STE for the assessment of recovery after LVAD implantation.

Not all ECHO parameters with impact on weaning decisions can be reliably measured in all patients because of poor image quality in some LVAD recipients, particularly if off-pump Doppler and STE measurements have to be performed during rotor-speed reduction instead of complete pump-stop. At present, there are no generally valid guidelines for ECHO assessment of cardiac recovery in LVAD recipients, and evidence for core applications is also limited. For newer CF pumps, there are also only few studies, some of which show conflicting results.[23]

Right-heart catheterization. RHC is the second major cornerstone for the assessment of LVAD-promoted cardiac improvement.[24,40] RHC is necessary before preliminary decision-making in weaning candidates (particularly in those with borderline ECHO data and/or long-lasting preimplant HF).[14] Final hemodynamic measurements during a $\geq$ 15-minute off-pump trial in the operation room are mandatory for the decision in favour of or against LVAD explantation.[10,14] In CF pump recipients, preliminary RHC-derived data are more reliable if measurements are preceded by occlusion of the outflow cannula with an inflated balloon, allowing complete pump-stops without any misleading retrograde blood flow into the LV.[24,38]

Normal (or at least borderline-normal) and stable off-pump hemodynamic parameters are requirements for decisions in favour of LVAD explantation.[10,24] A resting cardiac index (CI) > 2.6 L/min/m^2 that remains stable during the final pre-explant off-pump trial is an essential precondition before LVAD explantation. In patients with borderline ECHO data and a long history of preimplant HF, resting CI

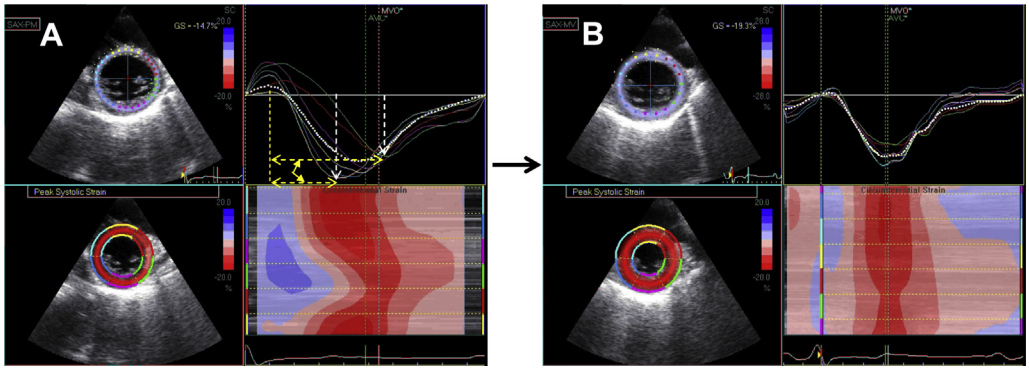

Figure 2. Postweaning improvement of left ventricular (LV) function in a patient with idiopathic dilated cardiomyopathy as the underlying cause for LV assist device (LVAD) implantation. Two months after LVAD explantation (**A**), speckle–tracking-derived recordings of LV circumferential strain revealed regional differences in both the time-to-peak systolic strain and the peak systolic strain value (ie, relevant systolic asynchrony and dyssynergy). The delayed contraction of the lateral wall also persists in the early diastole. Two months later (**B**), both asynchrony and dyssynergy disappeared, the global systolic circumferential strain improved from −14.7% to −19.3% (ie, 31.3% increase), and the LV relaxation has become quite normal.

values $\geq$ 2.8 L/min/m^2 are desirable.[24,40] Other pre-explant requirements are off-pump pulmonary capillary wedge pressure (PCWP) $<$ 12 mm Hg and right atrial (RA) pressure $<$ 10 mm Hg.[24,40]

RHC measurements during a supine bicycle exercise test for the assessment of cardiac recovery were also performed in a small number of LVAD recipients.[41] So far, there are no data about the risk-to-benefit ratio of RHC measurements during exercise for the evaluation of recovery.

Cardiopulmonary exercise testing. Exercise capacity of HF patients with full LVAD support as measured by peak oxygen consumption (pVO_2) and VO_2 at the anaerobic threshold can be comparable with that of heart transplant recipients, even in LVAD recipients without improvement of the native LV function.[42] However, cardiopulmonary exercise testing (CPET) during reduced LV support (ie, LVAD flow reduction to $\approx$1.6 L/min) can already result in $\approx$ 25% lower pVO_2 in comparison with the pVO_2 value attained by the same patients with full hemodynamic LVAD support.[6] Thus, assessment of cardiac recovery by means of CPET also necessitates a short-term interruption of the LVAD support.

Because exercise capacity is also related to extracardiac factors, a low pVO_2 alone does not always reliably identify patients with severe hemodynamic dysfunction during exercise.[43,44] The multifactorial dependency of pVO_2 may explain why some HF patients can have a favourable prognosis despite low pVO_2. The combined use of pVO_2 measurements (expressed as the percentage of its maximal predicted values) and variables of exercise hemodynamics (eg, peak exercise CO and stroke work index) facilitates categorization of the patients with low pVO_2 regarding the severity of their myocardial dysfunction.[44]

CPET with full LVAD support and during temporary interruption of the support (CF pump turn-down to $\approx$ zero flow) was also used for assessment of recovery in LVAD recipients.[15,45] Nevertheless, a multicentre study revealed that the CPET-derived variables have only limited capability to reflect cardiac organ function in LVAD recipients.[45] Therefore, pVO_2 and other CPET-derived variables should be used with caution in the evaluation of LVAD-promoted cardiac recovery. Considering that recovered hearts are initially vulnerable to hemodynamic stress, the question also arises whether it is worth taking the risk of myocardial overstressing when the CPET-derived measurements have only limited ability to reflect cardiac pump function.[29] The Berlin group weaned a total of 136 patients from their VAD between 1995 and 2015 without using CPET for the assessment of recovery.[10]

Prognostic value of ECHO and RHC for postweaning cardiac stability

TTE parameters in connection with RHC-derived hemodynamic measurements collected during short-term interruptions of LVAD support allow identification of patients with the potential to remain free from postweaning HF recurrence for several years after LVAD explantation. This applies particularly when the stability of TTE measurements during and between the LVAD interruption trials (performed over the next 2 to 4 weeks after maximum LV improvement) is also considered (Table 2).[21,24,26]

A clinical profile that should encourage the consideration of elective LVAD explantation is that of shorter duration of HF, nonischemic etiology, younger patient age, and cardiac improvement within the first 6 months of LVAD support.[4,5,16,21,22,46]

In patients with normal RHC-derived off-pump hemodynamics before explantation, off-pump LVEF $\geq$ 45% at rest showed a predictive value of 74% for $\geq$ 5-years postexplant cardiac stability.[24] In combination with either HF duration of $\leq$ 5years before LVAD support or normal final off-pump LV end-diastolic size and/or geometry, or LV peak systolic wall-motion velocity (Sm) $\geq$ 8cm/s, that predictive value can reach 86%.[21,24] When considering the pre-explant stability of LV size, geometry, and EF during the time period between LV maximum improvement and LVAD removal, as well as during the off-pump TTE trial before LVAD explantation, the predictive value of TTE for postexplant stability for the next $\geq$ 5years can reach 93%.[24] In patients with normal

Table 1. Echocardiographic measurements and measurement-derived parameters for evaluation of cardiac recovery during off-pump/pump turn-down trials[2,5,15,20-24,36,38]

ECHO techniques	Measurements and key parameters
M-Mode and 2D ECHO	• Left ventricle (LV) - End-diastolic diameter (LVEDD) in the PSLAX view - End-systolic diameter (LVESD) in the PSLAX view - End-diastolic relative wall thickness (RWT_{ED})* in the PSLAX view - End-diastolic short/long axis ratio (S/L_{ED}) in the apical 4C view - Ejection fraction (LVEF) • Right ventricle (RV) - End-diastolic dimensions (on parasternal and apical views) - End-diastolic short/long axis ratio (S/L_{ED}) - Fractional area change (FAC) - Tricuspid annulus peak systolic excursion (TAPSE)
Flow-Doppler imaging (CW-Doppler, PW-Doppler colour-flow mapping)	• Parameters and indices of LV diastolic function (apical 4C views) - Transmitral flow E and A wave velocity, E wave deceleration time, E/A velocity ratio - Isovolumetric relaxation time • Parameters for LV systolic function - Isovolumetric contraction time (apical 4C view) - Stroke volume (SV)† • Detection and quantification of cardiac valve regurgitations • Pulmonary arterial systolic pressure estimation (apical 4C view, in patients with TR)
Tissue-Doppler imaging	• LV systolic wall motion peak velocity (Sm) (measured with PW-TD at the basal posterior wall on parasternal view images) • Tricuspid lateral annulus peak systolic wall motion velocity (TAPS') (measured with PW-TD on apical 4C view images).
Speckle tracking 2D-strain imaging	• LV radial, circumferential and longitudinal global peak systolic strain and strain rate • LV intraventricular dyssynchrony index of contraction ($IVDSI_{LV}$)‡ • LV dyssynergy index of contraction§

2D, 2-dimensional; A wave, late filling velocity (atrial contraction); CW, continuous wave; ECHO, echocardiography; E wave, early filling velocity; 4C, 4 chamber; PW, pulsed wave; PW-TD, pulsed-wave tissue Doppler; PSLAX, parasternal long axis; TR, tricuspid valve regurgitation.

*RWT_{ED} = (end-diastolic interventricular septum thickness + end-diastolic posterior wall thickness) / LVEDD.

†SV = LV outflow tract (LVOT) cross-section area (in the PSLAX view). velocity time integral obtained by tracing the PW-Doppler signal's envelope in the LVOT (measured on apical view images).

‡$IVDI_{LV}$ = standard deviation (SD) of the time-to-peak systolic strain (TPS) / mean value (M) of time-to-peak systolic strain ($IVDI_{LV} = SD_{TPS} / M_{TPS}$).

§LV dyssynergy index = coefficient of variance of the 6 regional strain values at the end of the LV systole, before the aortic valve closure, and/or at the LV mid-systole.

pre-explant off-pump hemodynamics, stable off-pump LVEF $\geq$ 45% at rest, plus normal and stable LV size and/or geometry, the probability of freedom from HF recurrence over the next 10 postexplant years can reach 90%.[24]

Off-pump hemodynamic data alone are insufficiently predictive for postexplant long-term freedom from recurrence of HF.[10,24] Only the combined use of ECHO- and RHC-derived measurements can predict postexplant stability of cardiac function in weaning candidates who appear suitable for LVAD explantation. DSE and ESE can also be used for pre-explant prediction of cardiac function after LVAD removal.[15,32,33] Dobutamine-induced improvement in LVEF and dP/dt with simultaneous decrease in LVEDD, plus an increase in the CI, might be helpful findings for the prediction of sustained cardiac stability after LVAD explantation.[15,33]

There are many risk factors for postexplant recurrence of HF that are detectable by ECHO and RHC. In patients with pre-explant LVEF < 45%, and in those with unstable LVEF $\geq$ 45% (ie, LVEF alteration in comparison with previously attained maximum values and/or LVEF reduction in the course of the final off-pump trial), the predictive value for recurrence of HF during the first 3 postweaning years can reach 88% and 90%, respectively.[21,24] In patients with pre-explant LVEF $\geq$ 45%, but insufficient reverse remodelling of the LV or unstable LV geometry during the final off-pump trial, the predictive value of these measurements for recurrence of HF within the first 3 years after LVAD removal can reach up to 89% (Table 3).[21,24] In patients with pre-explant LVEF $\geq$ 45%, but with low or unstable Sm values, predictive values for recurrence of HF during the first 3 postexplant years can reach between 83% and 90%.[21,24]

Assessment of Recovery in BiVAD Recipients

Recovery assessment in long-term BiVAD recipients

ECHO and RHC are also the mainstays of cardiac remission/recovery assessment in BiVAD recipients and decision making in favour of or against BiVAD explantation or only RVAD explantation (switching from BiVAD to LVAD). Criteria for weaning from long-term BiVADs, although possible, are less likely, owing to the severity of the initial disease prompting BiVAD implantation.[10,14,47] Nevertheless, for patients who become eligible for weaning, BiVAD removal can provide long-term results comparable to those reported for LVAD explantation.[10]

Assessment of cardiac remission after BiVAD implantation is similar to that after LVAD implantation but more challenging. It is necessary that both pumps be stopped, but the RV pump should be stopped ~ 30s earlier than the LV pump.[10,24] Even under optimal anticoagulation therapy, the repeated pump-stops should be short (only 3 to 5minutes). In patients with insufficient recovery, as already shown during the first 3minutes, the off-pump trial should be cancelled. In those with relevant cardiac remission, the final decision in favour of or against BiVAD explantation must be preceded by a final off-pump trial of $\geq$ 15 minutes in the operating room.[10] During the off-pump trials, special attention should be paid to the RV size, geometry, and load as well as to the TR. RV end-diastolic diameter and short-/long-axis ratio increase and/or an increase in TR, as well as a RA pressure rise up to $\geq$ 10 mm Hg, indicate inadequate RV function. This can be caused by insufficiently improved RV myocardial contractility, by an increase in resistance in the pulmonary circulation (due to insufficiently improved LV function), or

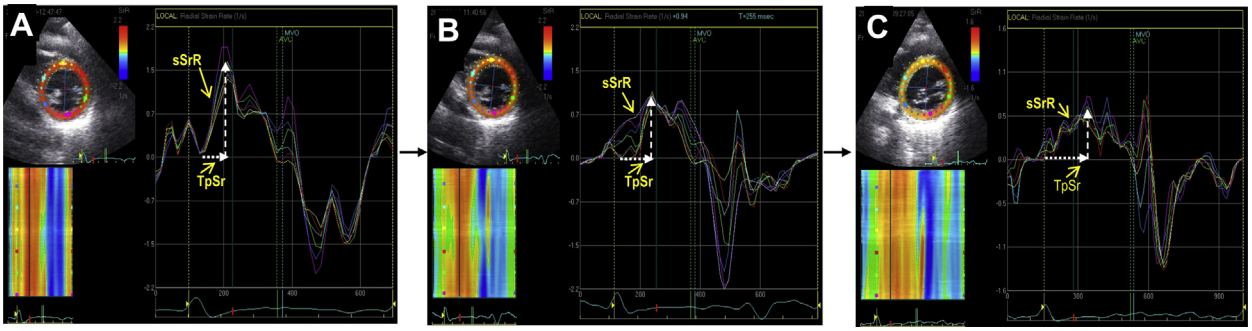

Figure 3. Off-pump systolic radial strain rate alterations before LVEF worthening in a left ventricular assist device (LVAD) recipient with a previously overlooked giant cell myocarditis. After LVAD implantation, there was initially an improvement of LV systolic function. At the time of maximal improvement (**A**), the LV ejection fraction (LVEF) reached 55%, and the global peak systolic radial strain rate (sSrR) reached its maximum value (1.6/s). Two weeks later (**B**), although the LVEF remained stable (55%), the global peak sSrR dropped down (0.98/s) and was also accompanied by a prolongation of the time-to-peak strain rate (TpSr). After another 4 weeks (**C**), the global peak sSrR reached only 0.68/s (57.5% below the maximum value) and was accompanied by further prolongation of the TpSr. In addition, there was a rather mild reduction of the LVEF to 50%. The weaning process was cancelled after the subsequently performed endomyocardial biopsy revealed signs of a giant cell myocarditis. With a striking delay of ~ 4 weeks, the off-pump LVEF dropped down to 35%.

by insufficient improvement of both ventricles. In such cases, if the PCWP is < 12 mm Hg, and the PAP remains unchanged or even declines, the cause for the RV morphological and functional alterations is insufficient improvement of RV contractility. In contrast, if RV alterations during the off-pump trial are accompanied by PCWP increase up to ≥ 13 mm Hg, plus relevant increase in the PAP, the main cause for RV changes is a high RV afterload, generated by still-impaired LV function.

If there is no evidence of adequate LV improvement but repeated interruptions of only the RV supporting pump do not lead to alterations in RV size and geometry, tricuspid valve

Table 2. Clinical value of echocardiography and RHC for pre-explant prediction of long-term freedom from HF recurrence in case of LVAD explantation[2,15,21,24,35,38-40]

Examination	Parameters and parameter-derived measurements during pre-explant off-pump trials (at rest, without inotropic myocardial support)	Predictive value for ≥ 5 years postweaning cardiac stability
TTE in patients with off-pump RHC measurements in the normal range	• LVEF ≥ 45% during the last pre-explant TTE off-pump* trial	74%†
	• LVEF ≥ 45% plus normal LVEDD (≤ 55 mm at BSA ≤ 1.8 cm^2) during the last pre-explant TTE off-pump* trial	86%†
	• LVEF ≥ 45% plus RWT_{LV} ≥ 0.38	87%†
	• Stable pre-explant LVEF ≥ 45% after maximal LV improvement and during the last pre-explant TTE off-pump* trial	86%†
	• LVEF ≥ 45% plus Sm ≥ 8cm/s, stable after maximum improvement and during the last pre-explant TTE off-pump* trial	87%†
	• Stable pre-explant LVEF ≥ 45% plus stable normal LVEDD after maximal LV improvement and during the last pre-explant TTE off-pump* trial	94%†
	• Stable VTI in the LVOT (PW-Doppler) during the last pre-explant TTE off-pump* trial (ie, stable LV stroke volume)	Alone not predictive for long-term post-explant freedom from HF recurrence, but all these Doppler-derived measurements, plus the exclusion of RV dilation, are a precondition for weaning success
	• No or only mild MR and/or AR	
	• No RV dilation (end-diastolic RVOT diameter < 35 mm, RV short/long axis-ratio in the apical 4C view < 0.6)	
	• No or less than grade II tricuspid and/or pulmonary valve regurgitation	
RHC‡	• CI > 2.6L^{-1}/m^2 BSA, without continuous reduction up to the end of the final pre-explant off-pump trial	RHC data are alone not predictive for long-term postexplant freedom from HF recurrence, but are a precondition for successful weaning
	• PCWP < 13 mm Hg, without continuous increase up to the end of the final pre-explant off-pump trial	
	• Right atrial pressure (mean) < 10 mm Hg without continuous increase up to the end of the final off-pump trial	

BSA, body surface area; CI, cardiac index; 4C, 4 chamber; HF, heart failure; LV, left ventricle LVAD, left ventricular assist device; MR and AR, mitral regurgitation and aortic regurgitation, respectively; LVEF, left ventricle ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVOT, LV outflow tract; PCWP, pulmonary capillary wedge pressure; PW, pulsed wave; RWT_{LV}, left ventricular relative wall thickness ([posterior wall thickness + ventricular septum thickness]/LVEDD); RHC, right heart catheterization; TTE, transthoracic echocardiography; VTI, velocity-time integral.

* Off-pump measurements imply either temporary pump stops (true off-pump trial) or temporary pump turn-down to values resulting in ± zero flow in 1 cardiac cycle, depending on whether the LVAD is a pulsatile- or a continuous-flow pump.

† Predictive value of the TTE parameter for ≥ 5years freedom from HF recurrence is valid only for patients with normal RHC-derived off-pump hemodynamic measurements before explantation.

‡ Measurements obtained during repeated pump stops with balloon occlusion of the outflow graft in CF LVAD recipients.

Table 3. Clinical value of echocardiography for pre-explant risk assessment for HF recurrence after LVAD explantation[2,15,21,24,35,38-40]

ECHO approach	Parameters and parameter-derived measurements during pre-explant off-pump trials in LVAD recipients with not worse than borderline RHC-derived off-pump hemodynamic measurements	Predictive value for HF recurrence after ≤ 3 years
Standard TTE at rest during interruption of LVAD support	• LVEF < 45% during the last pre-explant off-pump trial	88%
	• LVEF < 45% during the last pre-explant off-pump trial plus pre-implant HF duration of > 5 years	≈ 100%
	• Unstable LVEF ≥ 45% with pre-explant alteration of > 10% of best value	90%
	• LVEF ≥ 45% without normalization of LV size (insufficient reverse remodelling with LVEDD > 55 mm at BSA ≤ 1.8 cm^2)	89%
	• LVEF ≥ 45% with insufficient reverse remodelling (RWT_{LV} < 0.38)	82%
	• LVEF ≥ 45% with unstable reverse remodelling (RWT_{LV} reduction of > 8% during the last pre-explant off-pump trial)	87%
	• LVEF ≥ 45% with unstable LV geometry (S/L_{ED} increase of > 10% during the last pre-explant off-pump trial)	85%
	• LVEF ≥ 45% in the presence of low systemic AP_d (≤ 50 mm Hg)	Proven risk factors no data on their predictive value
	• Transmitral restrictive flow-profile (accentuation or new appearance)	
	• VTI reduction in the LVOT (= stroke volume reduction) during the final off-pump trials	
	• TR (new appearance or accentuation) and/or TR jet velocity increase during the final off-pump trials	
	• RVEDD increase ± RV geometry alterations during the final off-pum p trial	
TDI & 2D-STE at rest during interruption of LVAD support	• LVEF ≥ 45% with low wall-motion velocity (Sm < 8 cm/s)	83%
	• LVEF ≥ 45% with unstable wall-motion velocity (Sm alteration of > 10% during the final off-pump trials)	90%
	• LV myocardial asynchrony and dyssynergy during the final off-pump trials	Risk factor; no data on predictive value
Off-pump DSE	• Minor LVEF increase during DSE (absolute increase in LVEF by < 5%)	Risk factors; no data on their predictive value
TTE after 6 MW	• LVEF < 50% after 6MW	

AP_d, diastolic arterial pressure; BSA, body surface area; DSE, dobutamine stress echocardiography; ECHO, echocardiography; HF, heart failure; LV, left ventricle; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; RHC, right heart catheterization; RV, right ventricle; RVEDD, RV end-diastolic diameter; RWT_{LV}, LV end-diastolic relative wall thickness; S/L_{ED}, LV end-diastolic short/long axis ratio; 6MW, 6-minute walk; Sm, systolic wall motion peak velocity at the basal LV posterior wall; TR, tricuspid regurgitation; TDI, tissue Doppler imaging; TTE, transthoracic echocardiography; 2D-STE, 2-dimensional speckle tracking-derived echocardiography; VTI, velocity-time integral.

competence, right-sided heart filling pressures, and LV pump-flow, a switch from BiVAD to LVAD support should be considered. This is because RV improvement accompanied by reduction of RV pump-flow increases the probability of RV pump thrombosis, with a high risk for pulmonary embolism.[48,49]

Assessment of RV recovery in LVAD recipients with temporary RVADs

Because RV failure (RVF) is more likely reversible than similar magnitudes of LV failure, and reversal of both remodelling and impaired contractility usually require only short-term RV support, temporary RVADs (t-RVADs) are beneficial for LVAD recipients with RVF. More than 60% (> 80% in recent studies) of RVF cases in LVAD recipients become reversible by short- to medium-term RVAD support.[47,50-52]

In long-term LVAD recipients with additional t-RVAD support, candidate selection for t-RVAD removal can usually be started 48 to72 hours after t-RVAD implantation. Weaning candidates are clinically stable patients with adequate renal, hepatic, pulmonary, and neurologic function who show regression of RV dilation, improvement of RV-wall motion, and no significant TR.[53,54] Weaning is usually started with gradual reduction of RV pump-flow to 2L/min at 0.5-L/day increments under ECHO guidance and monitoring of hemodynamic responses (t-RVAD flow reduction below 2.0L/min for a prolonged period is not recommended).[53,55-57] PVR reduction by a phosphodiesterase-5 inhibitor can be beneficial for RV recovery assessment.[55] Septum-shifting toward the LV (sign for RV dilation), TR increase, RA pressure rise, and CI decrease (or LVAD-index decrease) during reduction of t-RVAD flow are major signs of insufficient RV recovery, necessitating interruption of the weaning process and a return to the initial RVAD settings.[55,58] If ECHO and RHC measurements remain stable during moderate reduction of t-RVAD flow, a short (5- to 10-minute) interruption of RV support is necessary for the actual assessment of RV recovery. If ECHO parameters remain stable and RHC measurements continue to be within the normal range, stable RV recovery is very likely (Fig. 4). For more reliable estimation of RV functional reserve in the absence of RVAD support, it can be useful to calculate the RV load adaptation index (LAI_{RV}) using the following formula: $LAI_{RV} = (VTI_{TR} \cdot L_{ED}) / A_{ED}$, where VTI_{TR} is the TR velocity-time integral (corresponds to the mean pressure-gradient between the RV and RA during RV systole), L_{ED} the end-diastolic RV long-axis length in the apical 4-chamber view, and A_{ED} the end-diastolic RV area (same view).[48,59,60] The LAI_{RV}, which is based on the relationship between RV load and RV dilation (including the RA pressure in the calculation), has proved to be highly predictive in LVAD candidates for the necessity of additional mechanical support for the RV.[60] An $LAI_{RV} \geq 18$ during interruption of RVAD support indicates normal ability of the RV to adapt its pump function to an increase in afterload, and therefore there

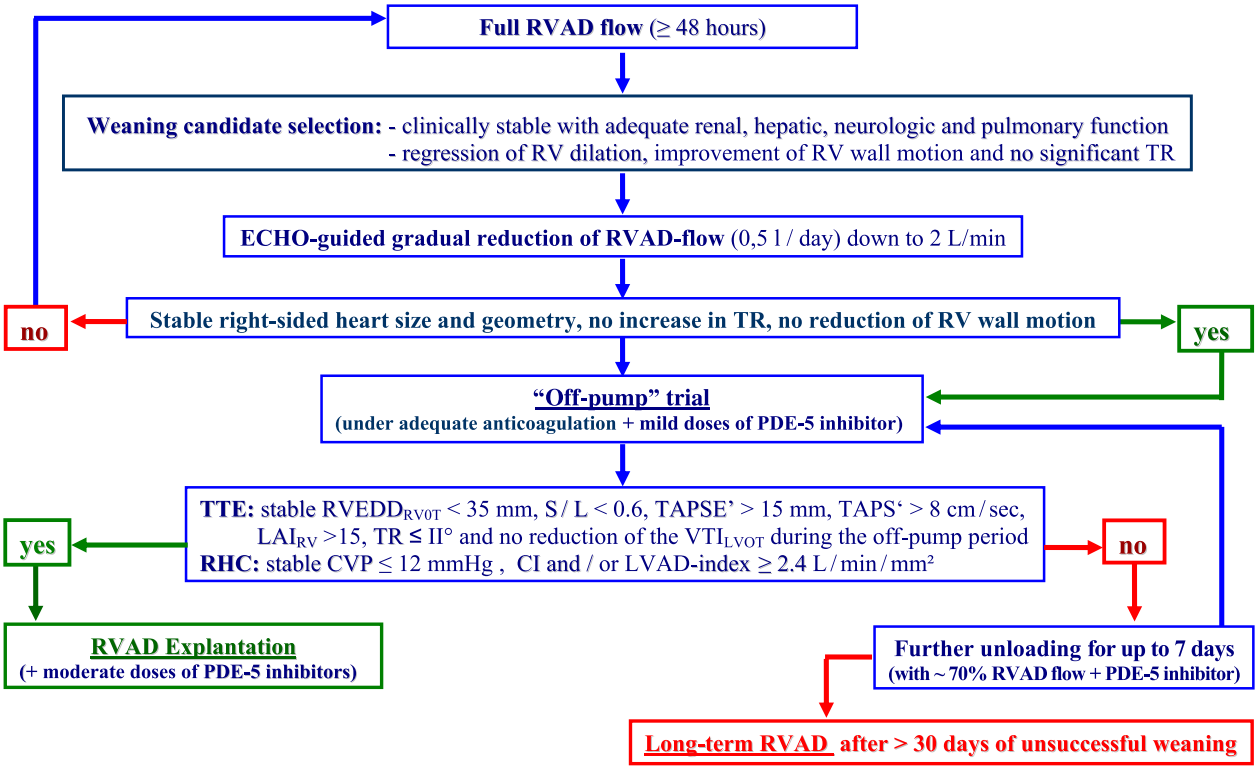

Figure 4. Proposed steps for assessment of RV recovery before decision making in favour of or against patient weaning from the RVAD. CI, cardiac index; CVP, central venous pressure; ECHO, echocardiography; LAI_{RV}, RV load adaptation index; PDE, phosphodiesterase; RV, right ventricle; RVAD and LVAD, right and left ventricular assist device; S/L, RV end-diastolic short-/long-axis ratio; $RVEDD_{RVOT}$, RV end-diastolic diameter at the RV outflow tract; TAPSE', tricuspid annulus peak systolic wall motion velocity; TR, tricuspid regurgitation; VTI_{LVOT}, velocity-time integral in the LV outflow tract.

will be no further need for the RVAD.[48,59] If there are no contraindications for further prolongation of the t-RVAD support, it can be useful to continue the support with the lowest possible RVAD flow for up to 24 hours. If ECHO and RHC measurements continue to remain stable, RVAD explantation is feasible, and freedom from recurrence of RVF after t-RVAD removal can reach 90%.[56] In patients whose ECHO and RHC parameters remain stable during short-term moderate reduction of RVAD flow but become unstable during the interruption of RV unloading, and in whom the LAI_{RV} does not exceed the value of 14, there is further need for RV support. Returning to the initial RVAD settings and continuation of full RV unloading for several days is therefore necessary before another off-pump trial (Fig. 4). After a failed weaning attempt, additional facilitation of RV recovery might be attained by enhancing pulmonary arteriolar vasodilator therapy for further reduction of the PVR. The use of inotropes during assessment of RV recovery can lead to misleading results and should be avoided.

Persistently low LAI_{RV} values indicate poor ability of the RV to adapt its pump function to afterload changes, even under a normal PVR.[60] In LVAD candidates, a low preoperative $LAI_{RV} \leq 14$ appeared highly predictive for RVF after LVAD implantation.[59] Accordingly, in LVAD recipients whose RV size, geometry, and wall motion remain normal and stable during the short periods of RVAD interruption—as long as the LAI_{RV} does not increase beyond 14—the risk for RVF recurrence after RVAD explantation remains high.

Weaning from t-RVAD in a BiVAD setting after only 24 to 48 hours is also possible. If such early weaning candidates are still on low-dose inotropic support, they must not necessarily be weaned from inotropes because some groups even initiate low-dose inotropic support before attempting to wean the patient from the device.[55] However, weaning decision making can be more challenging if RV recovery is assessed in the presence of inotropic support.

RV Recovery Assessment After Isolated RVAD Implantation

In the absence of drug-refractory pulmonary hypertension, the probability of adequate RV recovery during RVAD support can exceed 60%, also in patients with isolated RVF.[61-64]

In principle, weaning candidate selection and assessment of RV recovery in isolated RVAD recipients is similar to the assessment of RV recovery in long-term BiVAD recipients or LVAD recipients with additional t-RVAD. Weaning should be started with the same gradual reductions of RVAD flow under TTE guidance and invasive monitoring of hemodynamic responses. TTE should focus on possible changes in atrial and ventricular septum position, RV end-diastolic dimensions, and short-/long-axis ratio as well as on changes in TAPSE, TAPS', and FAC_{RV}. Attention must also be paid to TR and to the CW—Doppler-derived pressure gradient between the RV and RA. Serial velocity time integral measurements obtained from PW-Doppler signals in the LV outflow tract are useful for noninvasive monitoring of stroke

volume and CI stability. If RHC measurements remain within the normal range and ECHO parameters remain stable during that moderate reduction of the RVAD flow, the next step will be a short (5- to 10-minute) interruption of RV unloading. If ECHO and RHC parameters remain stable during complete interruption of RV unloading, RV recovery appears sufficient to allow RVAD explantation, particularly if the LAI_{RV} values are above 14. Persistent LAI_{RV} values ≤ 14 indicate a reduced RV ability to adapt its pump function to afterload changes even under normal circumstances (ie, normal PVR), and, in such cases, normal and stable LV function is mandatory to prevent postweaning recurrence of RVF.[59]

Conclusions and Practical Recommendations

Although several ECHO- and RHC-derived parameters have proved useful for assessing recovery and for prediction of weaning success, to date there is still no "gold standard" for recovery assessment. One future goal should be the collection of further knowledge to create a universal weaning protocol. Until then, the available data and information concerning this issue can be a useful guide for clinicians engaged in this important and very topical field. In this respect, the following practical recommendations, derived from past experience, may be particularly useful:

1. Considering the increasing reports of improvement in ventricular function in patients with prolonged VAD support, routine ECHO assessment for cardiac improvement in VAD recipients is strongly recommended. This may apply to patients whose VAD indication was either acute myocardial dysfunction or CCM.
2. ECHO and RHC are both mandatory for the assessment of VAD-promoted cardiac recovery and for weaning decision making.
3. Reliable ECHO and RHC data acquisition for recovery assessment of the native heart requires short-term interruption of ventricular support, which is particularly challenging in CF pump recipients.
4. According to the proposed steps for the assessment of LVAD-promoted reversal of cardiac alterations and selection of weaning candidates (Fig. 1), off-pump or pump turn-down to $\pm$ zero unloading trials should be performed only in patients who meet the eligibility criteria for such demanding tests.
5. The duration of VAD support interruptions should not exceed 15 minutes. It is safer for the patients to perform the necessary measurements stepwise during several short-term ($\sim$5 min) unloading interruptions.
6. After maximum cardiac improvement that is deemed sufficient to allow VAD explantation, stability of ventricular size, geometry, and function between and during the VAD support interruption trials performed over the next 2 to 4 weeks is predictive for long-term weaning success.
7. RHC off-pump hemodynamic measurements for the assessment of cardiac improvement are both indicated and necessary only if the patient's ECHO parameters fulfill the minimal requirements for possible weaning from the VAD.

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Supplementary Material

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