



Long-term mechanical ventricular assistance toward myocardial recovery

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As discussed in the preceding chapters, most devices are placed in anticipation of acute ventricular recovery (bridge to recovery, BTR), or as a stabilizing measure until cardiac transplantation can be undertaken (bridge to transplant, BTT). Recently, attention has been directed toward using ventricular assist devices (VADs) for permanent cardiac replacement, or destination therapy. This alternative to transplantation is necessary because of the limited number of available organs and the large number of heart failure patients who are not candidates for transplantation. Another recent development is the removal of long-term ventricular assist devices (VADs) in patients who have exhibited ventricular recovery after a prolonged period of ventricular unloading.

Patients for VAD weaning and explantation should be identified preoperatively, because this may influence device selection and method of cannulation. Of the many different available designs, VAD selection depends on patient body size and which ventricles need support (Table 1). The anticipated length of support is a critical factor in determining which device is used, and this is most dependent upon the anticipated outcome after device implantation. When recovery of ventricular function is expected acutely, or where the waiting time for transplantation is expected to be brief, a short-term or intermediate-term device may be appropriate. However, long-term devices are usually required when transplantation or recovery is expected to be significantly delayed.

Recovery of ventricular function after a period of mechanical support in an acute setting is not a new concept. The first use of a VAD was to support a patient in postoperative cardiogenic shock [1], and only later were these devices used as a BTT [2]. VADs continue to be used as a BTR in patients with acute cardiac decompensation who are expected to have rapid recovery of ventricular function. Using VADs as BTR for chronic heart failure is gaining acceptance as more reports describe successful explantation of long-term devices. Despite this expanding role for VADs in heart failure, the patient selection criteria for VAD insertion must be maintained to minimize the risk of having a nontransplantable patient supported by a device that cannot be weaned. This scenario will become less important as VADs gain acceptance as destination devices.

Rationale for myocardial recovery and ventricular assist device removal

In early times, rest and relaxation used to be the mainstay for the treatment of heart failure to allow the heart to recover function, which often required patient immobility and a significant decrease in quality of life. Current medical therapies continue to use myocardial rest to promote ventricular recovery but achieve this through the use of afterload reduction and β -adrenergic receptor blockade. VADs also provide myocardial rest by decreasing the work that the ventricle must perform, allowing for recovery to occur.

The fundamental physiologic changes present in heart failure are complex. They include alterations in the mechanical properties of the myocardium, as well as changes in the concentrations of

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Table 1
Ventricular assist devices commercially available in the United States

Name	Pump location	Pulsatile	Ventricle(s) supported	Length of support	Common uses ^a	Able to wean
Short-term						
Centrifugal pump	Extracorporeal	No	Right, left	Days	BTR, BTT, BTB	Yes
ECMO	Extracorporeal	No	Biventricular	Days	BTR	Yes
Abbiomed BVS 5000	Extracorporeal	Yes	Right, left	Days to weeks	BTR, BTT, BTB	Yes
Intermediate						
Thoratec	Paracorporeal	Yes	Right, left	Weeks to months	BTR, BTT	Yes
Long-term						
HeartMate	Intracorporeal	Yes	Left	Months to years	BTT, ? ATT	Reported
Novacor	Intracorporeal	Yes	Left	Months to years	BTT, ? ATT	Reported

^a Does not imply FDA approval for this indication.

Abbreviations: ATT, alternative to transplantation; BTB, bridge to bridge; BTR, bridge to recovery; BTT, bridge to transplantation.

many neurohormones and components of the inflammatory cascade. Reversal of heart failure often requires correction of the mechanical components of heart failure, as well as amelioration of the neurohormonal changes to prevent a recurrence of heart failure. Mechanical unloading of the ventricle may allow the myocardium to recover wall thickness and ventricular geometry and will lessen the signals that produced the alterations in the neurohormones. In addition, treatment with β -blockers and angiotensin-converting enzyme inhibitors helps to block the effects of the abnormally elevated neurohormones.

VAD insertion often heralds the need for cardiac transplantation, which currently offers the best chance of survival for most patients with heart failure. However, with limited donor availability, many patients die while waiting for an appropriate organ. Those who are transplanted are then faced with the cost and morbidity associated with immunosuppressive medications and a limited life expectancy. Therefore, if ventricular recovery occurs after a period of VAD support permitting device removal, the need for heart transplantation can be significantly delayed or eliminated.

Myocardial recovery after long-term ventricular assistance

Long-term ventricular support has been used primarily as a BTT and is usually reserved for patients who are suitable candidates for transplantation. Although ventricular recovery is getting recent attention, recovery on long-term VAD support has been occasionally noted since the

1960s. Recently, recovery has been reported in several patients who had evidence of improved ventricular function at the time of transplantation [3], and other reports have now documented the removal of permanent VADs after the appearance of myocardial recovery [4–10]. Interest in weaning long-term VADs has grown due to long transplant waiting times, organ shortages, and the possibility of curing a young heart failure patient without resorting to transplantation. However, cases of ventricular recovery on long-term VAD support remain uncommon, and the vast majority of patients continue to be listed for, and undergo, heart transplantation. As a result, most of the procedures developed for weaning long-term VADs are based on the observations of relatively few patients.

Patient identification and early management

Most of the patients who have undergone successful weaning and explantation of a chronically implanted LVAD have idiopathic dilated cardiomyopathy (IDC), as opposed to ischemic cardiomyopathy (Table 2). Nearly all patients with IDC can be considered candidates for eventual VAD removal, but there are occasional patients with ischemic cardiomyopathy who will regain ventricular function if VAD implantation is accompanied by, or followed with, a revascularization procedure.

Ventricular unloading is a key component of the recovery process. Historically, treatment for heart failure consisted of bed rest, but now consists of β -blockers and angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) to lessen the mechanical

Table 2
Reversibility of acute and chronic heart failure by cause

	Potentially recoverable	Nonrecoverable
Acute cardiac failure	Postcardiotomy cardiogenic shock Acute myocarditis Acute myocardial infarction Postpartum cardiomyopathy	Giant cell myocarditis
Chronic cardiac failure	Idiopathic dilated cardiomyopathy	Ischemic cardiomyopathy Amyloidosis/Sarcoidosis Toxic (alcoholic) cardiomyopathy Restrictive cardiomyopathy Acquired hypertrophic cardiomyopathy

work of the heart. When these drugs are ineffective, mechanical devices can effectively unload the work of the left ventricle. Although mechanical unloading of the heart is helpful, complete emptying of the ventricle does not always occur. In some patients, the LV will continue to eject blood during parts of the cardiac–VAD cycle and will generate high intraventricular pressures. As such, optimal treatment in patients considered for VAD weaning includes β -blockade and the use of an ACE-I or ARB to minimize LV stress. These drugs are used to maintain a systolic blood pressure < 110 mm Hg and a native heart rate less than 80 bpm [7].

The initial stages of the recovery process are monitored through the use of routine echocardiograms on VAD patients, assessing ejection fraction (EF) as well as ventricular dimensions. The period of recovery is highly variable, but often begins very soon after device implantation and can be maximal within 5 months [8]. Once evidence of ventricular recovery has been identified in a patient, formal testing and VAD weaning can be performed. Because assessment of ventricular function on full VAD support is difficult, the status of cardiac recovery is determined without any VAD contribution to the cardiac output. It is very important to monitor right ventricular performance during VAD support of the LV and during the weaning process, because the onset of right ventricular failure will preclude explantation.

Assessing ventricular recovery

Although many centers have reported the explantation of long-term VADs after ventricular recovery occurs, the overall number of patients successfully explanted remains small. In addition, they represent only a fraction of those in which devices are implanted. Because of the small

numbers of patients involved, each center has developed an individualized approach to assessing ventricular recovery. The three main techniques proposed include serial echocardiography [6–8], exercise echocardiography [4], and dobutamine stress echocardiography [11]. Of these, more patients have been assessed and weaned through the use of serial echocardiography.

Hetzer and colleagues at the German Heart Institute in Berlin, Germany, have extensive experience in the explantation of long-term LVADs, and they have developed a protocol for assessing the degree of ventricular recovery [6–8]. Once a patient has been identified as appropriate for potential LVAD weaning, the patient undergoes formal testing. After heparinization (10,000 units IV) the LVAD is placed in the fixed mode at a rate of 80 bpm. Biventricular function is monitored with transthoracic echocardiography, looking at EF and LV internal diameter in diastole (LVIDd). As long as ventricular function remains stable, the rate of the VAD is slowly decreased in increments of 10 bpm until the VAD rate is 30 bpm. If the patient maintains acceptable hemodynamics and the LVEF > 40% with an LVIDd < 55 mm, then VAD rate is decreased to 3 bpm (to prevent stasis and thrombus formation within the VAD) and ventricular function monitored for 10 minutes. If LVEF is > 45% and LVIDd < 55 mm for 10 minutes, then the patient undergoes a period of device weaning in anticipation of VAD explantation.

An alternative method to assess recovery combines the use of echocardiography with exercise testing [4]. An initial assessment of VAD weanability is performed by monitoring the patient's hemodynamics and echocardiogram in response to decreasing the rate of VAD ejection. Patients who maintain good hemodynamics during this protocol are then advanced to the next phase of evaluation, which consists of decreasing the VAD

ejection rate until the beat rate is 20 bpm unless symptoms are encountered. Patients who tolerate the decrease in beat rate undergo exercise testing at the reduced beat rate. The exercise protocol consists of a standardized program of increasing workload on a bicycle ergometer until exhaustion, with monitoring of hemodynamic variables. Patients are considered for explantation if they are able to demonstrate good hemodynamics during exercise testing and maintain acceptable ventricular function on echocardiogram taken in the first minute of recovery.

A final method of assessing ventricular recovery involves the use of dobutamine stress echocardiography (DSE) [11]. Under this protocol, patients who are identified as potential weaning candidates have their VAD changed from the automatic mode to the fixed rate mode. The beat rate is gradually decreased over several weeks. The VAD is then briefly turned off and they are subjected to DSE with dobutamine infusion rates up to 40 mcg/kg/min. Hemodynamic and echocardiographic data are then collected. Those who respond appropriately to the DSE are considered for explantation.

Weaning a patient from long-term ventricular assist device support

Explantation of a VAD under urgent conditions (infection, VAD failure, etc.) is associated with a high rate of death or recurrent heart failure. Many of these patients have not had sufficient time to fully recover myocardial function or may have conditions that are not readily amenable to ventricular recovery. In addition, it is likely that even patients who have undergone recovery will require a period of VAD weaning to allow the heart to re-acclimate to the required workload. Therefore, weaning and removal of a VAD under urgent conditions should be avoided if at all possible.

After evidence of recovery suggests that VAD removal may be possible, the VAD must be weaned to allow the ventricle to perform gradually increasing amounts of work. It is hoped that the weaning period will decrease the likelihood of ventricular failure that may occur with inappropriate, rapid VAD removal. One protocol for device weaning [7] consists of a 1-week period of LVAD support at a fixed rate of 80 bpm followed by assessment of cardiac function by echocardiography. If there is no deterioration of function, then the beat rate is decreased by 10 bpm and the

echocardiography repeated in 1 week. This process continues until the patient has been maintained on VAD support at a fixed rate of 50 bpm for a week, at which time the patient is scheduled for explantation of the device.

Ventricular assist device explantation

Removal of the VAD may be hazardous if not done carefully. The process depends on the particular type of VAD that is to be explanted. With any device, the patient is heparinized and the device maintained at a minimal rate to decrease the risk of thrombus formation. Ventricular function is monitored by transesophageal echocardiography for 20 minutes before proceeding with explantation. The Novacor device may be removed by reopening the abdominal portion of the incision. Both the inflow and outflow portions of the graft are ligated and transected through this incision [7], leaving portions of the grafts in the patient to minimize cardiac trauma that may occur with repeat sternotomy and complete graft excision. In contrast, the HeartMate LVAD has a solid inflow cannula from the ventricular apex. Removal of this device requires a repeat sternotomy and the use of cardiopulmonary bypass for cannula removal and closure of the apical ventricular defect.

The post-explantation care of these patients is critical in the success of device removal. Volume loading and the use of exogenous catecholamines should be minimized to limit the stress on the myocardium. Because these patients have had heart failure severe enough to require VAD support, they should continue to receive a β -blocker and an ACE-I or ARB postoperatively. Routine follow-up echocardiography is performed to look for slow and progressive ventricular deterioration. This may be insidious and may require re-listing for cardiac transplantation. In severe cases, the patient may require another period of VAD support while awaiting transplantation. Because the cannulas are left in place at the time of Novacor explantation, coumadin is continued for 6 months after VAD removal [7].

Long-term recovery

The success rate of weaning from a long-term VAD (arbitrarily defined as making the decision to attempt VAD weaning > 30 days from implantation) depends on the reason for removing it. The success rate is much better if the VAD is removed electively after a period of weaning rather than if

removal is required urgently for device infection or failure.

The largest single center experience in weaning patients from long-term LVAD support comes from the German Heart Institute in Berlin [8]. Of 95 patients who underwent long-term LVAD implantation for IDC, 28 patients (29%) have been weaned from the device and explanted. The mean age of explanted patients was 42 years, with an average duration of heart failure symptoms of 4 years. The explantation was elective in 24 patients, and urgent in four patients, each due to a significant pump-related complication after near-complete recovery had occurred.

Of the 28 weaned and explanted patients, 18 patients had achieved optimal hemodynamics (LVEF > 45%, LVIDd < 55 mm), whereas 10 had less than optimal hemodynamics (LVEF 30%–44%, LVIDd 56–64 mm) but underwent removal because of an underlying device-related complication [8]. Of the patients who underwent explantation, only 16 procedures were successful, with persistently normal ventricular function at a mean of 2.6 years follow-up. Nine patients experienced recurrent heart failure within 2 months of explantation; eight were re-listed and transplanted, and one died awaiting a donor heart. One of these patients had an acute exacerbation of failure after a period of heavy alcohol consumption and required LVAD reinsertion while awaiting transplantation [7]. Three others died after explantation from sepsis, pulmonary embolism, and massive pulmonary bleeding.

Unfortunately, there are few characteristics to predict the success of weaning before explantation. Those patients who demonstrated stable cardiac function for > 6 months after explantation had a shorter duration of heart failure before LVAD implantation (2 versus 9 years), shorter duration of assist before recovery occurred (118 versus 240 days), a smaller LV (pre-explantation LVIDd 51 versus 57 mm), and higher EF at 2 months of support (49% versus 39%) and at explantation (52% versus 43%) compared with those patients who demonstrated recurrent heart failure [8].

Tansley et al [9] have reported results on patients supported with the HeartMate LVAD (HeartMate I, n = 18; HeartMate II, n = 1) who were initially treated with β -blockade after device implantation. Once patients reached maximal improvement, as judged by echocardiography, they were treated for 1 month with the β_2 agonist clenbuterol to induce physiologic LV hypertrophy

[12]. Of 15 patients who survived device implantation, nine underwent successful explantation with follow-up ranging from 144 to 496 days. In addition, one other patient was awaiting explantation at the time of the report. Although these data have been published only in abstract form, they suggest that aggressive treatment with a heart failure regimen while on device support may be beneficial in the weaning process.

The hypothesis that concomitant heart failure treatment is necessary is supported by the low rates of explantation and post-explantation survival reported by several other centers. Mancini et al [4] reported five explantations in a retrospective review of 111 patients supported on a HeartMate device at Columbia Presbyterian Medical Center. Four of these patients had a dilated cardiomyopathy and one was ischemic. The devices were explanted between 2 and 12 months after implantation, and the patients included two electively explanted instead of transplantation and three who underwent explantation because of device infection. Of these patients, only one, who was explanted for infection, was alive and well at the time of the report. Two patients had died as a result of cardiac disease, and the other two underwent device reimplantation for recurrent heart failure [4]. In a prospective analysis of the next 39 HeartMate implants, one patient with a dilated cardiomyopathy was successfully explanted after completing an exercise protocol with the device weaned [4].

The Cleveland Clinic experience includes two patients with IDC out of 250 implants who underwent explantation after recovery [10]. Both experienced recurrent heart failure at 8 months and 2 years and died. Texas Heart Institute also reports a total of five patients explanted after long-term VAD implantation [5]. Four of the patients were supported on a HeartMate device, and one on a Thoratec. Four of the five patients are doing well 2 to 35 months after explantation, and the fifth died of multisystem organ failure after explantation. These patients represent a small percentage of the total implants at that institution.

Overall, these data demonstrate that weaning can be successfully undertaken in patients with IDC and that heart transplantation can be avoided or significantly delayed in these patients. It is impossible to know which factors lead to success, but it is likely that aggressive treatment of heart failure after device implantation and use of a well-designed weaning protocol will be key factors. These patients require diligent follow-up

to detect any recurrence of heart failure that can be aggressively treated before complete decompensation occurs. The success of device weaning may depend upon the urgency in which it is performed, and it is possible that successful weaning may only be accomplished safely in elective patients.

Unanswered questions

Only a few of the many patients supported with a chronic LVAD are considered for weaning and explantation. There is likely to be a significant selection bias in those who are weaned, so it can be difficult to make accurate generalizations about weaning in the larger group of VAD patients. Because of the limited experiences, there are many areas of disagreement among those who support VAD weaning and explantation, including patient selection, device selection, the degree of ventricular unloading, and the timing of the explantation. Many of these controversies arise because so little is known about the ability of the ventricle to undergo reparation and the optimal methods to achieve this process.

Patients have been successfully weaned of support using several different devices, but most of the successful cases have been reported using the Novacor implantable LVAD. Loebe et al [7] reported that they were able to explant devices from 19 of 65 patients with a Novacor device compared with only two of 23 with a HeartMate system and one patient out of more than 300 with the Berlin Heart (Mediport Kardiothechnik, Berlin, Germany) providing either univentricular or biventricular support [6]. In addition, the device wean rates reported were significantly higher than those reported by institutions that use the HeartMate VAD [4,5,10]. These data suggest that there may be device-specific advantages with some types of VADs. However, the explantation rate was also significantly higher in the data presented by Tansley et al [9] where the HeartMate device was used exclusively. There are many variables that may account for the differences in wean rates, such as the incidence of aggressive heart failure treatment while on device support, the rate at which patients are transplanted at different institutions, the timing of device insertion, and the diligence in which recovery is sought after device placement. Therefore, in the absence of a well-designed trial, it may be difficult to determine if one device has any advantage over the others.

It is unclear if the Novacor has design features that may make it a better device for weaning than

the HeartMate. The pressure in the aortic root increases significantly with each LVAD ejection. If the native heart is attempting to eject during this same period of time, the heart faces a higher afterload, increasing the stress upon the ventricle. Unlike the HeartMate, the Novacor is capable of operating in a mode where its ejections are synchronous with the cardiac cycle, eliminating this period of high afterload on the left ventricle. While the native heart could alter its own rate to synchronize with the HeartMate device, this was not seen in a recent study [13]. However, these differences may be clinically insignificant, because success in weaning the HeartMate device has been reported [4,5,9].

The optimal degree of left ventricular unloading to restore ventricular function is unknown. Complete unloading of the ventricle may result in ventricular atrophy from disuse [14]. To assess this, Maybaum et al studied the LV function and rest and exercise of patients who had either fully unloaded or partially loaded ventricles after placement of an implantable HeartMate LVAD. Patients with partial loading of the ventricle demonstrated improvements in peak oxygen consumption, resting myocardial blood flow, myocardial oxygen consumption, native LV index during exercise, and ability to exercise with the device turned off [15]. These data suggest that partial loading of the LV may be advantageous in promoting LV function. However, the data are observational only, and it is impossible to determine if the degree of decompression is a reflection of the function of the LV rather than a determinant of LV functional recovery.

No clear indication exists regarding how much recovery is required before successful device removal can be undertaken. This is of primary concern in the management of the patient presenting with a complication related to the VAD that favors early device removal. Although Hetzer et al [8] showed poorer results in patients supported for a longer time before recovery, and with a lower pre-explantation EF, Frazier et al [5] reported acceptable results with LVAD removal after a mean of 229 days of support with a mean LV EF of 29%. It is unclear if the differences in these data are due to chance, patient selection, type of device implanted, or other factors. Regardless, for patients who require urgent device removal, accelerated weaning may be necessary to retrain but not overstress the ventricle with premature device removal. Conversely, undue delay in explantation may be detrimental to the ability to wean the device if cardiac

atrophy begins. This may help to explain the low rate of explantation at some institutions, where time between device implantation and weaning may average more than 1 year and is performed only if necessary. In these situations, weaning occurs only when there are other factors that preclude transplantation or require urgent VAD removal. Higher wean rates are found in centers where signs of recovery are actively sought and the weaning protocol initiated as soon as possible [6–8], and it is likely that this aggressive approach to weaning is necessary if large numbers of patients are going to be successfully weaned from device support with acceptable long-term results.

Finally, it is unknown whether there is any surrogate marker or test that can predict the ability of the ventricle to undergo recovery or the time at which maximal recovery has occurred. Peri-implantation variables that can help to predict the success in device weaning include the percent of myocardial fibrosis and the LVIDd at the time of implantation [7], although the overlap in values between nonresponders and responders limits their predictive value. The pre-operative duration of heart failure is shorter in those patients who demonstrate long-term recovery compared with those who experience recurrent heart failure after explantation [8]. Heart failure is associated with alterations in concentrations of several neurohormones and inflammatory mediators, which often revert toward normal after a period of LVAD support. Patients with IDC who require LVAD support have elevated titers of the anti- $[\beta]_1$ -adrenoceptor-autoantibody [7], which tend to decrease after device implantation with a time-course that parallels myocardial recovery. Patients successfully weaned from device support without exhibiting recurrent heart failure have a more rapid decrease in these autoantibodies [16], but the difference (8 versus 9 weeks) may not be clinically significant. Neurohormones that are increased in heart failure and decrease with LVAD placement include epinephrine, norepinephrine, vasopressin, angiotensin II, and plasma rennin activity [10]. However, it is unclear if any of these values or their changes has predictive value. The importance of brain natriuretic peptide as a marker for heart failure is being recognized, and its levels may decline more rapidly in patients who can later be successfully weaned from device support [17]. Despite these potential predictors of recovery, the decision to wean and explant a long-term device must be made based on data from several sources,

combined with sound clinical judgment and intuition.

Summary

Myocardial recovery after VAD support provides a perfect example of reverse remodeling. It also establishes that heart failure may not be an end of the road situation. Although post-LVAD myocardial recovery has become a distinct entity, basis of reversal of the dedifferentiation process will need to be further explored. With this objective, several centers in the United States have formed the LVAD Working Group to: determine the incidence of myocardial recovery; obtain serial studies to determine the response of the LVAD-supported heart to stress; and study the tissue and serological changes as they relate to the recovery process. Patients enrolled in this study will receive anti-heart failure therapy and serial examinations after implantation and explantation. Stress evaluations will include dobutamine stress echocardiograms as well as bicycle exercise with right heart catheterization. A large database of prospectively collected data will likely result in a greater understanding of myocardial recovery and the LVAD weaning process.

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