

Left Ventricular Assist Device as a Bridge to Recovery

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The first successful bridge to transplant took place at the Texas Heart Institute in 1985 [1]. Ventricular Assist Devices (**VAD**) were first used as bridges to transplant and later as destination therapy, both of which they are still used for today [2,3]. Early studies showed that a compilation of changes in the assisted heart led to alterations in myocyte size and function, which led to decreased Left Ventricular (**LV**) size, and ultimately, restoration of the normal elliptical shape. These collective changes led to LV end-diastolic pressure-volume curves trending toward normal which has become known as “reverse remodeling.” Under certain circumstances, the myocardium may recover enough to eventually provide sufficient cardiac output without the continued need for device assistance [4]. Because reverse remodeling does not imply freedom heart failure, D. Mann [5] suggested the term “myocardial recovery” be used to describe “the normalization of the molecular, cellular, myocardial and LV geometric changes that provoked cardiac remodeling, that allow the heart to maintain preserved LV structure and function in the face of normal and/or perturbed hemodynamic loading conditions.” This definition implies and requires that myocardial recovery is associated with freedom from device and recurrent episodes of heart failure. While this currently is known to occur in a minority of patients with LVADs, a significant amount of

research has investigated reverse remodeling and the effects LVADs induce as a bridge to recovery at both the cellular and clinical levels. This chapter will review recent studies regarding the changes known to take place in the bridging heart, the importance of patient selection, clinical outcomes, and the methods that have been used to wean LVAD support with successful device explantation followed.

BIOLOGIC RECOVERY

At the cellular level, numerous studies have identified a number of histologic and functional changes that take place in the myocyte, but their significance is difficult to demonstrate as biologic recovery has yet to be shown to correlate well with clinical recovery. This chapter is far from all-inclusive, but we will review a few of the most important changes and mention others that are under scrutiny.

Myocyte Size

It is well known that myocyte hypertrophy occurs in patients with congestive heart failure and this is a marker of cardiac remodeling. By the same token, regression in myocyte size serves as a marker of reverse remodeling. Although further study is needed to elucidate the exact cause of reversal, we do know that LVAD unloading of the ventricle results in reversal of cardiac myocyte hypertrophy. Several pathways have been implicated in regulation of myocyte size in heart failure as a result of circulating hormones and alterations in mechanical load and myocyte stretch from heart failure. A few of these pathways include cyclooxygenase -2-induced Akt phosphorylation, the mitogen-activated protein kinase/Erk pathway, and the Akt kinase/glycogen synthase kinase 3β pathway, all of which have been shown to be down regulated by mechanical unloading of the ventricle [6]. A study by Narula [7] showed a 28%, 20%, and 36% reduction of cell volume, length, and diameter, respectively, in heart failure patients treated with LVAD for 75 ± 5 days. In a study by Baba, [8] the majority of the decrease in diameter has only been found to occur in subendocardial myocytes. This is thought to be due to the sub-endocardial layer being under the most stress and most susceptible to ischemia with elevated end-diastolic pressures. With ventricular offloading, the increase in perfusion is most significant to this area of myocardium improving its ability to undergo reverse remodeling. Though not demonstrated in humans at this time, animal models have shown normalization of cardiac hypertrophy followed by atrophy with continued unloading [9].

Extracellular Matrix Remodeling after LVAD

Extracellular matrix and collagen content is an area of much interest in heart failure as there is an accumulation of components of the extracellular matrix, specifically collagen, in congestive heart failure. Collagen is significant because the amount of collagen accumulation corresponds with the degree of heart failure [10]. This collection of extracellular matrix material, along with myocyte hypertrophy, is part of what contributes to the increased size and mass of hearts in heart failure. What's interesting is that the most recent studies documenting the impact of cardiac

off-loading on extracellular matrix volume and composition diverge greatly in their findings. While some studies have shown a decrease in fibrosis [11-13], other studies have paradoxically shown an increase in the amount of fibrosis [14,15] or others, even still, that show it is a biphasic phenomenon [16]. The differences in results seen in the various studies are not well understood, although it may be attributable to differences in duration of support, patient age, nature of insult, and even type of collagen present between the studies. Despite the differences in progression of fibrosis, one study found that less collagen and smaller myocytes at the time of LVAD implantation correlate with greatest improvements in ejection fraction [17].

Apoptosis

Several pathways have been shown to down regulate cardiac myocyte cell death due to unloading of the ventricle by LVADs. Some of these pathways include down regulation of iNOS production, NF- κ B and TNF- α among others [18]. The down regulation of iNOS production has also been demonstrated to reduce the incidence of apoptosis among cardiac myocytes after LVAD implantation [18]. It has also been demonstrated that prior to LVAD support in heart failure, TNF- α levels and cardiomyocyte apoptosis are directly correlated [10,19]. It has been shown that in the LVAD supported hearts, patients can be weaned from the devices once TNF- α expression and therefore myocyte apoptosis rates are significantly reduced. Lastly, we will mention the study by Grabellus [20] which reported a decrease in the expression of NF- κ B, a key regulator of apoptosis noted to be activated in heart failure, after institution of LVAD support. Several more cellular pathways have been identified to regulate apoptosis in heart failure and their importance in myocyte recovery continues to be investigated. These cellular pathways all may represent possible targets of future molecular therapies for treatment of heart failure.

Many other cellular aspects of heart failure have been investigated but cannot be covered in full detail within this chapter. Of note, studies have investigated the alterations that take place in cytoskeletal proteins, beta-adrenergic signaling and sympathetic innervation, metabolism and bioenergetics, natriuretic peptides signaling, gene expression, mRNA, and proteomic profiling to mention a few. Despite the extensive investigation into the biochemistry of the recovering heart and identification of numerous pathways which are involved in myocyte recovery, no reliable biological markers for evaluating the potential for recovery have been identified at this time nor has improvement at the cellular level been able to be directly correlated with clinical recovery [10].

PATIENT SELECTION

Historically, devices have been implanted in a small selective group of bridge to transplantation or destination therapy patients. Therefore, these devices have traditionally been used in the sickest of patients. Some of the outstanding, near miraculous results observed in these patients brought about the idea of bridge to recovery [21-23]. The concept of bridge to recovery completely shifts the overall mind-set of LVAD therapy, and opens the field of ventricular assist devices to a

broader pool of patients, not necessarily only those with perceived irreversible end stage heart failure. It's possible that by providing ventricular assistance earlier on, the heart avoids such severe decompensation that it is able to recover rather than fail and need indefinite support or transplant. Some studies have even advocated for the use of devices in INTERMACS class 4-6 [24]. With this in mind, overall recovery rates remain low in the majority of large scale studies which have investigated LVAD use over the past 15 years. This impresses upon us the importance of patient selection to maximize the odds of recovery.

Several studies have found a few unifying factors associated with successful sustained myocardial recovery and separation from device. These include young age (<40 years old), non-ischemic cause of heart failure, and a short duration of symptoms defined as less than one year [25-27]. Despite these findings, it must be noted that some centers have demonstrated recovery, although not as consistently, in patients with long standing symptoms in chronic heart failure as well. In a study by Birks [23] in the United Kingdom 20 patients received neurohormonal blockade concomitantly with pulsatile LVAD support. Of the eight patients with Heart Failure (**HF**) symptoms less than 6 months and 12 patients with HF symptoms greater than 6 months, eight (100%) and four (33%) of the patients recovered respectively. Patients with shorter duration of symptoms had higher rates of recovery but patients with long term symptoms demonstrated they also have recoverable myocardium.

Three of the highest recovery rates in prospective bridge to recovery studies come from patients with non-ischemic cardiomyopathy with recovery rates ranging from 45%-73% [15,23,28]. Of note, not only did all patients have a non-ischemic etiology of their heart failure symptoms, but all three of these studies used a standardized medical therapy approach in combination with LVAD. Although these are small studies with less than twenty patients in each study, they give us a glimpse of what can be accomplished with proper patient selection, adjuvant standardized medical therapy, and a coordinated care team with the goal of wean to recovery in mind. Overall, it is currently accepted that younger patients with shorter duration of heart failure symptoms due to non-ischemic causes are the best candidates for myocardial recovery. This population should therefore be aggressively targeted for bridge to recovery therapy.

DEVICE SELECTION

Several studies suggest better results with pulsatile devices with higher rates of recovery than patients with continuous flow devices [23,27,29], The study by Krabatsch [27] retrospectively reviewed 387 patients undergoing LVAD support for end-stage Idiopathic Dilated Cardiomyopathy (**IDCM**). Of patients who recovered, patients with a Pulsatile-Flow LVAD (**PFVAD**) had almost a threefold increase in myocardial recovery compared with Continuous-Flow LVAD (**CFVAD**). In this study, younger age was the only other variable predictive of higher chance of recovery. At their institution, PFVAD was more common in the early 1990s whereas CFVAD have become increasingly more common since 1998 relegating PFVAD for special indications of late. While the

improvement in recovery in patients with PFVAD support isn't completely understood, coronary flow and endothelial factors released due to the shearing stresses of pulsation may play a role [30]. A study by Ootaki [31] analyzed coronary flow patterns during CFVAD support in pigs. They found that as CFVAD flows increased, total coronary blood flow decreased primarily due to left anterior descending coronary artery and left circumflex coronary artery flow. It stands to reason that decreased coronary perfusion in CFVAD could be a significant contributing factor to the increase in odds of recovery seen in patients with PFVADs.

In general, CFVADs have all but replaced pulsatile devices in recent years due to their size, simple insertion, improved durability and comparable ability to support the systemic circulation. In essence, both continuous flow and pulsatile devices have similar abilities to effectively off-load the heart with regard to cardiac hemodynamics, but there are more factors involved in reverse remodeling and myocardial recovery [32]. Despite the observed higher LV recovery rates and improved remodeling with PFVADs, CFVADs are and will continue to be the majority device of choice for heart failure patients for the foreseeable future [25].

CLINICAL RECOVERY

The concept of biologic recovery versus clinical recovery is an important one. It has been difficult for most studies to identify biologic markers that correlate with clinical recovery. Clinical improvement can be divided into two primary categories: assessment of reverse remodeling and cardiac recovery. Improvements in left ventricular size and shape, degree of mitral regurgitation, left ventricular mass, and left ventricular ejection fraction have all been used as indicators of reverse remodeling [33]. As mentioned previously, clinical recovery necessitates recovery of the patient's cardiac function and the ability to separate from the device without recurrence of heart failure [5].

A prospective study by Drakos in 2013 focused on the impact of continuous-flow LVAD support alone [34]. It followed 81 patients with both ischemic and non-ischemic etiologies of heart failure with turn-down echocardiograms nearly every month for a year. They found that after 6 months, 34% of patients had a relative increase in LV Ejection Fraction (**LVEF**) of more than 50% and that 19% had a return of an absolute LVEF to greater than 40%. Improvement beyond 6 months was significantly less, but this study effectively documented reverse remodeling in some patients with LVAD support. Interestingly, the patients were divided into four groups based on amount of systolic functional response. In the two study groups with the greatest improvement in LVEFs, an ischemic etiology of heart failure accounted for 55% and 33% of the patients which is classically considered less likely to be recoverable.

Several studies have demonstrated that excellent results can be obtained with specific pharmacologic therapy in combination with LVAD use. Initially, medical therapy for LVAD patients was primarily used as a treatment modality of hypertension, arrhythmias, etc. rather than with the mindset of impacting the clinical recovery of the myocardium. While it is true

that simply mechanically unloading the heart may have profound impact on allowing cardiac recovery, medical therapy has been increasingly integrated into the treatment algorithm post-LVAD implant to enhance reverse remodeling and recovery.

Dr. Patel and the Montefiore study group combined maximal neurohormonal blockade with LVAD support [33]. Neurohormonal blockade consisted of maximum doses of carvedilol, and either lisinopril or hydralazine/nitrates along with spironolactone in the 57% of patients who tolerated such therapy. They demonstrated the following evidence of reverse remodeling four weeks after patients had reached maximum neurohormonal blockade on LVAD support: decreased LV size (LV internal diastolic diameter) from 6.7 ± 1.5 to 6.0 ± 1.6 cm ($p=0.003$), decreased left ventricular mass from 246.4 ± 109.4 to 177.3 ± 108.0 g ($p<0.001$), and increased mean LVEF from 17.4 ± 6.5 to $33.1 \pm 16.2\%$ ($p<0.001$). These numbers actually underestimate improvement as patients were on inotropic support during pre-implantation data collecting. Despite these impressive indicators of cardiac reverse remodeling; only 14% of the patients achieved explantation with long-term clinical success. This study, among others, underscores the significant improvement achievable in a relatively short period of time with a combined medical and mechanical approach.

A 2006 study in the United Kingdom by Birks was among the first to prospectively combine LVAD support with medications aimed to promote reverse remodeling and myocardial recovery [28]. In this study, 15 patients were treated with high doses of ACE inhibitors, beta-blockers, angiotensin-receptor blockers, digoxin, and spironolactone after placement of a pulsatile LVAD. After improvement in LV end-diastolic size to below 6.0 cm, bisoprolol and clenbuterol were initiated and carvedilol was stopped. This allowed for the highest recorded explantation rate to date at 73% (11 out of 15 patients). This study was followed up with a 19 patient cohort using continuous flow LVAD in combination with aggressive medical treatment with a 63.2% device explantation rate [23].

It is critical to keep long-term outcomes in mind as many physicians are considering bridge to recovery as an alternative to the already accepted bridge to transplant model. To this end, a 2012 study out of the UK compared long-term outcomes of patients bridged to recovery versus those bridged to transplant. The results were encouraging as survival rates at 1 and 7 years for the explanted and transplanted groups were 89.9% and 73.9% and 80.4% and 78.3% respectively. Of the transplanted patients, 4 required VAD support after transplantation and were subsequently weaned off [35].

A coordination of care teams including exercise and drug therapy targeted at heart remodeling are essential adjuncts to LVADs. Patients that are identified early as good candidates for myocardial recovery and treated systematically with a target end-point of recovery have much higher rates of bridge to recovery than they would otherwise [25].

With all this in mind, actual bridge to recovery remains a challenge for all physicians. A retrospective analysis of 1108 patients with continuous flow LVAD found an explantation rate was

1.8% [26]. Although, the patients were enrolled in the trial as bridge to transplant or destination therapy, it underscores the fact that bridge to recovery does not happen of its own accord in most cases. Furthermore, we must be diligent in the patients we choose for this path and they must be managed aggressively with all the tools at our disposal from the beginning.

WEANING CRITERIA

The ultimate goal of bridge to recovery is to explant the LVAD once the myocardium sufficiently improves, but determining the time for explantation and having the confidence that the heart can perfuse the body without support anymore can be difficult. For that reason, it is important to give the patients trials of minimal support at which time the cardiac function and overall patient hemodynamics can be assessed. Weaning criteria vary greatly amongst institutions, however, the core principals are the same. Weaning to explantation typically takes between 6 to 12 months of support. In most cases the majority of improvement in cardiac recovery is achieved by 6 months [34].

To assess markers of reverse remodeling and cardiac recovery, the implanted device must be essentially “turned off” to allow the heart to take over full responsibility for cardiac output as tolerated. The protocol for “turn down” attempts for each device is different. The Heart Mate II may safely be turned down to 6000 rpm at a rate of 400 rpm decrease each minute. The patient should be heparinized and monitored with echocardiography to assess for acute changes. At this rate, the investigators reported that there was no significant difference in forward flow with further speed reduction and concluded that 6,000 rpm is sufficient to assess native myocardial function [36]. In other devices, such as the Heart Ware, a balloon catheter may be used to occlude the outflow cannula temporarily to assess cardiac function without device support [37]. Regardless of the method to assess innate cardiac function, if a patient cannot tolerate such temporary cessation of LVAD support; they are not ready to be considered for separation from the device.

Once a method of “turning off” the device is established, the next step is to assess for improvement in cardiac function. A 2014 study by Ibrahim reported the criteria that they found to be compatible with a successful recovery during “off-pump” testing [38]. These included a LVEF >45%, left ventricular end-diastolic diameter less than 6.0 cm, left ventricular end-systolic diameter less than 5.0 cm, pulmonary capillary wedge pressure less than 12 mm Hg, cardiac index greater than 2.8 L/min/m² as well as a VO₂ max of greater than 16 mL/kg/min. The Montefiore study group noted in their series of 21 patients that no patient with a LVEF of <35% while fully unloaded by LVAD was able to achieve recovery which suggests that this may be a useful screening criteria to identify which patients will be the best candidate for bridge to recovery [33].

Many centers have used similar criteria with different cut-offs which they have found to be successful and some have even published step-wise algorithms to follow. The ultimate test of recovery comes once the device is explanted and the patient must sustain their cardiac output on their. For this reason, it is always better to error on the side of caution once it comes time to make the decision to explant.

FUTURE DIRECTIONS

The concept of augmenting and replacing cardiac function has made incredible strides over the past half of a century and continues to morph to our patients' needs every day. The idea that a patient may be placed on an LVAD with the intention of explanting the device is a relatively new concept that is under heavy scrutiny. "What changes take place in the heart?" and "how do we know who will recover?" are the two questions at the core of this challenge. As we continue caring for these patients, below are a few exciting new avenues that may become available in the near future.

Multiple studies have documented that the greatest improvements in reverse remodeling and recovery have been demonstrated in patients with non-ischemic etiologies of heart failure. However, this is being largely contested in more recent studies and is an area which requires further investigation with large prospective studies [34]. If we are able to show similar improvements in patients with ischemic etiologies, we would be able to expand the patient pool of bridge to recovery patients significantly.

We mentioned that continuous flow devices are currently the primary device implanted at present but that historically pulsatile devices have shown some superior outcomes and measures. In an attempt to achieve the benefits of both styles of device, some manufacturers are experimenting with linking software with the cardiac cycle to increase and decrease flows of the continuous flow pump rapidly to emulate pulsatility [25].

As with all fields, the more we learn about the biochemistry of the human genome, the more gene therapy becomes a potential area to induce change. As just one example, a study found that an over expression of SERCA 2b in the heart leads to an increase in sarcoplasmic reticulum calcium transport which in turn leads to increased cardiac contractility [39]. The increase in sarcoplasmic reticulum calcium transport is similar to the effect that LVAD support has shown on the failing heart. Therefore, induction of over expression of SERCA 2b has become a target of gene therapy trials in an effort to enhance cardiac contractility in these patients [38].

Another recent study suggested that LVAD therapy may promote cardiomyocyte cell division in the failing heart. This was demonstrated by a decrease in polypoidy cells and an increase in diploidy cells after LVAD support which may represent division of cardiomyocytes and correlate with the recovery seen in some patients after unloading [40]. Promotion of cardiomyocyte division and regeneration should represent an excellent target for gene therapy trials in the LVAD community. This represents only a few of the exciting future directions of supplementing our approach to the heart failure patient with LVADs in whom bridge to recovery is the goal.

CONCLUSION

Despite how far we have come in circulatory support, to this day very few patients are able to achieve device separation without undergoing a transplant. Some of the key factors which predict

ability to explant the device successfully are age less than 40, duration of heart failure symptoms for less than 1 year, and non-ischemic cause of heart failure. However, all of these notions are constantly being challenged along with the ongoing debate over the impact of pulsatile devices versus continuous flow devices. It is apparent that the use of neurohormonal medications to supplement LVAD support does improve cardiac reverse remodeling and improve the chance of recovery. Ultimately, there are still many questions about which patients will achieve recovery but any patient being considered for bridge to recovery must be managed aggressively by a multi-disciplinary team with close monitoring as soon as the decision is made.

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