Myocardial Recovery by Mechanical Unloading With Left Ventricular Assist System

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It has been generally believed that advanced congestive heart failure (HF) is progressive, but there is increasing evidence that mechanical unloading with the use of left ventricular assist system (LVAS) occasionally reverses the progress of HF and permits device explantation. This “bridge to recovery” strategy is attracting interest, not only for the treatment of severe HF, but also in the study of the pathophysiological mechanisms involved in remodeling and its regression, with the hope of establishing reliable indicators of sustained recovery and strategies to enhance this process. Tissue samples obtained at the time of LVAS implantation and at explantation enabled study of the effects of LV unloading at the cellular and gene levels. However, the problem with these analyses is the lack of correlation between clinical improvement and cellular or molecular changes. Clinically, there are still many questions about the application of this strategy. The evaluation of LV function while on LVAS and the prediction of sustained recovery after explantation of the device have been the major concerns. Pharmacological regimens to promote recovery have been proposed, but require validation by multicenter study. Further investigation of the underlying mechanisms may help to establish strategies to enhance the recovery process. (Circ J 2009; 73: 1386–1392)

Key Words: Cardiomyopathy; Heart failure; Left ventricular assist device; Reverse remodeling

Advanced congestive heart failure (CHF) has been generally believed to be progressive and associated with substantial morbidity and mortality. Cardiac transplantation has been the only curative treatment for end-stage CHF, but the number of heart transplantation is severely limited, especially in Japan. Instead, there has been increasing application of left ventricular assist systems (LVAS) for the treatment of severe CHF. The LVAS consists of an electrically or pneumatically driven pump, installed either extra- or intra-corporeally. The main purpose of the LVAS is a “bridge to transplantation”, but recent refinements in the engineering of the devices have enabled long-term use as “destination therapy.”

The pump transports blood from the left ventricle (LV) to the ascending aorta, thereby restoring the systemic circulation to normal. Moreover, the pump provides potent pressure and volume unloading of the LV. These favorable effects have lead to a new indication for the use of LVAS, because there is increasing evidence that mechanical unloading with the LVAS occasionally reverses the progress of CHF and permits device explantation. This “bridge to recovery” with the LVAS is an attractive strategy for the treatment of patients with severe CHF for whom heart transplantation or permanent LVAS use has been the only treatment option. Interest relates not only to the treatment of severe CHF but also to the study of the mechanisms involved in the remodeling process and its regression (ie, “reverse remodeling”). The pathophysiological mechanisms involved in the reverse remodeling induced by mechanical unloading have become a focus of intense research, with the hope of establishing reliable indicators of sustained recovery and strategies to enhance this process.

Clinically, there still exist many questions about the application of this strategy. The evaluation of LV function while on the LVAS and the prediction of sustained recovery after device explantation have been the major concerns regarding the use of this strategy for a wider range of patients. How to evaluate LV function and decide when LVAS explantation is performed are the focus of studies. Furthermore, to promote the recovery process, pharmacological, surgical or cell-based therapies combined with LVAS, are under intense investigation. In Japan, the donor supply is severely limited and almost all patients on LVAS are waiting nearly 3 years for a heart transplant. Therefore, we have been forced to adopt more generous criteria for LVAS weaning compared with those used in studies from other countries. Based on this, we evaluated the factors that predict successful explantation of the LVAS and sustained functional LV recovery to determine if we can expand the population of patients who can benefit from the LVAS as a bridge to recovery. Both the clinical and laboratory findings, including our own of bridge to recovery experience with mechanical circulatory support, are reviewed.

Clinical Observations

An early echocardiographic study demonstrated that long-term LVAS support decreases the LV end-diastolic and...
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end-systolic volumes and increases the wall thickness. It has also been shown that LVAS improves the hemodynamic condition and resultant change in the neurohormonal axis; plasma levels of rennin, angiotensin II (AngII), norepinephrine, natriuretic peptides, and vasopressin all decreased during LVAS support. LVAS unloading induces reversal of electrophysiologic remodeling, manifested as a decrease in the duration of both QTc and QRS. These favorable effects resulted in successful explantation of the LVAS in isolated patients with acute myocarditis or post-cardiomyotony heart failure (HF) in early studies. Similar changes were observed in patients with idiopathic dilated cardiomyopathy (DCM). However, the systolic and diastolic functional changes in those patients were considered transient only as long as the ventricle was unloaded. A small number of patients with chronic DCM have been successfully weaned from LVAS support and cases of CHF recurrence after LVAS weaning were reported with a caution.

In 1997, Müller et al from the German Heart Institute, Berlin, reported their scheduled weaning protocol of combined use of the LVAS and pharmacological treatment: 5 of 11 DCM patients achieved significant recovery of LV function demonstrated by periodic LVAS off test; they were successfully weaned from LVAS support and maintained improved functional recovery. Similar observations were presented after the Berlin report. Although the clinical observations vary in each report, relatively common findings are that recovery more likely occurs in patients clinically characterized by younger age, shorter history of CHF and use of the apical drainage type of LVAS. An updated series of 35 idiopathic DCM patients followed over 12 years was recently reported by the Berlin group. 18.6% of the idiopathic DCM patients underwent LVAS implantation during the same time period, 70.7% had a 10-year survival rate with their native heart after LVAS explantation, and the HF recurrence rate at 5 years was 37.1%. The report showed that the clinical history of CHF over the 5 years before LVAS implantation is a significant predictor for recurrence of CHF in less than 5 years after LVAS removal. In contrast, a recently reported prospective multicenter study from the United States demonstrated that only 4% (2/46) of patients with chronic CHF had successful device explantation for recovery. Although those patients were not managed with aggressive medical therapy and the decision to remove the LVAS was not based on uniform clinical criteria, this low rate of device explantation in DCM patients was consistent with that in several other studies.

This large discrepancy in the population of DCM patients successfully bridged to recovery may have been related to many factors. The level of aggressiveness of pharmacological treatment during LVAS support and the drug regimen varied. The duration of LVAS support differed, as bridge-to-transplant cases were included in most of the previous reports and the waiting time differs between countries and regions. The time course of recovery of LV function is not clearly understood. Several reports have stated that early improvement of cardiac function is one of the predictors of successful recovery. Müller et al showed that the LV diastolic dimension (LVDd) and LV ejection fraction (LVEF) at 2 months after LVAS implantation significantly correlated with sustained LV recovery. Sodian et al demonstrated that the brain natriuretic peptide level in the first week after LVAS implantation was significantly lower in patients who recovered LV function. Moreover, there are concerns about myocardial atrophy with prolonged LVAS unloading; but as we previously reported, some patients only show significant recovery after 1 year of LVAS support. As the decision for LVAS explantation is not well established, patients with sufficient recovery for device removal may have been transplanted or maintained on support, so the rate of successful recovery could be underscored.

Differences in the type of device may also affect the functional recovery. Large, pulsatile-type devices such as the Novacor or HeartMate-I, which replace almost the entire LV function, can provide potent unloading of the LV compared with the small extracorporeal-type device. This difference in the amount of LV unloading may influence recovery. A recent important progress in device technology is the clinical application of continuous flow devices that use impellers in an axial or centrifugal flow system. Large pulsatile devices do not coordinate with LV ejection, so may rather increase the afterload, whereas continuous flow pumps synchronously eject blood and do not paradoxically increase afterload. This difference in the mode of unloading according to the type of device is under investigation and no conclusive data exist at this point in time. Future device development should focus on the introductory effect on the LV recovery.

Morphological Changes

Morphological changes in the hearts of patients with CHF are characterized by compensatory hypertrophy of cardiomyocytes and increased interstitial fibrosis. Many studies have reported significant decreases in cell length and diameter after LVAS support. An early report comparing the myocardium before and at 2.5 months after LVAS operation showed a 28% decrease in cell volume, a change that correlated with the duration of mechanical support and was more prominent in the LV than in the right ventricle, which is not directly unloaded by mechanical support. Those observations suggest that regression of hypertrophy is a direct effect of LV unloading. Cytoskeletal protein changes have been analyzed in several studies. De Jonge et al demonstrated that actin, tropomyosin, troponin C, troponin T and titin, which were severely damaged at the time of LVAS implantation, recovered after LVAS support although not to the normal levels. Vatta et al demonstrated a disruption to the amino-terminus of dystrophin in patients with cardiomyopathy and reversal of this change after LVAS support.

Whether a reduction of interstitial fibrosis occurs with LVAS is still controversial. Bruckner et al demonstrated a significant decrease in the total collagen content after LVAS support and Müller et al demonstrated a significant reduction of the fibrosed area in 5 patients successfully weaned from LVAS. However, Klotz et al demonstrated that actin, troponymosin, troponin C, troponin T and titin, which were severely damaged at the time of LVAS implantation, recovered after LVAS support although not to the normal levels. Vatta et al demonstrated a disruption to the amino-terminus of dystrophin in patients with cardiomyopathy and reversal of this change after LVAS support.

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changes directly translate into functional recovery of the LV. A recent LVAD Working Study Group report showed a discrepancy between the reduction in hypertrophy and the collagen content and improvement of contractile function.\cite{31} In our early experience, 5 of 11 patients had successful explantation of the LVAS after 239–663 (mean, 453) days of support. Myocardial fibrosis did not resolve, but rather worsened in all the patients during LVAS support. However, myocardial fibrosis was less severe in the recovered group (% fibrosis 17.7±8.2% at LVAS implantation vs 20.1±5.2% at explantation) compared with the non-recovered group (30.5±13.2% vs 48.4±5.1%) at both pre- and post-LVAS. Our histological analyses showed that the degree of fibrosis did not regress, but rather worsened, in most cases, including the 5 recovered patients, although the progression was slower in the recovery group.\cite{6}

### Table 1. Cellular and Molecular Changes Induced by LVAS Support

<table>
<thead>
<tr>
<th>Cell size</th>
<th>Regression of LV hypertrophy</th>
</tr>
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<tbody>
<tr>
<td>Cytoskeletal proteins</td>
<td>Actin, tropinin C&amp;T, tropomyosin, titin, desmin, β tubulin partially improved</td>
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<tr>
<td>β-adrenergic pathway</td>
<td>β-receptor density increased</td>
</tr>
<tr>
<td>Cytokine and neurohormonal changes</td>
<td>Decreased IL-6, IL-8, TNF-α</td>
</tr>
<tr>
<td>Calcium cycling</td>
<td>SERCA-2a expression increased</td>
</tr>
<tr>
<td>Apoptosis and signaling</td>
<td>Bcl-2, Bcl-XL, activated</td>
</tr>
<tr>
<td>Extracellular matrix</td>
<td>LV collagen content increased or decreased (controversial)</td>
</tr>
<tr>
<td></td>
<td>Collagen cross-linking increased</td>
</tr>
<tr>
<td></td>
<td>MMP/TIMP ratio decreased</td>
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<tr>
<td></td>
<td>Biphasic changes in volume (increased then decreased)</td>
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</tbody>
</table>

LVAS, left ventricular assist system; IL, interleukin; TNF, tumor necrosis factor; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; SERCA, sarcoplasmic reticulum Ca\(^{2+}\)-ATPase; NF-κB, nuclear factor; JNK, c-Jun N-terminal protein kinase; MEK, mitogen-activated protein kinase kinase; ERKs, extracellular signal-related kinases; GSK, glycogen synthase kinase; IGF, insulin like growth factor; MMP, matrix metalloproteinase; TIMP, tissue inhibitors of metalloproteinases.

### Mechanism of Functional Recovery

Tissue samples obtained at the time of LVAS implantation and at explantation either by transplantation, expiration or scheduled weaning, enable study of the effects of LV unloading at the cellular and molecular levels. Apoptosis contributes to progressive cardiomyocyte loss and functional decline of LV in cardiomyopathy patients. Several studies have demonstrated a significant decrease in apoptotic myocytes after LVAS support.\cite{32,33} Changes in both the pro- and anti-apoptotic factors and markers of apoptosis during LVAS support have been reported. LVAS unloading resulted in overexpression of the anti-apoptotic proteins, Bcl-2 and Bcl-XL.\cite{32,34} NF-κB is known to be associated with regulation of factors involved in the pathogenesis of CHF, including IL-6, TNF-α, Bcl-XL and hemo-oxygenase-1. NF-κB is abundantly detected in the cardiomyocytes of the failing heart and significantly decreases after LVAS support.\cite{34} Altered activity of mitogen activated protein kinase families, such as ERKs, JNK, p38, and Akt, after LVAS support have been reported.\cite{33} These kinases show a sensitivity to mechanical stress of the myocardium and the changes may contribute to the favorable effect of LVAS support on myocardial apoptosis and hypertrophy.

Ogletree-Hughes et al demonstrated that LVAS support restored β-adrenergic receptor density and the inotropic response to isoproterenol in isolated trabecular cardiomyocytes by comparing those from failing hearts with or without LVAS and a normal control.\cite{36} Reversal of contractile function is known to be associated with altered expression of Ca\(^{2+}\) handling proteins, such as sarcoplasmic endoreticular Ca\(^{2+}\) ATPase subtype 2a, and the ryanodine receptor. Isolated myocytes demonstrated normalization of the magnitude and time course of intracellular Ca\(^{2+}\) transients.\cite{37}

Remodeling of the ECM plays a critical role in adverse LV remodeling and dysfunction. An imbalance of matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitors of MMPs (TIMPs)) promote adverse ECM and LV remodeling. Cumulative evidence has shown that LV unloading with the LVAS does not necessarily result in favorable ECM change. Klotz et al demonstrated a decreased MMP-1/TIMP-1 ratio and an increased tissue level of AngII after LVAS support, suggesting decreased degradation and increased synthesis of the ECM. This finding may be explained by the fact that fibroblast function is not load dependent. Strategies to promote favorable ECM changes under LVAS support need to be investigated further.

There have been many other reports analyzing factors related to the reverse remodeling by LVAS (Table 1). However, a problem with these analyses is the lack of correlation between clinical improvement and cellular or molecular improvement. No data exist to suggest which molecular change most predicts the functional recovery of the LV.
Prediction of Myocardial Recovery

There have been limited reports of the criteria for LVAS explantation, but most have used echocardiographic measurements and hemodynamic parameters from right heart catheterization during the temporal LVAS halt as the criteria for explantation. The LVAS off test is performed after intravenous administration of heparin with the device completely turned off for 10–15 min. The Berlin Heart Institute group has used the criteria of LVEF >45%, LVDd <55 mm, and pulmonary artery and central venous pressures in the normal range during the pump off test as sufficient LV recovery for scheduled LVAS explantation. Birks et al also used almost the same echocardiographic criteria (LVEF >45%, LVDd <60 mm, LVDs <50 mm), but added maximal oxygen consumption during exercise testing >16 ml · kg⁻¹ · min⁻¹ as a consideration for LVAS explantation. The Texas Heart Institute group used dobutamine stress echocardiography and reported that 6 of 9 patients with a favorable response to dobutamine load up to 40 μg · kg⁻¹ · min⁻¹ survived after LVAS explantation. Therefore, “near complete” recovery of cardiac function has been considered a requirement for successful LVAS explantation, but the long-term sustainability of LV recovery in these patients remains unclear. Some of the past reports described early recurrence of LV failure once the recovered heart is re-exposed to hemodynamic stress. Recent long-term follow-up data from Berlin have analyzed factors for >5 years of cardiac stability after LVAS removal. LVEF <45%, LVDd >55 mm, and CHF history >5 years were significant risk factors. More than 10% worsening of LVEF, LVDd, and the relative wall thickness of the LV (interventricular septum + posterior wall thickness/LVDd) at the final off test compared with the best off-test results, which may reflect instability of LV function at the time of LVAS removal, were other risk factors. The post-weaning LVEF and LVDd worsening in the first 6 months were significant risk factors. Therefore, close observation in the first 6 months is mandatory.

Correlation of the histological data at LVAS implantation and LV functional recovery was studied by Bruckner et al who demonstrated that in the patients who had significant improvement of LVEF, significantly less fibrosis and myocyte size was observed at the time of LVAS implantation compared with those who did not have EF improvement. None of their patients, however, had device explantation.

**Osaka University Experience**

There have been limited reports of the results of LVAS explantation from patients with only partial recovery of cardiac function. In Japan, donor supply is severely limited and almost all patients on LVAS are awaiting heart transplant for nearly 3 years; so more generous criteria for LVAS weaning have had to be adopted. From December 1999 to April 2008, 74 patients underwent LVAS implantation at Osaka University Hospital; data from 34 of them who underwent the LVAS off test using echocardiography and right heart catheterization were analyzed. Mean age was 32.8±17.8 years (range, 7–69 years) and the diagnosis was DCM in 20 patients, ischemic cardiomyopathy in 9, secondary cardiomyopathy in 3, and myocarditis in 2. Our protocol for scheduled LVAS weaning is shown in Figure. To facilitate future LVAS explantation, adjunctive operative procedures such as mitral annuloplasty (n=17), LV pacing lead implantation for cardiac resynchronization therapy (CRT) (n=5) or LV restoration (n=4) were performed at the time of LVAS implantation if indicated. As soon as the patient’s general condition was stabilized and organ dysfunction recovered, medical treatment for HF was instituted. Our regimen includes angiotensin-converting enzyme inhibitors (ACEI), spironolactone, and β-blocker.

**Table 2. Criteria for Weaning at the LVAS Off Test and Results in Each Category**

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>1. Standard criteria (near complete recovery)</td>
<td>LVEF ≥45%, LVEDd ≤55 mm, Pulmonary artery and central venous pressure in normal range</td>
<td>→ 7 patients fulfilled the standard criteria and underwent LVAS removal.</td>
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<tr>
<td></td>
<td>CHF recurred in 2 patients (LVAS re-implantation at 3 and 22 months)</td>
<td>All have been symptom free</td>
</tr>
<tr>
<td>2. Expanded criteria (partial recovery)</td>
<td>45% ≥ LVEF ≥30%, 55 mm ≤ LVEDd ≤ 65 mm</td>
<td>→ 5 patients fulfilled the expanded criteria and underwent LVAS removal.</td>
</tr>
</tbody>
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LVAS, left ventricular assist system; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic dimension; CHF, congestive heart failure; PCWP, pulmonary capillary wedge pressure.
(carvedilol). Carvedilol is initiated at a dosage of 2.5 mg/day and doubled every week until a dosage of 20–40 mg/day is reached.

The LVAS was removed in patients who met the standard criteria proposed by the Berlin group (LVEF >45%, LVDd <55 mm, and pulmonary artery and central venous pressures in the normal range). Even if the patient did not meet the standard criteria, the LVAS was removed electively in those who had LVEF >30%, LVDd <65 mm, no significant decrease in LVEF and no increase in the pulmonary capillary wedge pressure (PCWP) (Table 2). The rationale for the expanded criteria is as follows. Each patient has a different degree of volume loading, so only 1 point of hemodynamic parameter can not fully address LV performance. We can speculate about the systolic and diastolic LV performance from the change in LVdVd, LVEF and PCWP when the LV is volume-loaded by turning off the LVAS. If a patient has a decrease in LVEF when the LV is loaded that ventricle may have poor systolic function. If the PCWP increases significantly when the LV is loaded, that LV may have poor compliance. In contrast, even if the absolute values of LVEF and LVDd are below the standard criteria, increased LVEF with minimal PCWP change by loading the LV by stopping LVAS suggests preserved systolic and diastolic function. A total of 16 patients underwent LVAS explantation after 376±244 days (range, 76–743 days) of LVAS support, and 9 have been free from recurrence of HF for a mean duration from LVAS explantation of 4.5±1.8 years. All 7 patients who met the standard criteria underwent LVAS removal; CHF recurred in 2 and LVAS re-implantation was required at 3 and 22 months, respectively, after LVAS removal. Five patients met the expanded criteria; 4 of them underwent LVAS removal and have been symptom-free for 3.7±2.1 years. Five patients who did not meet either the standard or expanded criteria underwent emergency LVAS removal because of severe life-threatening LVAS-related complications, and all of them had recurrence of HF.

We also found that the degree of cardiac fibrosis and myocyte size correlated significantly with improvement of the echocardiographic and hemodynamic parameters at the LVAS off test. More importantly, the degree of cardiac fibrosis and of cellular hypertrophy predicted successful LVAS removal. The optimal cut-off values for cardiac fibrosis and of cellular hypertrophy predicted successful LVAS removal. The optimal cut-off values for cardiac fibrosis and myocyte size to predict successful explantation were 12.5% and 26.5 μm, respectively. Two patients who fulfilled the standard criteria, but had a recurrence of HF, had relatively higher cell diameter and fibrosis and at least 1 of those parameters was above the cut-off line. Therefore, by combining the results of the LVAS off test and the histological findings at LVAS implantation, we may be able to predict the sustainability of LV function more precisely. Our results may lend support to the application of expanded criteria to patients with partial recovery of LV function, especially in the situation of severely limited heart donors and lack of reliable devices for long-term use.

**Strategies to Enhance Myocardial Recovery**

Pharmacological treatment during LVAS support could be an important factor in enhancing myocardial recovery. Large clinical trials of pharmacological therapy for CHF have shown that β-blockers, ACEI, aldosterone antagonists, and AngII blockers (ARB) can reduce or sometimes partly reverse remodeling. Several centers, including Berlin, our own and Harefield, which have reported a relatively high incidence of successful recovery cases, have used sufficient doses of these pharmacological treatments during LVAS. All the patients received ACEIs, ARBs, aldosterone antagonists, and β-blockers, which were initiated during LVAS support and continued after explantation. Some of the patients were in severe HF and could not tolerate pharmacological therapy, especially β-blockers, preoperatively. LVAS enabled sufficient pharmacological therapy in all the patients, which might have contributed to the functional LV recovery. A recent report demonstrated that ACEIs decreased the tissue AngII concentration and the total and cross-linked collagen, normalized the MMP-1 and TIMP-1 ratio, and decreased LV mass and myocardial stiffness during LVAS support. Interestingly, in the right ventricle, ACEIs decreased AngII and normalized the MMP-1/TIMP-1 ratio, but not the collagen content or the chamber volume and stiffness. Therefore, both unloading and ACEIs are required to decrease collagen and stiffness. These findings highlight the importance of the pharmacological agents used during LVAS therapy.

Birks et al demonstrated a high rate (11 of 15 DCM patients) of recovery with the use of clenbuterol, a selective β2 agonist, together with a β1 antagonist. They implanted the LVAS and treated the patient with lisinopril, carvedilol, spironolactone, and losartan. When the maximal decrease in the LV dimensions was obtained, administration of clenbuterol was initiated and carvedilol was replaced by the β1-selective blocker, bisoprolol. The rationale of their strategy, the so-called “Harefield protocol”, is to achieve maximal reverse remodeling by a combination of LVAS and pharmacological treatment, followed by stimulation of physiological hypertrophy by clenbuterol. As previously demonstrated, there are concerns about myocardial atrophy with prolonged LVAS unloading. 3,22 β2 agonists are known to induce skeletal muscle hypertrophy and improve performance, and also to stimulate physiological hypertrophy of the myocardium without an increase of apoptosis. Transgenic mice over-expressing β2 receptors have enhanced myocardial function with normal survival. 4,6,7 Insulin-like growth factor 1 gene expression is enhanced by clenbuterol, which could exert several beneficial effects, including anti-apoptosis, adaptive hypertrophy and reduction of fibrosis. However, this protocol did not show a significant improvement of cardiac function in another facility. 4,4 A larger multi-institutional study is required to elucidate the effectiveness of clenbuterol therapy.

Support with the LVAS can serve as a platform for other modalities reversing HF, which may include not only surgical or pharmacological treatment, but also gene- or cell-based therapy. CRT is another possible contributor to successful recovery. One of our patients demonstrated improvement of LV function and hemodynamic parameters during the LVAS off test after undergoing CRT. LVAS therapy is reported to be associated with improved dyssynchrony by LV unloading, but not all the patients on LVAS have normalization of dyssynchrony. CRT could be a treatment option promoting recovery of LV performance. In the same manner, the operative procedure concomitantly performed with LVAS implantation, such as mitral repair or LV restoration, may play a role in the recovery of LV performance and sustained improvement of CHF symptoms. However, these operative adjuncts may increase the operative risk, thus careful consideration of possible benefits obtained from those procedures is required for each.
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Conclusions

LVAS support leads to improved cardiac performance in a subset of patients with profound HF. Many morphological and molecular changes are demonstrated after LVAS use and some of the pathophysiological processes involved in progression of CHF have been identified as reversible. However, there is a discrepancy between these molecular changes and clinical observations. Further understanding of the basic biology related to this process may help establishing novel pharmacological or cell- or gene-based therapies combined with LVAS in the future.

References

matrix after prolonged left ventricular assist device support follows a biphasic pattern. *J Heart Lung Transplant* 2006; **25**: 1091–1098.


