Long-Term Results in Patients With Idiopathic Dilated Cardiomyopathy After Weaning From Left Ventricular Assist Devices

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Background—Since our first successful left ventricular assist device (LVAD) explantation in a patient with idiopathic dilated cardiomyopathy (IDCM) in 1995, an additional 31 IDCM patients have been weaned in our department. Echocardiographic evaluations during repeated “off-pump” trials were the cornerstone for weaning decisions. After 9 years of experience, we assessed the reliability of our weaning criteria in light of the long-term results.

Methods and Results—We evaluated all of the IDCM patients who were weaned between March 1995 and March 2004 with regard to preservation of cardiac function without LVAD support and survival after weaning. Additionally, we reviewed our echocardiographic data to assess their predictive value for long-term stability of cardiac function after weaning. The 32 weaned IDCM patients showed a survival rate of 78.3%±8.1 at 5 years after LVAD explantation. Heart failure (HF) recurred during the first 3 years after weaning in 31.3%. Only 2 patients died because of HF after weaning; the other patients with HF recurrence were successfully transplanted. Off-pump LV end-diastolic diameter >55 mm and/or LVEF <45% before LVAD removal, as well as history of HF ≥5 years before LVAD implantation, appeared to be major risk factors for early recurrence of HF. Patients without any of these 3 risk factors showed no HF recurrence during the first 3 years after weaning, but at the same time, all of those with at least 2 of these 3 risk factors developed early recurrence of HF. In patients with HF recurrence during the first 3 postweaning years, a significant LVEF decrease already occurred during the first month after weaning, whereas in those with long-term stable cardiac function even at the end of the sixth postweaning month, the LVEF was not different from that before LVAD removal.

Conclusions—For selected patients with IDCM, weaning from LVADs is a clinical option with good results over 9 years and should, therefore, be considered in those with cardiac recovery after LVAD implantation. Off-pump echocardiographic data are reliable for the detection of LV recovery and prediction of long-term cardiac stability after weaning.

Key Words: cardiomyopathy ■ heart assist device ■ heart failure ■ survival ■ echocardiography

For the majority of patients with end-stage heart failure (HF), heart transplantation (HTx) continues to be the “ultimate” therapeutic option. However, the increased demand for donor organs has resulted in increasing waiting times from listing up to HTx. The use of mechanical assist devices is often the only possible means of supporting these patients in the form of bridging to transplantation until a donor heart becomes available.

The bridge-to-transplant concept is life-saving for the individual patient, but it does not solve the basic problem, that is, limited donor organ supply. Promising potential alternatives are the permanent use of ventricular assist devices, especially for patients with high risk for HTx, or their temporary application with the goal of long-term myocardial improvement (“bridge to functional recovery”).

Most cases of cardiac recovery with ventricular assist devices have been noted in individuals with postcardiotomy HF and in patients with acute myocardial infarction in whom the stunning of potentially viable myocardium had occurred.1 There is also increasing evidence that severe acute myocarditis and noncoronary shock can completely reverse after weeks to months of mechanical ventricular support.2–4 Also, some patients with more chronic, advanced end-stage HF because of idiopathic dilated cardiomyopathy (IDCM) have been seen to show astonishing left ventricular (LV) size reduction during unloading with a left ventricular assist device (LVAD) with improvement or even restoration of cardiac function.5–7

Elective explantation of an LVAD (Novacor) implanted because of severe IDCM was first performed in our institution in March 1995, in a 39-year-old man, after 160 days of mechanical circulatory support.8 Since then, attempts to wean IDCM patients from LVADs have been limited in number, and, therefore, data on the outcome of patients who were
Many open questions have to be answered before the use of ventricular assist devices as a “bridge to myocardial improvement” is feasible. Such questions are as follows: (1) Is persistent long-term recovery possible? (2) Which criteria indicate complete and stable cardiac recovery on ventricular assist devices? (3) What is the ideal time to remove the device once recovery appears to have occurred? (4) Is it possible to predict reliably the long-term success of weaning from ventricular assist devices primarily designated as bridge to transplantation? (5) Will it also be possible to prospectively identify patients who would benefit from elective LVAD insertion primarily designated as a bridge to myocardial improvement? (6) Which additional treatment should be applied to enhance and stimulate myocardial improvement?

After >9 years of experience with IDCM patients who showed relevant myocardial improvement after LVAD implantation, we assessed their long-term results to provide more data on the stability and reliability of cardiac recovery after weaning from LVAD. Because echocardiographic evaluation of ventricular function during repeated off-pump trials was the cornerstone for weaning decisions, we also assessed the predictive value of echocardiographic data for the long-term stability of cardiac function after LVAD removal.

Methods

Patients

All of the patients >14 years of age with nonischemic IDCM who were weaned from LVADs in our department between March 1995 and March 2004 were evaluated with regard to the preservation of stable cardiac function without LVAD support and survival after weaning. We restricted the evaluation to patients in whom there was no angiographic evidence of coronary stenoses, myocardial tissue specimens obtained before LVAD implantation showed no histological signs of acute myocarditis, and virological examinations did not reveal evidence of a virus infection that could have caused the myocardial disease. Polymerase chain reactions for cytomegalovirus, enterovirus, and adenoviruses were negative. In situ hybridization for these viruses, as well as for coxackievirus, Epstein-Barr virus, and herpes viruses were also negative. Of 35 patients with IDCM without evidence of acute myocarditis who were weaned during the evaluation period, 32 fulfilled these criteria and were included in the evaluation. One patient with IDC was excluded; because he received a biventricular assist device. Another patient who was successfully weaned 33 months ago was excluded, because no myocardial tissue specimens for histological examination were obtained before pump implantation and also because the device he had was a biventricular assist device. A third patient who was successfully weaned from an LVAD 19 months ago was excluded because of angiographic evidence for coronary artery stenoses, although the severity of LV dilation and the diffuseness of functional impairment could hardly be related only to his moderate degree of coronary disease.

Before LVAD implantation, all of the patients had irreversible end-stage HF and required positive inotropic support without any possibility of weaning from IV catecholamines. During LV unloading, all of the patients were treated with β-blockers (metoprolol or carvedilol), angiotensin-converting enzyme inhibitors (enalapril or ramipril), aldosterone antagonists (spironolactone), low-dose loop diuretics (furosemide or torsemide), and digitals. This pharmacological regimen was aimed at the reduction of cardiac work. The doses of each pharmacological agent were individually adapted to reduce both heart rate toward the optimum of 55 bpm and blood pressure to the lowest optimally tolerated value, as well as to maintain optimal renal function, ensuring favorable natriuresis without excessive loss of potassium and magnesium. This treatment was also continued in all of the weaned patients.

Cardiac Assist Devices

Between March 1995 and March 2004, LVADs were implanted in 131 patients with end-stage nonischemic IDCM. Of these, 32 (24.4%) were weaned from the LVAD after evidence of relevant and stable cardiac improvement. Of the weaned patients, 27 had a Novacor LVAD, 3 had a TCI LVAD, and 2 patients had a Berlin Heart LVAD (one of them a Berlin Heart Incor axial flow pump).

All of the patients consented to device implantation as a bridge to transplantation. No attempts have been made to use assist devices electively with the aim of myocardial recovery only.

The LVAD implantation and explantation procedures have been described in detail previously. The explanation followed the fundamental rule of maintaining the recovered heart in a state as unmolested as possible. Therefore, during LVAD removal, the intrathoracic part of both cannulas was left in place in the cardiac structures after careful closing by ligation or blocking with a preformed plug. Early in the postexplantation period, we also avoid inotropic therapy as much as possible and minimize volume loading.

Assessment of Cardiac Recovery During Mechanical Unloading

Although LVADs were implanted as the ultimate life-saving therapeutic option for patients with inotrope-dependent, chronic end-stage HF, after implantation we monitored the cardiac function in all of the patients to select those in whom cardiac improvement might be sufficient and stable enough to allow LVAD removal. Noninvasive follow-up examinations by echocardiography were used for recovery assessment.

To monitor myocyte recovery during LV unloading, we also looked for anti-β1-adrenoeceptor autoantibodies (A-β1-AABs) immediately before LVAD implantation and, thereafter, weekly during the entire period of mechanical circulatory support. The underlying principle of the bioassay for A-β1-AAB measurement was registration of the chronotropic effect of A-β1-AABs on primary cultures of neonatal rat cardiomyocytes. The increase in number of contractions after the addition of the IgG fraction prepared from the patient’s serum is defined and given in laboratory units (LU). Values ≤0.5 LU are considered negative, and values >3 LU positive.

The effects of unloading on LV size, shape, and contraction were evaluated by weekly echocardiographic examinations. If, with the regularly running pump, the LV wall motion and diameters showed tendencies to normalization, the pulsatile pumps were set at the lowest pumping frequency and then intermittently stopped for few minutes (off-pump trial) to evaluate the heart without mechanical support. To prevent thrombus formation inside the pump, heparin was administered IV before each off-pump trial. Additionally, during the off-pump period, the device was allowed to pump once a minute. In patients with axial flow pumps, which generate negative pressures at their inflow site, stopping or low-rotor speed leads to retrograde flow of different degrees into the ventricle, which can be misleading for the evaluation of cardiac function. Therefore, in these cases, we reduced the rotor speed to a value that results in a zero net flow over the time of 1 cardiac cycle. In patients with evidence of relevant cardiac recovery, such off-pump examinations (or trials with reduced rotor speed in the case of axial pumps) were conducted once a week until the final decision for LVAD explantation was made. Once the degree of recovery was deemed complete, as previously described in detail, the working mode of the pumps was also changed to exert moderate load on the ventricular muscle. To avoid excessive stimulation of the unloaded myocardium during the process of recovery, dobutamine stress echocardiography was not performed during the off-pump trials.
To evaluate cardiac recovery, the following echocardiographic parameters were measured: (1) LV end-diastolic and end-systolic internal diameters (LVIDd and LVIDs, respectively); (2) LV ejection fraction (LVEF); (3) LV end-diastolic relative wall thickness (RWT = 2 × xterior wall thickness/LVIDd); (4) LV systolic wall thickening (%) at the interventricular septum and posterior wall; (5) short to long axis ratio (sphericity index); (6) Doppler derived stroke volume as the product of time velocity integral (measured with pulsed-wave Doppler at the LV outflow tract) and cross-sectional area of the LV outflow tract; (7) Doppler indices of diastolic function (transmitral flow and isovolumetric relaxation time); (8) right ventricular diameters and ejection fraction; and (9) estimated pulmonary arterial systolic pressure in patients with tricuspid valve regurgitation.

During the last 5 years, LV recovery was also evaluated by measurements of systolic wall motion peak velocities (Sm) at the basal posterior wall with pulsed-wave tissue Doppler. To evaluate LV subendocardial circumferential and midmyocardial longitudinal wall motion, pulsed-wave tissue Doppler was obtained in each patient from the basal posterior wall, in the parasternal axis view at the level of the mitral leaflet edges, and in the apical long axis view 1 cm above the mitral annulus. The methodology was identical to that used routinely by us for follow-up examinations after HTx and has been described previously. In 10 patients we also evaluated by histomorphometry the amount of fibrosis in both myocardial samples obtained during LVAD implantation and biopsy material taken before pump explantation, using a methodology previously described in detail.

Criteria for Weaning From LVAD

During repeated follow-up echocardiographic examinations while on LVAD, the majority of patients demonstrated some improvement of cardiac function. In 32 IDCM patients, myocardial recovery was deemed sufficient to allow safe pump explantation with a low risk of short-term recurrence of HF. In 27 of these patients, the decision for weaning was made electively. In 5 patients, pump explantation was prompted by pump-related complications (pump pocket or valve infection, thromboembolism, or intractable pain at pump pocket), when recovery, as shown by echocardiography, was less than complete but seemingly sufficient for safe LVAD explantation.

Because of the lack of clinical data on the outcome of IDCM patients with their native hearts after LVAD explantation, the stability of cardiac improvement after LVAD removal was not predictable before our first attempts to wean patients with IDCM. However, after the successful weaning of 2 patients from LVAD, one with off-pump LVAD of 48 mm and LVEF of 55%, the other with off-pump LVAD of 46 mm and LVEF of 45%, LVAD removal was considered to be safe if, during repeated off-pump trials performed over several days, the maximum LVIDd was 55 mm and the minimum LVEF 45% while the right ventricular diameters and function remained stable. In patients without off-pump restrictive transmural flow patterns who showed a normal stroke volume and no relevant alteration of LV geometry (RWT > 0.30 and sphericity index < 0.8), less than complete recovery in LV size (LVIDd 56 to 60 mm) and/or ejection fraction (LVEF 30% to 44%) was accepted as being sufficient for safe LVAD explantation. Thus, in 8 patients, LVAD removal was performed electively, although off-pump LVAD was 56 to 60 mm and LVEF was 30% to 44%.

In patients selected by echocardiography for possible weaning, right heart catheterization with hemodynamic measurements was also performed during ≥ 1 off-pump trials. Evidence of relevant pulmonary arterial and central venous pressure increase beyond the normal ranges was considered a contraindication for immediate LVAD explantation, especially for patients with borderline echocardiographic data (off-pump LVIDd > 55 mm and/or LVEF < 45%). We did not consider any histological aspects for our weaning decisions.

Follow-Up Examinations After Weaning

For the evaluation of cardiac function after LVAD removal, the same echocardiographic parameters that were used for weaning decisions were measured during the routine follow-up examinations. These parameters were also the cornerstone for the decision to list the weaned patients for HTx. During the first postweaning week, echocardiographic follow-up was performed daily; thereafter, it was performed each second day. During rehabilitation, follow-up checks were performed weekly. Three to 5 weeks after device removal, the patients were discharged home. In outpatients, the frequency of scheduled follow-up visits varied according to the postweaning time between monthly (during the first postweaning year) and every 6 months (after 3 years).

Exercise tolerance after LVAD removal was evaluated by a maximum (symptom-limited) incremental treadmill exercise test according to Naughton’s protocol. This examination was not performed before 2 to 3 months postoperatively. During the last 2 years, at each follow-up examination, plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) were also measured in all of the patients weaned from ventricular assist devices.

Predictability of the Outcome After LVAD Removal

To calculate the predictive value of echocardiographic parameters for long-term stable cardiac function, we used the echocardiographic data obtained during the final off-pump trial (or final trial with reduced rotor speed in the case of axial pumps) before LVAD explantation.

Statistics

For all of the quantitative data, means and SDs were calculated. Differences between groups were measured using the Mann-Whitney test. Differences between values before explantation and at other time points were calculated by the Wilcoxon signed rank test. The Bonferroni-Holm method was used to adjust for multiple testing. Kaplan-Meier curves were performed for survival and freedom from transplantation. Odds ratios and 95% CIs were calculated for dichotomized risk factors.

Results

Of the 32 evaluated IDCM patients who were weaned from LVAD (age, 41.8 ± 12.6 years), 30 (93.8%) were men. The duration of HF before LVAD implantation was 4.3 ± 3.7 years, and the duration of LVAD support was 4.6 ± 4.4 months (range, 3 weeks to 8 months). None of the weaned patients had an implantable cardioverter-defibrillator, and none of these patients underwent resynchronization therapy, either before LVAD implantation or after weaning.

Survival After Weaning From LVAD

Of the 32 weaned IDCM patients, a total of 6 (18.75%) died during the first 3 years after weaning (Figure 1). However, 4 (66.7%) of these 6 early postweaning deaths were unrelated to cardiac disease. Thus, during the first week after LVAD removal, 1 patient with infection at the LVAD conduits before weaning died because of septic shock, and 1 patient died because of severe pulmonary bleeding. The other 2 deaths unrelated to cardiac disease occurred later, after longer asymptomatic periods with optimally stable cardiac function. One of these patients died suddenly 4 months after weaning because of acute pulmonary arterial emboli; the other died 2.5 years after LVAD removal because of severe infection at the residual apical inflow conduit. With the option of HTx or second LVAD implantation, the 5-year survival rate after LVAD removal reached 78.3 ± 8.1% (Figure 2a).
Recurrence of HF during the first 3 years after LVAD removal was found in 31.3% of the weaned patients. In 4 patients, HF recurred beyond the third postweaning year (Figure 1). HTx was performed in 11 of the 14 patients with recurrent HF. Only 2 patients with postweaning HF recurrence died before HTx or implantation of another LVAD could be performed. One of these died on the third postweaning day, but for him neither a second LVAD implantation nor HTx were indicated, because of severe diffuse cerebral lesions and pump pocket infection, which were already present before LVAD removal. The other cardiac death occurred during rapid worsening of cardiac function after 2 years of postweaning cardiac stability in a patient with a long history of HF (>6 years) before LVAD implantation.

LVAD reimplantation before HTx was performed in 2 patients, one with HF recurrence at 6 months after weaning and the other with late recurrence of HF after >5 years of optimally stable cardiac function. With these optimally timed transplantations or LVAD reimplantations, there were no significant survival differences between the weaned patients with and without HF recurrence (Figure 2b). Of the weaned patients, by 3 years and 5 years after LVAD removal, 69.4±8.5% and 58.2±10.2%, respectively, were free from recurrent HF (Figure 2c).

Among the 17 patients without cardiac alteration during the first 3 years after LVAD removal, 15 (88.2%) were in functional New York Heart Association (NYHA) class II or lower at the end of the third postweaning year. The other 2, who also showed good cardiac function, were not capable of great physical activities because of neurological sequelae after cerebral vascular accidents, which occurred before LVAD removal. Of 15 patients with stable cardiac function during the first 3 postweaning years who were <50 years of age, 12 (80.0%) were able to resume their professional activities.

In patients with long-term cardiac stability after LVAD removal, exercise testing performed between the third and fourth year (3.6±0.6 years) after weaning revealed good exercise tolerance. Thus, expressed as a percentage of the predictive values, the maximum oxygen uptake reached 78±4.3%, the anaerobic threshold was 88.7±16.7%, the maximum oxygen pulse (quotient of the oxygen uptake and heart rate) was 93.1±9.7%, and the oxygen uptake to work rate relationship (ΔVo2/WR) was 94.2±18.2%. The ventilatory equivalent for CO2 was 30.2±3.3 in these patients.

We found significant differences between patients with and without recurrence of HF during the first 3 years after LVAD removal with regard to their age at LVAD removal, history of HF before LVAD implantation, duration of mechanical support, and LVEF and LVIDd before LVAD removal (Table 1). Thus, patients with HF recurrence during the first 3 postweaning years were older and had a longer history of HF before LVAD implantation, the duration of LVAD support necessary for recovery was longer, and, at the time of LVAD removal, the LVEF was lower and the LVIDd was larger than in patients without early recurrence of HF. Among the 17 patients without cardiac alteration during the first 3 years after LVAD removal, 11 (64.5%) had an HF history of >2 years before LVAD implantation. Of the other 5 patients with shorter HF history, 1 had familial (autosomal dominant) dilated cardiomyopathy, and 1 had a long history of ventricular arrhythmias before the first evidence of HF. LVEF and LVIDd measured before LVAD implantation were not significantly different between patients with and without long-term (>3 years) freedom from recurrent HF (Table 1).

Of the 32 weaned patients, 31 (96.9%) tested positive for A-β1-AABs before LVAD implantation, and in 30 (96.8%) of these the auto-antibodies disappeared after 3 to 31 weeks of LV unloading. Between patients with and without HF recurrence during the first 3 years after weaning, there were no significant differences for serum levels of A-β1-AABs at the time of LVAD implantation or for the disappearance time of A-β1-AABs during LVAD support (Table 1). In patients with recurrence of HF during the first 3 years after LVAD removal, significant LVEF decrease (from 41.1±4.9% to 33.7±8%) already occurred during the first month after weaning, whereas in the group with stable cardiac function after weaning even at the end of the sixth postweaning month, the LVEF values were not significantly lower than before LVAD removal (Figure 3).

All of the patients with cardiac stability after weaning showed systolic radial and longitudinal wall motion peak velocities (Sm) at the basal posterior wall >8 cm/s. Patients with cardiac stability after LVAD removal showed only slightly elevated NT-proBNP levels even late after weaning (156.9±89.3 pg/mL at 6.6±2.0 years after weaning).

Predictability of Long-Term Cardiac Stability After LVAD Removal

As mentioned before, off-pump values of ≥45% for LVEF and ≤55 mm for LVIDd were considered reliable for safe LVAD removal. Indeed, follow-up monitoring showed that 80% of those with LVEF ≥45% at the time of LVAD removal were free from HF recurrence during the first 3 postweaning years. The risk for early recurrence of HF appeared 24 times higher for those with preweaning LVEF <45% in comparison with those with LVEF ≥45%. The risk for early recurrence of HF was also 30 times higher for patients with preweaning off-pump LVIDd >55 mm than for those with off-pump LVIDd ≤55 mm. Also, patients with a
history of HF of ≥5 years before LVAD implantation showed
88.9% probability for HF recurrence during the first 3 years
after LVAD removal and were at 64-times higher risk for HF
recurrence during this time than those with a history of HF
<5 years.

LVIDd >55 mm and/or LVEF <45% before LVAD
removal, as well as history of HF ≥5 years before LVAD
implantation, appeared to be major risk factors for early
recurrence of HF after weaning (Table 2). Without any of
these 3 risk factors, there was no HF recurrence in our IDCM
patients during the first 3 postweaning years, and only 33.3%
of those with 1 of these 3 risk factors showed early recurrence
of HF. However, not only all of the patients with all 3 risk
factors, but also all of those with only 2 of these 3 risk factors
showed HF recurrence during the first 3 years after LVAD
removal. None of the patients with long-term cardiac stability
had LVEF <40% and/or LVIDd >60 mm or experienced
IDCM for >6 years. Off-pump LVEF <40% appeared to be
100% predictable for early recurrence of HF.

Off-pump LVEF values of ≥45% showed a positive
predictive value of 80% for long-term (≥3 years) cardiac
stability after weaning (Table 3). All 4 of the patients with
early recurrence of HF despite LVEF values ≥45% at the
time of LVAD removal had HF histories of >5 years before
LVAD implantation. Using LVEF and LVIDd together, we
found for LVEF ≥45% and LVIDd ≤55 mm a positive
predictive value of 93.8% for long-term cardiac stability
(Table 3).
Although the prevalence of patients with high-sphericity index values (≥0.75) at the time of LVAD removal was higher in the group with early recurrence of HF than in the group with long-term (>3 years) cardiac stability after weaning, the mean values of this index were not significantly different between patients with and without early recurrence of HF. The RWT and systolic wall thickening measured at the time of LVAD removal were also not significantly different between patients with and without early recurrence of HF after LVAD removal. There were also no significant differences between Doppler indices of diastolic function (transmitral early rapid filling (E)/atrial contraction (A) flow velocity ratio (E/A), deceleration time of the E wave and isovolumetric relaxation time) measured before LVAD removal in patients with and without early recurrence of HF after weaning.

The small amount of histological data was insufficient for the evaluation of their predictive value for functional cardiac recovery. Comparative histomorphometry showed a $34.7\pm27.2\%$ reduction of the relative content of fibrosis during unloading. In only 1 of the 10 investigated patients was there no reduction in fibrosis during LV unloading.

### Table 1. Comparison of IDC Patients With Heart Failure Recurrence During the First 3 Years After VAD Removal With Those Who Exhibited Long-lasting Cardiac Recovery

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Recurrence of HF (n=10)</th>
<th>Lasting Recovery (n=17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>47.6±10.6</td>
<td>36.8±10.3</td>
<td>0.020</td>
</tr>
<tr>
<td>LVIDd (mm) at time of LVAD implantation</td>
<td>77.9±7.1</td>
<td>74.1±7.1</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%) at time of LVAD implantation</td>
<td>15.7±3.7</td>
<td>15.4±3.2</td>
<td>NS</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>7.6±4.1</td>
<td>2.5±1.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Serum A-β1-AABs (LU) at time of implantation</td>
<td>5.4±1.8</td>
<td>5.0±2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of mechanical support, months</td>
<td>7.0±6.0</td>
<td>3.1±2.1</td>
<td>0.040</td>
</tr>
<tr>
<td>LVIDd (mm) at time of LVAD removal</td>
<td>58.3±5.9</td>
<td>50.9±4.6</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF (%) at time of LVAD removal</td>
<td>41.4±4.7</td>
<td>49.4±4.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time (months) to disappearance of serum A-β1-AABs</td>
<td>2.3±0.9</td>
<td>2.7±1.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant.

![Figure 3. Time course of LV ejection fraction (top) and end-diastolic diameter (bottom) during the first 6 months after LVAD removal in patients with IDCM.](http://circ.ahajournals.org/)

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Regression of myocardial hypertrophy during unloading was also shown in 9 of the 10 weaned patients in whom a comparative histological evaluation was retrospectively possible.

Discussion

Myocardial Improvement in IDCM Patients During LV Unloading

The present data confirm our previous observation that restoration of heart size and function can be obtained by LVAD support, even in patients with advanced IDCM, a disease that, until recently, was considered to be almost irreversible. It remains, however, difficult to characterize patients who may have the potential for optimal and stable cardiac recovery. Our IDCM patients with lasting recovery for ≥3 years after weaning were younger and had shorter HF histories before LVAD implantation. Hearts that were less chronically altered appeared to have a better prospect for recovery, but neither the LVIdd nor the LVEF measured before LVAD implantation appeared predictive for myocardial improvement. At present, it is still not possible to prospectively identify those IDCM patients who would benefit from elective LVAD insertion primarily designated as a bridge to functional recovery.

In the weaned patients, the duration of mechanical unloading necessary to reach the maximum possible degree of reverse remodeling and functional improvement ranged between 3 weeks and 8 months and was significantly shorter for patients who showed long-term cardiac stability after weaning. However, the maximal value of LVEF obtained during LV unloading did not correlate with the duration of mechanical support. Among the 17 patients with lasting cardiac recovery, 16 (94.1%) were weaned after <6 months of mechanical support, and 6 of the 7 patients (85.7%) who were weaned after >6 months of LVAD support showed HF recurrence during the first 3 postweaning years.

Although echocardiography was decisive for evaluation of cardiac improvement, other clinical data were also considered for the final decision with regard to LVAD explantation. Thus, stable sinus rhythm and lack of pulmonary hypertension were considered paramount for weaning decisions. However, echocardiographic improvement up to levels considered to be reliable for safe LVAD removal was achieved only by patients with sinus rhythm, and off-pump stability in LV size and function was always associated with stable pulmonary hemodynamics. A lack of clinical symptoms during LVAD unloading appeared to be not necessarily associated with relevant LV myocardial recovery.

Because all of the IDCM patients with LVAD support received similar HF medication, we cannot make any statement on the value of this treatment for remodeling and/or myocardial functional improvement. All of the IDCM patients who received a LVAD required positive inotropic support before implantation and, thus, no conclusions can be drawn with regard to the influence of inotropic infusion before LVAD implantation on the weaning rate. The influence of inotropic medication on myocardial improvement after LVAD implantation was not investigated in our patients.

Survival, Cardiac Stability, and Exercise Tolerance After LVAD Removal

The long-term survival of our IDCM patients reached nearly 80% at 5 years after LVAD removal, although in 5 of the weaned patients (15.6%), cardiac recovery was not complete, but LVAD explantation was prompted by diverse complications. These outcome data suggest that in patients with life-threatening pump-related complications, LVAD removal might be considered even if myocardial improvement appears insufficient for long-term survival without HTx or another LVAD implantation.

At the present time, 3 patients with HF histories of 2 to 4 years before LVAD implantation still show stable cardiac function after LVAD removal, although the postweaning time has reached 8.5 to 9 years. It is important to emphasize that myocardial improvement during LVAD support from inotropic-dependent NYHA class IV to NYHA class I/II was also associated with this strikingly high survival rate. How-

TABLE 2. Risk for Heart Failure Recurrence During the First 3 Years After LVAD Removal in Patients With Nonischemic IDCM

<table>
<thead>
<tr>
<th>Selected Risk Factors for HF Recurrence After Weaning</th>
<th>Odds Ratio</th>
<th>95% CI*</th>
</tr>
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<tbody>
<tr>
<td>Off-pump LVEF &lt;45%</td>
<td>24.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Off-pump LVIdd &gt;55 mm</td>
<td>30.0</td>
<td>3.5</td>
</tr>
<tr>
<td>History of HF ≥5 years</td>
<td>64.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*The results of a ROC analysis on LVEF, LVIdd, and history of HF agree with the chosen cut-points. Sensitivity and specificity both range between 60% and 95%.
ever, without the option of HTx or another LVAD implantation, the survival of our weaned patients would be much lower than 80%, because at 5 years after LVAD removal, freedom from recurrent HF was attained only by 58.2% of the weaned patients. Thus, the high survival rates may be partially explained by the very careful follow-up of these patients, which allowed us to anticipate HF recurrence and, consequently, to put the patients on the waiting list for HTx before they encountered life-threatening situations. Nevertheless, it is also possible that, for a restricted number of IDCM patients who once had end-stage HF, the myocardial improvement by LV unloading might provide higher functional stability than that usually shown by IDCM patients who never had relevant signs of HF.

Long-term survival after ventricular assist device use as a bridge to functional recovery for acute cardiomyopathies and myocarditis was found to be equivalent to survival after the use of these devices for bridging to HTx. Survival and freedom from recurrent HF at 3 years and 5 years after LVAD removal in our weaned IDCM patients are comparable with survival and freedom from recurrent HF reported after HTx. The exercise test data shown by our IDCM patients with postweaning times of >3 years are even better than those reported for heart transplant recipients with post-HTx times >3 years. Thus, for transplanted patients after >3 years, the age- and sex-predicted values for VO$_2$max reported by different groups range between 61% and 70%. The relatively high VO$_2$max (78±14.3% of the predicted values) and the nearly normal ventilatory equivalent for CO$_2$ (30.2±3.3) measured in our IDCM patients >3 years after LVAD weaning suggest that evaluation of weaning possibilities should be a goal after LVAD implantation, not only in patients with acute myocarditis but in all IDCM patients.

It has already been reported that reduction of fibrosis may contribute to the recovery of cardiac function associated with long-term LVAD support. Our data support this conclusion, but the limited number of comparative histomorphometric examinations performed do not allow any additional statements on this issue.

Predictability of Cardiac Stability After LVAD Removal

The simple parameters LVIDd and LVEF measured during off-pump trials appeared predictive for cardiac stability after weaning. The predictive value of these parameters for the postweaning outcome appeared to be higher if history of HF was also considered. Thus, according to our data, the chances for long-term cardiac stability after weaning in IDCM patients are good, as long as the patients have a history of HF <5 years before LVAD implantation, and the final off-pump LVEF and LVIDd reach a minimum of 45% and a maximum of 55 mm, respectively, before LVAD removal. By contrast, patients with off-pump LVEF values ≤40% showed practically no chance for long-term stable cardiac function after weaning, regardless of their HF duration before LVAD implantation. In patients with a recurrence of HF during the first 3 years after weaning, significant LVEF decrease already occurred during the first month after weaning, whereas in those with long-term stable cardiac function after weaning, even after 6 months the LVEF did not differ from that before LVAD removal. Thus, patients with an early alteration of LVEF after LVAD removal are at high risk for HF recurrence and should be carefully observed, even if the LVEF still exceeds 40%, and there are as yet no changes in clinical symptomatology. Once the LVEF drops below 40%, early listing for HTx should be considered even before the first clinical signs of HF appear, because, according to our observations, cardiac decompensation develops in these patients relatively fast, within a few weeks or up to 6 months. Recently, it was shown that dobutamine stress echocardiography may help to identify patients who recover enough myocardial function to tolerate LVAD explantation.

Study Limitations

The relatively small cohort and the lack of randomization limited our study. Because our weaning strategy produced a higher prevalence of long-term stable cardiac function, positive predictive values might be lower and negative predictive values higher in a sample with lower prevalence of long-term cardiac stability. Therefore, definite cut-off values for the investigated parameters allow more reliable prediction of early recurrence of HF than of long-term cardiac stability after weaning. However, this limitation is not avoidable, because weaning can be performed only in patients with relevant myocardial improvement and, unfortunately, these patients are still a minority of those with LVAD support. Another limitation is the intraobserver and, even more important, the interobserver variability of LVEF measurements, which is high and, therefore, makes the use of definite cut-off values very difficult.

The use of tissue Doppler imaging (TDI) parameters may improve the reliability and predictive value of echocardiographic data, because it has been shown that wall motion analysis by TDI can detect ventricular dysfunction earlier than is possible with conventional echocardiography, and in patients without regional wall motion disturbances, alterations in LV contractility are better reflected by myocardial velocity than by LVEF changes. The reproducibility of TDI measurements is also high and less dependent on 2D image quality than the LVEF. However, because TDI was introduced in our weaning protocol only a few years ago, the data available at present are insufficient for reliable conclusions, and the predictive value of TDI parameters remains to be established by future studies. However, our preliminary data suggest that only patients with Sm of ≥8 cm/s can attain long-term stability of cardiac function after weaning.

Conclusions

For selected patients with IDCM, weaning from the LVAD is a clinical option with potentially successful results for >9 years and should, therefore, be considered in all patients with relevant recovery of cardiac function after LVAD implantation. The very low mortality and the only exceptional need of repeated LVAD implantation because of the recurrence of HF during the first 2 years after LVAD removal in our IDCM patients indicates that, with the option of HTx, weaning from LVAD is sufficiently safe to be also considered in patients.
with incomplete cardiac improvement if additional LVAD support is associated with life-threatening complications.

Echocardiographic data obtained during off-pump trials are reliable for the detection of myocardial improvement during mechanical unloading. However, definite cut-off values for the investigated parameters allow more reliable prediction of early recurrence of HF than of long-term cardiac stability after weaning.

Our data suggest that LVAD removal should be considered as contraindicated if off-pump LVEF does not exceed 40%. Also, patients with a history of HF of >5 years should be monitored very carefully after weaning because of the very high risk for early recurrence of HF. Neither the LVIDd nor the LVEF measured before LVAD implantation are predictive for potential myocardial improvement during mechanical unloading.

Acknowledgments
We thank Anne Gale, Editor in the Life Sciences, of the Deutsches Herzzentrum Berlin for editorial assistance.

References
Long-Term Results in Patients With Idiopathic Dilated Cardiomyopathy After Weaning From Left Ventricular Assist Devices
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Circulation. 2005;112:I-37-I-45
doi: 10.1161/CIRCULATIONAHA.104.525352
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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