Pre-Explant Stability of Unloading-Promoted Cardiac Improvement Predicts Outcome After Weaning From Ventricular Assist Devices

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Background—Detection of cardiac recovery that allows long-term cardiac stability after ventricular assist device (VAD) explantation is a major goal. After normalization of ventricular diameters during unloading, the pre-explant left ventricular ejection fraction (LVEF) allows the detection of patients with the potential to remain stable after VAD explantation. However, some patients with LVEF >45% before VAD explantation show early recurrence of heart failure (HF). We aimed to find out if unstable improvement can be recognized before VAD explantation.

Methods and Results—Among 96 patients weaned from VADs since 1995, a relatively homogenous group of 53 patients with nonischemic chronic cardiomyopathy (CCM) was selected for the study. The pre-explant stability of major parameters of LV function, size, and geometry that were measured by echocardiography during serial “off-pump” trials was tested for relationship with cardiac stability after VAD explantation. LVEF, systolic peak wall motion velocity (Sm), end-diastolic diameter (LVEDD), end-diastolic relative wall thickness (RWTED) and end-diastolic short/long-axis ratio (S/L ED) were selected for evaluation. In postweaning unstable patients, the selected parameters showed relevant instability already before VAD explantation during the time period between best cardiac improvement and VAD explantation and also during the final off-pump trial just before VAD explantation. For all parameters, there were significant differences (P<0.05) in pre-explant changes between patients with and without postweaning cardiac stability. Using the optimal cutoff values obtained from receiver-operating characteristic analysis, we found for our selected parameters predictive values for postexplant cardiac stability of ≥1 year, ≥3 years, and ≥5 years, ranging between 94% and 100%, 92%, and 100%, and 78% and 100%, respectively. Using for all parameter changes the cutoff value of 10%, we found similar predictive values for cardiac stability of ≥1 year, ≥3 years, and ≥5 years, ranging between 93% and 97%, 90% and 96%, and 83% and 92%, respectively.

Conclusions—Our results strongly suggest the possibility to improve the prediction of postexplant transplant/VAD-free outcome in CCM patients with cardiac improvement during VAD support by analyzing the pre-explant stability of several LV off-pump echocardiographic parameters during serial off-pump trials. (Circulation. 2012;126[suppl 1]:S9–S19.)

Key Words: cardiomyopathy ■ heart failure ■ ventricular assist devices ■ myocardial recovery ■ survival ■ risk factors

Mechanical circulatory support for end-stage heart failure (HF) is a life-saving procedure that will later become either a bridge to transplantation or definitive therapy for patients with contraindications for heart transplantation (HTx). However, end-stage failing hearts have often shown remarkable ability to recover at cellular and structural level, and there is also increasing evidence that in some patients, initial “bridge to transplantation” can turn into “bridge to myocardial recovery.”1,2 It has been observed that during mechanical unloading there is high a probability of improvement in cardiac histology (ie, regression of hypertrophy) and myocardial contractile properties, restoration of adrenergic receptor density, and responsiveness and also improvement in calcium handling.1,3–6 Unfortunately, translation of these changes into functional recovery at organ level is less frequent, and stable cardiac improvement that might allow long-term transplant-free outcome after ventricular assist device (VAD) explantation occurs only in relatively few patients.1,7,8 It was observed that acute myocarditis and noncoronary shock can completely reverse during left ventricular assist device (LVAD) support.9 Outcome data for patients with chronic end-stage heart failure who were elec-
tively weaned from VADs are relatively few but encouraging. Recovery appears to be related to the etiology of myocardial damage and the duration of heart disease.1,13–15 Cardiac recovery appeared to be more common in patients without excessive LV dilation and also in those with less fibrosis and shorter history of HF.5,13,16 However, recovery during mechanical unloading is not reliably predictable before VAD implantation, and it is still not possible to prospectively identify patients who would benefit from elective VAD implantation primarily designated as bridge to myocardial recovery.

After VAD implantation, certain parameters of “off-pump” cardiac function, as well as LV geometry and size, appeared not only essential for the assessment of cardiac recovery but also very useful for the detection of patients with the potential to remain stable for several years after VAD explantation.14,17 Although neither significant improvement in myocyte structural and mechanical parameters nor restoration of β-adrenergic receptor signaling appeared predictive for cardiac improvement to levels allowing VAD explantation, they can be helpful for weaning decisions in borderline cases.1 Assessment of myocardial improvement at molecular and cellular levels may also provide a platform for future adjunct therapies (pharmacological, cell-based, or gene therapy) aimed to increase the number of weaning candidates.

Detection of cardiac improvement that allows long-term transplant-free outcome after VAD explantation is a major goal.18,19 Echocardiography continues to be the cornerstone for weaning decisions.4,13,17 In patients with normalization of LV diameters during unloading, the pre-explant “off-pump” left ventricular ejection fraction (LVEF) usually allows the distinction between patients with and without the potential to remain stable after weaning.1 However, about 20% of our patients with off-pump LVEF >45% before VAD removal showed early recurrence of HF, whereas some others with LVEF between 40% to 45% remained stable for years. Also, some of our patients with final off-pump LVEF >45% and normal LV size and geometry showed relevant postweaning instability of LV size and geometry after LVAD removal, before any alteration of LV systolic function, whereas other patients with the same final off-pump LVEF but with moderately altered LV size and geometry remained stable after LVAD removal and had no further alteration of LV size and geometry.10 During 16 years of weaning experience, we have had several potential weaning candidates with relevant cardiac improvement, which deteriorated again before our final decision to explant the VAD, and, during the last years, it has become increasingly evident that patients with myocardial recovery during mechanical unloading are very inhomogeneous with regard to the preweaning stability of improvement after the recovery has reached its maximum level. Having these observations in mind, the aim of the present study was to find out whether, in patients with relevant cardiac recovery during mechanical unloading, a potentially dangerous instability of this improvement with relevant impact on postweaning patient outcome can already be recognized before VAD explantation.

Methods

Patients

Of 1038 patients who between January 1995 and September 2011 received a long-term VAD primarily designed as bridge to transplant or permanent therapy, 96 (9.2%) patients with relevant cardiac improvement underwent VAD explantation. From those 96 weaned patients, we aimed to evaluate a more homogenous patient group by including in the evaluation only those with nonischemic chronic cardiomyopathy (CCM) as the underlying cause for HF. Thus, weaned patients with coronary artery disease and patients weaned from VADs after recovery from postcardiotomy HF were not included in the study. Also, patients with histological evidence of acute myocarditis and patients with prosthetic valves, as well as children younger than 14 years of age, were excluded from the evaluation. Inclusion criteria were fulfilled by 53 of the 96 weaned patients who all consented to VAD implantation as a bridge to transplantation and provided written informed consent before VAD implantation and VAD removal. These 53 weaned patients represented 13.8% of all patients with nonischemic CCM who received a VAD during the evaluation time. Of these 53 patients, all with the clinical diagnosis of dilated cardiomyopathy, 47 (88.7%) had truly idiopathic disease, 5 (9.4%) had histological evidence of chronic myocarditis before VAD implantation, and in 1 patient (1.9%) the disease appeared to be related to cytostatic therapy. All patients received emergency VAD implantation because of end-stage irreversible life-threatening HF unresponsive to medical treatment, including continuous inotropic support, and were weaned from VADs after cardiac improvement which was deemed sufficient to allow VAD removal with a low risk of short-term recurrence of HF. No attempts have been made to use VADs electively with the aim of myocardial recovery only.

Of the 53 patients evaluated, 50 (94.3%) were weaned from LVADs and only 3 (5.7%) from biventricular assist devices (BVADs). Of 50 explanted LVADs, 32 (64.0%) were pulsatile pumps (Novacor, TCI) or Berlin Heart EXCOR; the other 18 (36%) were “continuous flow” pumps (INCOR, Heart Mate II, and HeartWare).

Data Collection and Study Design

We aimed to assess the impact that the stability of myocardial recovery before VAD explantation might have on patient postweaning outcome and the possibility of recognizing a potentially dangerous instability of cardiac improvement already before VAD explantation. We therefore focused this retrospective study on echocardiographic parameters that were prospectively recorded according to a well established protocol in all patients during the follow-up “off-pump” trials performed between maximum cardiac improvement and VAD explantation. To attain our goals, we evaluated the preservation of stable cardiac function after VAD removal in relation to the preweaning time course of echocardiographic parameters not only between off-pump trials but also during the final off-pump trial.

VAD Explantation Criteria

As mentioned in our previous publications,1,17 after successful weaning from LVADs of our first 3 IDCM patients, who had final “off-pump” LV end-diastolic diameters (LVEDD) <50 mm and LV ejection fractions (LVEF) between 45% and 55%, we considered LVAD explantation to be safely possible if, during repeated off-pump trials performed over several days, the maximum LVEDD was 55 mm and the minimum LVEF was 45%, whereas the right ventricular (RV) size and function remained stable. However, until 2002, VAD explantation was not limited to patients with normal LV size and LVEF of ≥45%. Thus, 9 patients with IDCM were weaned from VADs although the final off-pump LVEDD was 56 to 66 mm and/or LVEF 30% to 44%, but in 5 of these patients VAD explantation was prompted by pump-related complications. Therefore, no further VAD explantation was performed in patients with LVEF <45% and LVEDD >55 mm.

In addition to echocardiography, the final off-pump hemodynamic data measured by right heart catheterization were another corner-
In patients with cardiac improvement, such trials were conducted weekly until the recovery reached its maximum and there was no further improvement. During recovery the working mode of pumps was also changed. Thus, in patients with optimal off-pump cardiac function but still moderately enlarged LV, to promote further reverse remodeling, we increased the unloading of the ventricle, whereas in those with normal or relatively small LV diameters we reduced the pump performance to exert moderate load on the myocardium. To avoid misleading overestimations of LV systolic function induced by extremely low afterload, we aimed to perform the final off-pump trials at diastolic systemic blood pressure values not below 55 mm Hg.

Invasive hemodynamic measurements for detection of recovery were not routinely performed. Right heart catheterization for “off-pump” hemodynamic measurements was routinely scheduled only for patients who were already selected for VAD explantation and was performed in the operation room 1 hour before VAD explantation. However, in patients with borderline echocardiographic parameter values, we performed a right heart catheterization before any decision in favor or against VAD explantation was made. In patients with axial flow pumps, where stopping or low rotor speed leads to retrograde flow into the LV, which can be misleading for the evaluation of hemodynamics and cardiac function, we avoided the operation room during off-pump hemodynamic measurements with a balloon.

Pharmacological Therapy
During mechanical unloading, all patients were treated with β-blockers (metoprolol or carvedilol), angiotensin-converting enzyme inhibitors (enalapril, ramipril, or lisinopril), aldosterone antagonists (spironolactone), loop diuretics (furosemide or torasemide), and digitalis. Medication doses were individually adapted to reduce heart rate toward 55 to 60 bpm, and blood pressure to the lowest optimally tolerated value, as well as to maintain optimal renal function. However, in patients with relevant cardiac improvement, before the final decision for LVAD explantation, we aimed to avoid systemic arterial diastolic pressure values below 50 mm Hg, which can be misleading for the evaluation of LV function and adapted the medical treatment accordingly. Treatment with β-blockers, angiotensin-converting enzyme inhibitors and spironolactone (with/without low-dose loop diuretics) was continued permanently in all patients after VAD explantation.

Table 1. Main Weaning Criteria Used Since March 2002∗

<table>
<thead>
<tr>
<th>Examination</th>
<th>Parameters and Parameter-Derived Measurements Obtained During the Final Pre-Explantation Off-Pump Trial†</th>
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</thead>
<tbody>
<tr>
<td>Echocardiography</td>
<td>LV end-diastolic diameter ≤ 55 mm</td>
</tr>
<tr>
<td></td>
<td>LV ejection fraction ≥ 45%</td>
</tr>
<tr>
<td></td>
<td>No or less than grade II mitral and/or aortic valve regurgitation</td>
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<tr>
<td></td>
<td>No RV dilation (RVOT diameter &lt;35 mm, short-/long-axis ratio &lt;0.6)</td>
</tr>
<tr>
<td></td>
<td>No or maximum grade II tricuspid or pulmonary valve regurgitation</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>Cardiac index &gt;2.6 L/min per m²</td>
</tr>
<tr>
<td></td>
<td>Pulmonary capillary wedge pressure (mean) &lt;13 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Right atrial pressure (mean) &lt;10 mm Hg</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Sinus rhythm</td>
</tr>
<tr>
<td></td>
<td>Heart rate &lt;90 beats/min</td>
</tr>
<tr>
<td></td>
<td>Not more than 25% heart rate increase during off-pump trials</td>
</tr>
<tr>
<td>Brachial artery pressure</td>
<td>Mean &lt; 65 mm Hg</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; RVOT, right ventricular outflow tract.

∗The main change after 2002 was the limitation of ventricular assist device explantation to patients with LV ejection fraction ≥45% and LV end-diastolic diameter not larger than 55 mm.
†Measurements performed at rest, without any isotropic support.

Assessment of Cardiac Recovery
After VAD implantation and before patients were discharged home, the effect of unloading on cardiac size, shape, and function was monitored weekly by echocardiography. Thereafter, the frequency of follow-up examinations varied between 1 and 4 weeks.

Off-pump echocardiography at rest was used for detection and monitoring of cardiac recovery. After unconvincing results of stress echocardiography in the first 3 patients who underwent dobutamine stress echocardiography, to avoid excessive stimulation of the myocardium during recovery, stress echocardiography was not further used during the off-pump trials.

For patients with LVADs, off-pump trials evaluating the heart without VAD support were started after the LV reduced its end-diastolic diameter to 60 mm and showed relatively good wall motion. Before pump-stops, heparin was given (60–100 IU/kg according to the prothrombin time reported as INR) to prevent thrombus formation inside the pump. Patients with heparin-induced thrombocytopenia received Argatroban infusion (2 µg/kg per minute), which was started 1 hour before the off-pump trials. For pulsatile LVADs, trials consisted of stepwise pump frequency reduction to the lowest, followed by intermittent pump-stops lasting initially between 3 and 4 minutes. Later, in patients who appeared to be severe weaning candidates the duration of pump stops was extended to 15 minutes. In patients without cardiac improvement sufficient for possible LVAD explantation, as already shown during the first 3 minutes, the off-pump trial was not extended beyond 3 minutes. In patients with axial flow pumps, where pump stop leads to retrograde flow into the LV, which can be misleading for the evaluation of cardiac function, we reduced the rotor speed stepwise over a time period of between 2 and 3 minutes to values that result in close to zero flow in 1 cardiac cycle. In patients with BVADs, the RV pump was stopped 30 seconds earlier than the LV pump, and then both pumps remained inactive for up to 15 minutes to allow the evaluation of cardiac function.

In patients with cardiac improvement, such trials were conducted weekly until the recovery reached its maximum and there was no further improvement. During recovery the working mode of pumps was also changed. Thus, in patients with optimal off-pump cardiac function but still moderately enlarged LV, to promote further reverse remodeling, we increased the unloading of the ventricle, whereas in those with normal or relatively small LV diameters we reduced the pump performance to exert moderate load on the myocardium. To avoid misleading overestimations of LV systolic function induced by extremely low afterload, we aimed to perform the final off-pump trials at diastolic systemic blood pressure values not below 55 mm Hg.

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Evaluated Echocardiographic Parameters
In the present study, we assessed for each off-pump parameter the differences (“interval change” in percent) between the value measured at the time when the highest improvement of cardiac function was detected (“best”) and that measured just before VAD explantation (“pre-explant”). The evaluated parameters were LVEF, LVVDD, LV end-diastolic relative wall thickness (RWTED), LV end-diastolic short/long axis ratio (SLED), and LV peak systolic wall motion velocity at the basal posterior wall (Sm).

For LVDD, RWTED, SLED, and Sm, we also selected for evaluation their changes during the last off-pump trial before the final decision in favor of VAD explantation (“pre-explant off-pump change” in percent) after the first 30 seconds of complete pump stop (or rotor speed reduction for axial flow pumps, which results in a close to zero net flow in one cardiac cycle) until the end of the 3rd minute of the trial.

LVDD and end-diastolic wall thickness measurements were performed on parasternal long-axis views. RWTED was calculated by dividing the sum of end-diastolic interventricular septum thickness
and LV posterior wall thickness by the LVEDD ([(IVS\_ED + PW\_ED) / LVEDD]). The measurements of the short and long axes for calculations of S/LED (sphericity index) values were performed on apical 4-chamber views. For short-axis measurements, we used the largest diameter below the mitral valve ring. Sm measurements, which were routinely a part of our weaning protocol since 1999, were performed on both parasternal and apical long-axis views. Methodological details of Sm measurements were described previously.20

Statistics

Statistical analysis was performed using SPSS 18.01 for Windows (SPSS Inc, Chicago, IL). Quantitative data, representing the values of off-pump echocardiographic parameters and parameter changes between off-pump trials and during the final off-pump trial, were either expressed as means and standard deviation (if distribution of data was not skewed) or as medians and quartiles (for parameters with more skewed distribution). For normally distributed data, differences between patients with lasting recovery and those with recurrence were analyzed using the Student t test. For data without normal distribution (medians and quartiles instead of means and standard deviations due to highly skewed distribution), nonparametric Mann-Whitney U test, Pearson χ2 test, and Gehan test, differences between groups were considered significant for 2-sided \( P \leq 0.05 \). Given the nature of the study, no adjustments in probability values were made for multiple comparisons. Receiver-operating characteristic (ROC) curves were used to evaluate the discriminatory value of different parameter changes to test their diagnostic accuracy in prediction of freedom from HF recurrence after VAD explantation. Sensitivity, specificity, and predictive values were expressed as percentages and calculated for selected echocardiographic parameter changes according to both prespecified cutoff points of 10% and optimal cutoff derived from ROC analysis. The 95% exact binomial confidence intervals were also calculated. Kaplan-Meier curves were applied for freedom from HF recurrence and survival after VAD explantation. The probability of freedom from HF recurrence at a given point of time as derived from the Kaplan-Meier estimation was expressed in percent±SE. Univariable Cox proportional hazards models were used to investigate possible main risk factors for HF recurrence. Proportional hazard assumptions were checked by the method of Grampsch and Therneau. For change of LVEF, LVEDD, L/S_{ED-axis} ratio, and RWT_{ED} before VAD explantation, a stepwise multivariable Cox proportional hazard regression was also calculated.

**Results**

There were no complications during off-pump trials in the 96 weaned patients. Among 62 other patients who appeared to be potential weaning candidates and therefore underwent 1 or more off-pump trials, only 4 patients had shortly after the pump stop sudden dizziness, sweating, and dyspnea (low cardiac output), which were completely reversible in less than 1 minute after cessation of the trial. In the 53 evaluated patients, the median time necessary to reach the best unloading-promoted cardiac improvement was 3.3 (0.6–15) months, and it was significantly shorter in patients who showed ≥5 years postexplant cardiac stability in comparison to those with HF recurrence during the first 5 years after VAD explantation [2.5 (0.6–7) versus 5.4 (2–20) months, respectively; \( P = 0.02 \)]. Of 36 patients who underwent VAD explantation >5 years before the present evaluation 22 reached ≥5 years of postexplant cardiac stability, the other 14 showed HF recurrence during the first 5 years after VAD explantation.

**Clinical Features at VAD Explantation**

Weaned patient characteristics at the time of VAD explantation are shown in Table 2. The off-pump LVEF and LVEDD values measured in the 53 weaned patients at the time of best cardiac improvement ranged from 40% to 60% and between 39 and 54 mm, respectively. During the final off-pump trials before VAD explantation the average LVEF values were lower and the LVEDD values were higher, ranging from 30% to 60% and from 40 to 64 mm, respectively. All patients had a cardiac index of >2.5 L/min/m² and a mean right atrial pressure of ≤10 mm Hg. Of the 53 patients, 50 (94.3%) had

### Table 2. Weaned Patient Characteristics at the Time of VAD Explantation

<table>
<thead>
<tr>
<th>Main Characteristics</th>
<th>All Evaluated Patients (n = 53)</th>
<th>Cardiac Stability ≥5 y (n = 22)</th>
<th>HF Recurrence in ≤5 y (n = 14)</th>
<th>Cardiac Stability Versus HF Recurrence P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42.5 (14–65)*</td>
<td>41 (14–62.5)*</td>
<td>44 (31.8–64.5)*</td>
<td>0.05</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (86.8)</td>
<td>19 (86.4)</td>
<td>12 (85.7)</td>
<td>0.95</td>
</tr>
<tr>
<td>Female</td>
<td>7 (13.2)</td>
<td>3 (13.7)</td>
<td>2 (14.3)</td>
<td></td>
</tr>
<tr>
<td>History of HF, y</td>
<td>4 (0.5–16.4)*</td>
<td>2.1 (0.5–6.6)*</td>
<td>5.8 (2–16.4)*</td>
<td>0.01</td>
</tr>
<tr>
<td>VAD support duration, y</td>
<td>3.5 (0.7 to 18)*</td>
<td>2.8 (1–7.3)*</td>
<td>6 (2.3–22)*</td>
<td>0.04</td>
</tr>
<tr>
<td>Off-pump LVEDD, mm</td>
<td>51.6±5.7</td>
<td>50.0±4.1</td>
<td>57.3±6.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Off-pump S/LED-axis ratio†</td>
<td>0.63±0.08</td>
<td>0.62±0.08</td>
<td>0.71±0.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Off-pump RWT_{ED}‡</td>
<td>0.40±0.04</td>
<td>0.42±0.03</td>
<td>0.35±0.03</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Off-pump LVEF, %</td>
<td>47.5±5.8</td>
<td>49.4±4.3</td>
<td>42.9±5.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Off-pump Sm, cm/s§</td>
<td>8.4±1.1</td>
<td>9.0±0.8</td>
<td>7.3±0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rhythm, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>52 (98.1)</td>
<td>22 (100)</td>
<td>13 (92.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (1.9)</td>
<td>0</td>
<td>1 (7.1)</td>
<td></td>
</tr>
</tbody>
</table>

VAD indicates ventricular assist device; HF, heart failure; LVEDD, left ventricular end-diastolic diameter.

*Medians and quartiles instead of means and standard deviations due to highly skewed distribution.

†End-diastolic LV short-/long-axis ratio (S/LED-axis ratio) measured on 4-chamber views.

‡LV end-diastolic relative wall thickness (RWT_{ED}) measured on M-mode recordings from parasternal long-axis views.

§LV systolic peak wall motion velocity measured at the basal posterior wall.
a PCWP of $<13$ mm Hg. All patients with final off-pump LVEF $<45\%$ and LVEDD of $>55$ mm were weaned from their VADs before March 2002.

**Heart Function After VAD Explantation**

To date, postweaning recurrence of HF occurred in 20 (37.7\%) of the evaluated patients. Kaplan-Meier estimates revealed a probability of $67.1\pm7.6\%$ and $47.3\pm9.2\%$ for 5-year and 10-year freedom from HF recurrence after VAD explantation, respectively (Figure 1A). Of the 20 HF recurrences, 11 (55\%) occurred during the first 9 months after VAD explantation. However, only 1 (9.1\%) of these 11 very early HF recurrences occurred during the last 9 years, when no VAD explantations were performed in patients with an LVEF $<45\%$ and/or a LVEDD $>55$ mm. Of the 20 patients with HF recurrence, 15 (75\%) received heart transplantation (1 after a second LVAD implantation), 3 received another LVAD, but no HTx and 2 patients who had no indication for another VAD implantation died suddenly on the transplantation list. There were no differences in freedom from HF recurrence between patients who recovered on pulsatile devices and those who recovered on continuous flow devices (Figure 1B).

Among the 18 weaned patients who have so far survived for $>5$ years without HF recurrence, 15 (83.3\%) were in functional New York Heart Association (NYHA) class II or lower at the end of the 5th postweaning year. Another 2 patients, who also showed good cardiac function, were not capable of intense physical activity because of neurological sequelae after cerebral vascular accidents that occurred before VAD explantation, and 1 patient oscillated between NYHA class II and III.

**Patient Survival After VAD Explantation**

At the time of evaluation, 38 (71.7\%) of the 53 studied patients were still alive. Kaplan-Meier estimates of overall survival after VAD explantation (including post-HTx survival for those with HF recurrence) revealed probabilities of $72.8\pm6.6\%$ and $67.0\pm7.2\%$ for 5- and 10-year survival, respectively (Figure 1C). Of 15 patients who have died to date, only 6 (40\%) died due to explantation-related complications or due to HF recurrence that could not be treated in time by HTx. The vast majority of patients with HF recurrence underwent HTx and thus assessment of postweaning survival from HF recurrence or weaning-related complications by Kaplan-Meier
estimates revealed high probabilities for 5- and 10-year survival, reaching 87.8 ± 5.3% and 82.6 ± 7.3%, respectively (Figure 1D). As in our previous evaluations, there was no between-group difference in the Kaplan-Meier estimates of overall survival for patients with and without HF recurrence after VAD explantation (P = 0.930).

Final Off-Pump LV Size and Function in Patients With and Without HF Recurrence

The average of the best LVEF values measured in the 53 evaluated patients before VAD explantation was 50.5 ± 4.6%. However, because in 33 (62.3%) of these patients the final off-pump LVEF was lower than the previously measured best off-pump value, at the final off-pump trial, the mean LVEF was only 47.5 ± 4.3%. The mean LVEDD, S/LED axis ratio, RWTED, and Sm reached only 47.5 ± 11.0% of the pre-explant value, at the final off-pump trial, the mean LVEF was lower than the previously measured best value. However, because in 33 (62.3%) of these patients the final off-pump trial before ventricular assist device explantation was 50.5 ± 4.6%.

Predictive Value of Cardiac Stability Before VAD Removal

Table 4 shows the predictive value of the stability of echocardiographic LV parameters for the postexplant patient outcome. Using the optimal cutoff values obtained from ROC analysis, we found predictive values for cardiac stability of ≥ 1 year, ≥ 3 years, and ≥ 5 years ranging between 94% and 100%, 92% and 100%, and 78% and 100%, respectively. Using for all parameter changes the same cutoff value of 10%, which might be more useful from a practical point of view (especially because of the interobserver and intraobserver variability of measurements), we found similar predictive values for cardiac stability of ≥ 1 year, ≥ 3 years, and ≥ 5 years ranging between 93% and 97%, 90% and 96%, and 83% and 92%, respectively. In patients with pre-explant LVEF ≥ 40% an "interval change" of < 10% for LVEF, LVEDD, and RWT_Ed revealed predictive values of 88.0%, 91.9%, and 91.3% for ≥ 5 years postexplant cardiac stability.
The ROC curves for prediction of HF recurrence during the first 5 years after VAD removal (Figure 4) show high values for the areas under the curves (between 0.892 and 0.975), which indicate high ability of pre-explantation instability ("interval change" and "pre-explant change") in LVEF, LVEDD, S/L ED-axis ratio, RWT ED, and Sm to correctly classify patients with and without long-term cardiac stability after VAD removal. Univariable Cox regression analysis (Table 5) confirmed the relevance of pre-explant parameter changes for postweaning cardiac stability. Thus, with each unit of S/L ED-axis ratio increase or RWT ED decrease during the time period between best cardiac improvement and VAD removal, the risk for postweaning HF recurrence became 1.29 times and 1.28 times, respectively, higher. Also, with each unit of LVEDD increase or Sm decrease during the final off-pump trial, the risk for postweaning HF recurrence became 1.30 times and 1.29 times, respectively, higher.

Multivariable Cox proportional hazard regression revealed only the S/L ED-axis ratio change after best pre-explant cardiac improvement until the day of VAD explantation as an independent predictor for the postweaning stability of cardiac function ($P<0.05$).

**Discussion**

The majority of patients with myocardial recovery during long-term ventricular mechanical unloading resulting in cardiac improvement that allowed VAD explantation were patients with acute myocarditis and nonischemic CCM.\textsuperscript{1,13–16,21} Recurrence of HF appeared to be the most frequent complication after VAD explantation, especially in patients with chronic myocardial alterations before VAD implantation.\textsuperscript{13,14,16} Therefore, further improvement of postexplant patient outcome will depend mainly on better prediction of postexplant cardiac stability.

To improve future weaning decisions in patients with CCM as the underlying cause of VAD insertion, the present study focused on the potential prediction of postexplant cardiac stability by analyzing the pre-explantation stability of several LV off-pump echocardiographic parameters and indices. We identified several parameters and indices related to LV size, geometry, and function, which in patients who deteriorated...
after explant showed relevant changes already during the time period between best pre-explant cardiac improvement and VAD explantation (“interval change”) and/or during the final off-pump trial just before VAD explantation (“pre-explant change”). Pre-explant alterations in LV size and geometry appeared to be a potential risk factor for HF recurrence even in patients with preweaning LVEF ≥45%. Also the LV systolic wall motion velocity (Sm) decrease during the time period between best improvement and VAD explantation and/or during the final off-pump trial appeared to be a risk factor for postweaning HF recurrence. However, only the S/L-axis ratio interval change during the time between best cardiac improvement and VAD explantation appeared to be an independent predictor for the postexplant stability of cardiac function. It is not surprising that the instability of LVEF in patients with LVEF ≤40% showed less predictive value for the stability of cardiac function after VAD explantation than the instability of LV size and geometry. Thus, it is well known that end-diastolic RWT reduction and/or an increase of the sphericity index (S/L-axis ratio) is associated with wall stress increase.22 The relatively high predictive value of Sm and its stability before VAD removal for cardiac stability after weaning is also not surprising. Thus, because the final part of ejection occurs by inertial effects after myocyte contraction is finished, Sm, like peak systolic global strain rate, being an early systolic event, is more closely related to contractility than the EF and impaired systolic function can be detected earlier by Sm than by EF measurements.23,24

Our data show that not only the optimal cutoff values derived from ROC analysis but also the simple use of 10% change as cutoff value for pre-explant changes in LVEF, LVEDD, S/L-axis ratio, RWT, and Sm are able to allow the distinction between patients with and without the potential to maintain cardiac stability for >5 or even >7 years after weaning. Because the optimal cutoff values derived from our ROC analysis were close to the interobserver and intraobserver variability of measurements, the use of 10% change as cutoff value for our selected parameters might be more useful from a practical point of view. This especially seems to be possible for LVEF, LVEDD, RWT, and Sm, where ROC analysis–derived optimal cutoff values ranged between 7% and 10% (Table 3). The ROC analysis–derived optimal cutoff value for S/L-axis ratio changes was only 4%, but, whereas the predictive value of ≤4% change appeared to be absolutely predictive for 5 year postexplant cardiac stability, the predictive value of >4% changes for HF recurrence during the first 5 postweaning year ranged only between 56% and 67% (Table 3). Thus, even for the S/L-axis ratio, the use of 10% change as the cutoff value might be possible.

Our data suggest that the assessment of pre-explant stability of LV function, size, and geometry in patients with off-pump LVEF ≥45% can improve future weaning decisions. As shown in Table 3, the pre-explant LV stability during serial off-pump trials revealed positive predictive values for ≥5 years postweaning HTx/VAD-free survival of between 78% and 100%. The prediction of HTx/VAD-free

Figure 3. Comparison between preweaning changes in off-pump left ventricular end-diastolic diameter (LVEDD) (column A), end-diastolic short/long-axis ratio (S/L-axis ratio) (column B), and end-diastolic relative wall thickness (RWT) (column C) in patients with recurrence of heart failure during the first 5 postweaning years and those with ≥5-year postweaning cardiac stability. The differences between the 2 patient groups were statistically significant (P<0.05) for all parameters.
survival for ≥10 years appeared also possible but less reliable. However, if weaned patients indeed survive 5 years after VAD removal, much has been accomplished. The very high predictive values (94% to 100%) of the selected parameters for short-term (≥1 year) postweaning cardiac stability suggest that in patients with persistent and relevant life-threatening complications on their VADs, even if the off-pump LVEF is only between 40% and 45%, VAD explantation followed by HTx after a few months of recovery can be safer than keeping such patients on their VAD.

The possibility to improve the prediction of postweaning HTx/VAD-free outcome by analyzing the pre-explantation stability of several LV off-pump echocardiographic parameters and indices is the main finding of our present study. However, our data are insufficient for a reliable answer to the question whether it is necessary to measure all selected parameters or whether it might be sufficiently reliable to select for future weaning decisions only the off-pump parameter with the highest predictive value for long-term stable cardiac function after VAD explantation. Because of the vital importance of any weaning decision, it appears improper to rely only on the off-pump parameter with the highest predictive value for long-term stable cardiac function after VAD explantation. Our data showed that a pre-explant stable LVEF of ≥45% in patients with pre-explant stable LVEDD of ≥55 mm is reliably predictive for long-term postweaning cardiac stability. Thus, provided that echocardiographic measurements are reliably reproducible, serial LVEF and LVEDD measurements before VAD explantation might be sufficiently reliable for weaning decisions. However, especially in borderline cases, it can be helpful also to take into account the pre-explant value and stability of other parameters such as Sm, S/LV, and RWT. Therefore, it remains important to measure all parameters of LV size, geometry, and function at each off-pump trial.

Overall, our present results suggest that with the additional inclusion in weaning protocols of data on pre-explant stability of improvement in off-pump LV size, geometry, and function, prediction of postweaning long-term cardiac stability can become more reliable. In IDCM patients, we previously found that patients with stable myocardial recovery for >3 years after VAD explantation needed significantly shorter duration of mechanical support until weaning becomes possible in comparison to those who showed early postweaning recurrence of HF.13 In a more recent study on IDCM patients, we also found the necessity of mechanical support of >3 months before VAD explantation to be a risk factor for postexplant HF recurrence (76% predictive value for HF recurrence during the first 3 years after VAD explantation).17

Our present data suggest that in patients with ≥10 years of improvement in off-pump LV size, geometry, and function during the time period between maximum improvement of LV function and VAD removal and during the final off-pump trial.

### Table 4. Predictive Value for Short-Term and Long-Term Postweaning Patient Outcome of Changes in Off-Pump LV Size, Geometry, and Function During the Time Period Between Maximum Improvement of LV Function and VAD Removal and During the Final Off-Pump Trial

<table>
<thead>
<tr>
<th>Parameter Change</th>
<th>Cutoff † %</th>
<th>Sens, % (CI)</th>
<th>Spec, % (CI)</th>
<th>NPV ‡ % (CI)</th>
<th>PPV ‡ % (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>70</td>
<td>82 (95-95)</td>
<td>95 (82-95)</td>
<td>95 (82-95)</td>
<td>82 (95-95)</td>
</tr>
<tr>
<td>Interval change*</td>
<td>95</td>
<td>79 (100)</td>
<td>100 (79-100)</td>
<td>100 (79-100)</td>
<td>79 (100)</td>
</tr>
<tr>
<td>LVEDD</td>
<td>70</td>
<td>100 (67)</td>
<td>100 (67)</td>
<td>100 (67)</td>
<td>100 (67)</td>
</tr>
<tr>
<td>Interval change*</td>
<td>70</td>
<td>100 (48)</td>
<td>100 (48)</td>
<td>100 (48)</td>
<td>100 (48)</td>
</tr>
<tr>
<td>Pre-explant change†</td>
<td>61</td>
<td>100 (62)</td>
<td>100 (62)</td>
<td>100 (62)</td>
<td>100 (62)</td>
</tr>
<tr>
<td>S/LV ratio</td>
<td>62</td>
<td>100 (51)</td>
<td>100 (51)</td>
<td>100 (51)</td>
<td>100 (51)</td>
</tr>
<tr>
<td>Interval change*</td>
<td>72</td>
<td>100 (38)</td>
<td>100 (38)</td>
<td>100 (38)</td>
<td>100 (38)</td>
</tr>
<tr>
<td>Pre-explant change†</td>
<td>72</td>
<td>100 (44)</td>
<td>100 (44)</td>
<td>100 (44)</td>
<td>100 (44)</td>
</tr>
<tr>
<td>RWT</td>
<td>72</td>
<td>100 (46)</td>
<td>100 (46)</td>
<td>100 (46)</td>
<td>100 (46)</td>
</tr>
<tr>
<td>Interval change*</td>
<td>72</td>
<td>100 (48)</td>
<td>100 (48)</td>
<td>100 (48)</td>
<td>100 (48)</td>
</tr>
<tr>
<td>Pre-explant change†</td>
<td>62</td>
<td>100 (59)</td>
<td>100 (59)</td>
<td>100 (59)</td>
<td>100 (59)</td>
</tr>
<tr>
<td>Sm</td>
<td>72</td>
<td>100 (90)</td>
<td>100 (90)</td>
<td>100 (90)</td>
<td>100 (90)</td>
</tr>
<tr>
<td>Interval change*</td>
<td>72</td>
<td>100 (90)</td>
<td>100 (90)</td>
<td>100 (90)</td>
<td>100 (90)</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; VAD, ventricular assist device; CI, confidence interval; LVEF, LV ejection fraction; LVEDD, LV end-diastolic diameter.

*Change between maximum cardiac improvement and VAD removal.
†Change during the final off-pump trial.
‡Optimal cutoff derived from ROC analysis.
§Negative predictive value (NPV) is prediction for cardiac stability.
||Positive predictive value (PPV) is prediction for heart failure recurrence.
a relative contraindication for VAD explantation only in borderline cases concerning LV improvement.

**Limitations**

Data were obtained from a single-center, retrospective study of prospectively gathered information. The still relatively small cohort and the lack of randomization also limited our study. Because our weaning strategy produced a higher prevalence of long-term stable cardiac function, our positive predictive values may be lower and the negative predictive values higher than they would be in a sample with lower prevalence of long-term cardiac stability. Therefore, definite cutoff values for the investigated parameters allow more reliable prediction of early recurrence of HF than prediction of long-term cardiac stability after VAD explantation. Because the sample size to independent variable ratio is relatively low, the multivariate Cox results also need to be interpreted with caution. However, these limitations were unavoidable because weaning from VADs is not possible in patients without relevant myocardial improvement.

A potential limitation might be the fact that our weaned patients selected for evaluation had not the same major type of VAD. Of the 53 evaluated patients, 35 (66%) were weaned from pulsatile pumps that probably operated differentially with respect to unloading conditions in comparison with the continuous flow VADs that were removed from the other 18 (34%) patients. However, echocardiographic measurements for evaluation of myocardial recovery were all performed during off-pump conditions on ventricles working for a limited time without mechanical support, which allowed evaluation of the heart under the same circumstances that exist after VAD removal.

**Conclusions**

Weaning from VADs in patients with nonischemic CCM is feasible and can be successful even after incomplete cardiac recovery. The stability of certain “off-pump” parameters related to LV size, geometry and function both during the time period between maximum cardiac improvement and VAD explantation and during the final “off-pump” trials.

**Figure 4.** Receiver-operating characteristic curves for prediction of heart failure recurrence during the first 5 years after ventricular assist device (VAD) explantation in patients with nonischemic chronic cardiomyopathy (CCM). The high values for the areas under the curves that measure discrimination indicate a high ability of pre-explantation degree of stability in left ventricular ejection fraction (LVEF) and systolic peak wall motion velocity (Sm) (A), left ventricular end-diastolic diameter (LVEDD) (B), end-diastolic relative wall thickness (RWTED) (C), and end-diastolic short/long-axis ratio (S/LAX-axis ratio) (D) to correctly classify patients with and without cardiac stability after VAD removal. (1) indicates interval change (parameter change between “best” and “pre-explant”); (2), pre-explant change (parameter change during the final off-pump trial).
Table 5. Major Preweaning Predictors of HF Recurrence After VAD Removal

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>1.133</td>
<td>1.064–1.194</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF interval change*</td>
<td>1.105</td>
<td>1.065–1.147</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDD</td>
<td>1.217</td>
<td>1.105–1.341</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDD interval change*</td>
<td>1.178</td>
<td>1.106–1.254</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDD pre-explant change†</td>
<td>1.299</td>
<td>1.174–1.438</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S/LVEDD ratio interval change*</td>
<td>1.287</td>
<td>1.171–1.415</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S/LVEDD ratio pre-explant change†</td>
<td>1.271</td>
<td>1.159–1.394</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RWTED interval change*</td>
<td>1.275</td>
<td>1.158–1.402</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RWTED pre-explant change†</td>
<td>1.243</td>
<td>1.142–1.352</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sm interval change*</td>
<td>1.285</td>
<td>1.158–1.425</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sm pre-explant change†</td>
<td>1.291</td>
<td>1.168–1.428</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

H indicates heart failure; VAD, ventricular assist device; LVEF, LV ejection fraction; LVEDD, LV end-diastolic diameter.

*Change between maximum cardiac improvement and VAD explantation.
†Change during the final off-pump trial.
‡Proportional hazard testing yielded P values <0.05 for all variables.

allow the detection of patients with the potential to remain stable for a long time period after VAD explantation and also the recognition of those with high risk for early postweaning recurrence of HF despite an LVEF of $>40\%$. The S/LVEDD-axis ratio change between maximum cardiac improvement and VAD removal appeared to be an independent predictor for the postexplant stability of cardiac function.

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Disclosures

None.

References

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