CLINICAL RESEARCH

Heart failure reversal by ventricular unloading in patients with chronic cardiomyopathy: criteria for weaning from ventricular assist devices

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Aims	Unloading-promoted reversal of heart failure (HF) allows long-term transplant-free outcome after ventricular assist device (VAD) removal. However, because few patients with chronic cardiomyopathy (CCM) were weaned from VADs (the majority only recently), the reliability of criteria used for weaning decisions to predict long-term post-weaning success is barely known. After 15 years of weaning experience, we assessed this issue.
Methods and results	In 47 patients with CCM as the underlying cause for HF, who were part of a total of 90 patients weaned from bridge-to-transplant-designed VADs since 1995, we analysed data on cardiac morphology and function collected before VAD implantation, echocardiographic parameters recorded during 'off-pump' trials, duration of HF before implantation, and stability of recovery before and early after VAD removal. Post-weaning 5 year freedom from HF recurrence reached 66%. Only five patients (10.6%) died due to HF recurrence or weaning-related complications. Pre-explantation off-pump left ventricular ejection fraction (LVEF) of ≥ 50 and $\geq 45\%$ revealed predictive values for cardiac stability lasting ≥ 5 years after VAD removal of 91.7 and 79.1%, respectively. With each unit of LVEF reduction, the risk of HF recurrence became 1.5 times higher. The predictive value of LVEF $\geq 45\%$ also became $>90\%$ if additional parameters like pre-explantation LV size and geometry, stability of unloading-induced cardiac improvement before VAD removal, and HF duration before VAD implantation were also considered. Definite cut-off values for certain parameters (including tissue-Doppler-derived LV wall motion velocity) allowed formulation of weaning criteria with high predictability for post-weaning stability, also in patients with incomplete cardiac recovery.
Conclusions	Ventricular assist device removal in CCM patients is feasible and can be successful even after incomplete cardiac recovery. Parameters of pre-explantation cardiac function, LV size and geometry, their stability during final off-pump trials, and HF duration allow detection of patients with the potential to remain stable for >5 post-weaning years.
Keywords	Cardiomyopathy • Heart failure • Ventricular assist devices • Myocardial recovery • Survival • Risk factors

Introduction

Ventricular assist devices (VADs), which were primarily designed for bridge-to-transplant therapy, are today also used as permanent therapy for end-stage heart failure (HF). Evidence of myocardial reverse remodelling and functional improvement during VAD support in some patients suggests that the use of mechanical ventricular unloading as a therapeutic strategy aimed at cardiac recovery, allowing VAD removal instead of heart transplantation (HTx), may be another potential future indication for VAD implantation.[1–12]

During VAD support, cardiac improvement to levels that allow VAD removal instead of HTx is less frequent than myocardial recovery at molecular and cellular levels, which has more often been shown under these circumstances.[2,3,7,13,14] Recovery appears to be related to the aetiology of myocardial damage and the duration of heart disease.[2,15,16] More often, cardiac recovery allowing weaning from VADs was detected after acute myocarditis and post-cardiotomy HF, but recovery with long-term cardiac stability is also possible in idiopathic dilated cardiomyopathy (IDCM).[4−6,9,11,15−19] However, greatly differing recovery rates during VAD support have been reported, especially for IDCM.[12,16,18−20] These may arise from different weaning criteria, different medical treatments during mechanical unloading, differences in mechanical systems used for ventricular support, and also differences in patient selection for VAD implantation.

So far only a few patients with chronic myocardial failure had been weaned from VADs and the majority were weaned only recently, i.e. during the past 3−5 years.[2,6,16−21] However, if cardiac recovery is detected, it is essential to have reliable tools for the prediction of cardiac stability in the case of VAD removal. Therefore, data from weaned patients, especially from those with cardiac stability for >5 years after VAD explantation, are necessary to improve future weaning decisions. The low rate of myocardial recovery even at incomplete levels and the fact that weaning is possible only after relevant cardiac improvement limit the possibilities for prospective studies on myocardial recovery during ventricular unloading.

Previous evaluation of our IDCM patients with LVADs showed that certain 'off-pump' echocardiographic data are reliable for the detection of cardiac recovery with the potential for medium-term stability after LVAD removal.[5,16] Meanwhile, a larger number of our patients with chronic cardiomyopathy (CCM), including clinical entities other than IDCM, have reached post-weaning cardiac stability for between 5 and 15 years and it has become possible to investigate whether long-term stability can be reliably predicted before VAD removal for this larger and less homogeneous patient cohort. The present study aimed to identify both weaning criteria that can predict long-term cardiac stability after VAD removal and major risk factors for HF recurrence in patients with unloading-induced myocardial recovery from end-stage HF linked to CCM.

Methods

Patients evaluated

Between March 1995 and February 2010, a total of 90 patients who received emergency VAD implantation because of life-threatening HF unresponsive to medical treatment, including inotropic support, 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. Among these patients, we selected for evaluation those with CCM as the underlying cause for HF. Patients weaned from VADs after recovery from post-cardiotomy HF, acute myocarditis, and acute myocardial infarction and also children younger than 14 years of age were excluded from the study.

Inclusion criteria were fulfilled by 47 patients who consented to VAD implantation as a bridge to transplantation and provided written informed consent before VAD removal. Of these, 41 (87.2%) had IDCM, 4 (8.5%) had histological evidence of chronic myocarditis before VAD implantation, and 2 (4.3%) had chronic ischaemic cardiomyopathy with severe LV dilation. Before VAD insertion, all patients had irreversible end-stage HF and required continuous positive inotropic support. No attempts have been made to use VADs electively with the aim of myocardial recovery only.

Of the 47 patients evaluated, 45 (95.7%) were weaned from LVADs and only 2 (4.3%) from biventricular assist devices (BVADs). Of 45 explanted LVADs, 33 (70.2%) were pulsatile pumps (Novacor, TCI, or Berlin Heart EXCOR); the other 12 (29.8%) were 'continuous flow' pumps (INCOR and HeartMate II). Pump explantation followed the fundamental rule of maintaining the recovered heart in as unmolested a state as possible. Therefore, VAD removal was performed on the beating heart. During VAD removal, we aimed as much as possible to leave in place the intrathoracic part of both cannulas after they were reliably occluded. Intrathoracic cannulas were removed only in 13 patients (10 with 'continuous flow' LVADs and 3 with pulsatile LVADs). In these 13 patients and other 2 patients with Heartmate II LVADs, we used the heart−lung machine. Off-pump surgery was possible for the explantation of 32 pulsatile VADs (30 LVADs and 2 BVADs).

Study design and data collection

To assess the predictability of post-weaning outcome without HTx or other VAD implantation and to identify risk factors for post-weaning HF recurrence, we used the data collected before and during VAD support.

Pre-implantation data were used to evaluate their potential usefulness for weaning decisions by the assessment of their predictive value for post-weaning stability of unloading-induced cardiac improvement. For this reason, we compared the pre-implantation data of weaned patients with and without long-term post-weaning cardiac stability. Pre-implantation data were collected from our database before VAD removal and did not interfere with weaning decisions. In addition to diagnosis and NYHA class, the duration of heart disease, ECG, and echocardiographic data, as well as data provided by pre-implantation right- and left-heart catheterization (including coronary angiography) were collected for evaluation. Histological data on myocardial hypertrophy and interstitial fibrosis obtained in all evaluated patients from apical cores removed at VAD implantation were also collected for further evaluation. Methodological details have been previously described.[1,9]

After successful weaning of three IDCM patients from LVADs in 1995 who had off-pump left ventricular end-diastolic diameters (LVEDDs) of <50 mm and ejection fraction (LVEF) of between 45 and 55%, we presumed that LVAD removal might be safely possible if, during repeated off-pump trials, the maximum LVEDD was 55 mm and the minimum LVEF 45%, while the right ventricular (RV) size and function remained stable. Since then, off-pump echocardiographic data have been collected prospectively according to a well-established protocol, but until 2002 VAD removal was not absolutely limited to patients with normal LV size and LVEF of >45%. Thus, nine patients with IDCM were weaned from VADs although off-pump LVEDD was 56−66 mm and/or LVEF 30−44%. However, in five of these patients, VAD explantation was prompted by pump-related complications (pump infection, thrombo-embolism, bleeding complications). These five patients underwent VAD removal although cardiac improvement appeared less promising for long-term transplant-free outcome, but the risk of keeping them on their VADs appeared to be higher than the risk of removing the VADs with the option to perform HTx later (if necessary) after the treatment of VAD-related complications.

In 2002, we changed our weaning protocol by limiting VAD explantation to patients with off-pump LVEF ≥45% at LVEDD ≤55 mm, and no further VAD explantation was performed in patients

Table I **Main weaning criteria used since March 2002**

Examination	Parameters and parameter-derived measurements obtained during the final pre-explantation off-pump trial[a]
Electrocardiography	Sinus rhythm HR <90 b.p.m. Not more than 25% HR increase during off-pump trials
Brachial artery pressure	Mean $\geq$65 mmHg
Echocardiography	LVEDD $\leq$55 mm LVEF $\geq$45% No or maximum grade II mitral and/or aortic valve regurgitation No RV dilation (RVOT diameter <35 mm, short-/long-axis ratio <0.6) No or maximum grade II tricuspid or pulmonary valve regurgitation
Right-heart catheterization	Cardiac index >2.6 L/min/m^2 Pulmonary artery wedge pressure (mean) <13 mmHg Right atrial pressure (mean) <10 mmHg

[a]Measurements performed at rest, without any inotropic support.

with LVEF <45% and LVEDD >55 mm, because our first evaluations of post-weaning outcome showed good results only in those with pre-weaning off-pump LVEF $\geq$45% and LVEDD $\leq$55 mm. To verify these preliminary findings, we also compared the post-weaning outcome of patients who were weaned before March 2002 with that of those weaned thereafter. *Table 1* show our main weaning criteria used after March 2002.

Pharmacological therapy

During ventricular unloading, all patients were treated with beta-blockers (metoprolol or carvedilol), angiotensin-converting enzyme (ACE)-inhibitors (enalapril, ramipril, or lisinopril), aldosterone antagonists (spironolactone), loop diuretics (furosemide or torasemide), and digitalis. Medication doses were individually adapted to reduce heart rate (HR) towards 55–60 b.p.m. and blood pressure to the lowest optimally tolerated value, as well as to maintain optimal renal function. However, after the detection of cardiac improvement which was deemed sufficient to consider a patient as a potential weaning candidate, in those with off-pump systemic arterial diastolic pressure values <55 mmHg, we reduced the doses of ACE-inhibitors and diuretics. The aim was to increase the diastolic pressure to values of between 55 and 65 mmHg, which provided a more suitable after-load for the evaluation of LV systolic function. Treatment with beta-blockers, ACE-inhibitors, spironolactone, and low-dose loop diuretics was continued after VAD removal. In patients with post-weaning cardiac stability, coumadin anticoagulation therapy was maintained for 6–12 months after VAD removal [international normalized ratio (INR) 2–3]. Thereafter, stable patients were switched to Aspirin (daily 100 mg for at least 2 years).

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. Since 1999, in addition to conventional echocardiography, tissue Doppler imaging (TDI) was also used to assess ventricular function. For the evaluation of LV recovery, we measured the systolic wall motion peak velocity (S_m) at the basal posterior wall. Methodological details of S_m measurements were described previously.[16,22] To assess the RV systolic function, we measured the peak velocity of tricuspid annulus systolic excursion (S_{TA}) at the level of the free wall.

Off-pump echocardiography at rest evaluating the heart for a short time without VAD support under the same circumstances which will exist after VAD removal was the cornerstone for the assessment of cardiac recovery and for weaning decisions. Off-pump trials were started after the LV reduced its end-diastolic diameter to 60 mm and mitral regurgitation was $\leq$grade I. Before pump-stops, heparin was given to prevent thrombus formation inside the pump. Heparin doses varied between 60 and 100 IU/kg according to the pro-thrombin time reported as INR. Patients with heparin-induced throbocytopenia received Argatroban (synthetic direct thrombin inhibitor) infusions (2 µg/kg/min), which were started 1 h before the off-pump trials.

For pulsatile LVADs, trials consisted of pump frequency reduction to the lowest, followed by intermittent pump-stops lasting up to 15 min. Additionally, during the off-pump periods, the device was allowed to pump once a minute. 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 cardiac function, we reduced the rotor speed to values which result in a close to zero net flow in one cardiac cycle. In patients with BVADs, the RV pump was stopped 30 s earlier than the LV pump and then both pumps remained inactive for up to 15 min 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. At this point, the final decision in favour of or against VAD explantation was made. During recovery, as described previously, the working mode of the pumps was also changed in order to exert moderate load on the LV myocardium.[1,9] To avoid excessive stimulation of the myocardium during recovery, stress echocardiography was not routinely used. However, 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 mmHg.

Right-heart catheterization with 'off-pump' haemodynamic measurements was routinely scheduled only for patients who were already selected for VAD removal and was performed 1 h before VAD explantation. Invasive haemodynamic measurements for the assessment of cardiac recovery were not routinely performed.

To monitor myocyte recovery during ventricular unloading, in patients with non-ischaemic CCM we also looked for anti-β1-adrenoceptor auto-antibodies (A-β1-AABs) before VAD implantation, and thereafter weekly during the entire period of VAD support. The bioassay for A-β1-AAB measurement was described previously.[9,23] However, due to the lack of data on impact of A-β1-AAB disappearance on cardiac recovery during ventricular unloading, weaning decisions were made independently of A-β1-AAB measurement results.

Weaning decisions were also independent of histological data obtained from myocardial tissue specimens before VAD implantation because thereafter no routine biopsies for monitoring histological changes during ventricular unloading were performed and also because the impact of myocardial hypertrophy and interstitial fibrosis on the stability of unloading-promoted cardiac improvement was barely known. Nevertheless, before, during, or early after VAD removal, LV myocardial tissue specimens were obtained in 14 patients (12 myocardial biopsies performed during thoracic surgery and 2

endomyocardial biopsies obtained by arterial approach). In 10 other patients, we performed RV endomyocardial biopsies by venous approach before VAD removal. Histological data obtained from these weaned patients were used for the assessment of unloading-induced myocardial changes.

Post-weaning monitoring of cardiac function

Echocardiography remained the major tool for monitoring cardiac function after VAD removal. During the first post-weaning week, it was performed daily, thereafter each second day. During rehabilitation, it was performed weekly and in outpatients, the frequency of scheduled follow-up controls varied in accordance with the post-weaning time between monthly and every 6 months.

Exercise tolerance was evaluated by a maximum (symptom-limited) incremental treadmill exercise test according to Naughton's protocol. However, this test was not performed before 2−3 months postoperatively. During the past 7 years, at each follow-up examination NT-proBNP plasma levels were also measured.

Statistics

Statistical analysis was performed using SPSS 12.0 for Windows (SPSS, Inc., Chicago, IL, USA). Quantitative data, representing patient characteristics before VAD implantation and at the time of VAD removal, were expressed as means and standard deviation (SD). However, because we dealt with small data sets (small number of subjects) with non-normally distributed data, differences between patients with lasting recovery and those with recurrence of HF (independent groups) were analysed using the non-parametric Mann−Whitney U test and Fisher's exact test. For all tests, differences between groups were considered significant for two-sided P-value <0.05. Sensitivity, specificity, and predictive values were calculated for selected echocardiographic parameters and time parameters related to HF history and cardiac recovery during LVAD support according to pre-specified cut-off points and were expressed as percentages. Kaplan−Meier curves were applied for survival analysis and for freedom from HTx after LVAD explantation. The probability of survival and the probability of freedom from HTx at a given point of time as derived from the Kaplan−Meier estimation were expressed in percent ± standard error (SE). Univariate logistic regression was used to calculate odds ratios with 95% CI for main risk factors. Cox regression was also used to analyse the relevance of major risk factors. For Kaplan−Meier estimates of overall survival, we introduced into the analyses the time of survival after VAD removal (including the survival time after HTx), whereas for the Kaplan−Meier estimates of freedom from HF recurrence, we used only the time between VAD removal and reappearance of HF signs and symptoms which make it necessary to list the patient for HTx.

Results

Weaned patient characteristics at ventricular assist device implantation

Of the 47 patients evaluated, 17 (36.2%) were <40 years, 19 (40.4%) were 40−55 years, and 11 (23.4%) were between 56 and 65 years. Before VAD implantation, these patients had dilated LV (LVEDD: 64−93 mm), LVEF between 10 and 20%, mitral regurgitation ≥grade II, and high pulmonary arterial pressure (PAP) values (mean 32−54 mmHg). The duration of HF before VAD insertion was 4.1 ± 3.8 years. None had undergone previous resynchronization therapy. Weaned patient characteristics before VAD implantation are shown in Table 2.

Clinical features at ventricular assist device explantation

For the weaned CCM patients, the mean duration of ventricular unloading necessary for maximum cardiac improvement allowing VAD explantation was 4.9 ± 2.8 months. Left ventricular ejection fraction and LVEDD values measured during final off-pump trials before VAD removal ranged from 30 to 60% and from 40 to 64 mm, respectively. At VAD explantation, all patients had normal PAP values, normal aortic valve function, and no or not relevant mitral or tricuspid valve regurgitation (grade ≤I). In 38 of 39 weaned patients with non-ischaemic CCM who tested positive for A-β_1-AABs before VAD implantation, the auto-antibodies disappeared after 3−31 weeks of LV unloading. Comparative histomorphometry showed 18.1 ± 13.3% reduction of the relative content of fibrosis during unloading. Reduction of fibrosis in 64% and regression of myocardial hypertrophy in 91% of the weaned patients in whom comparative histology was possible were shown.

Outcome after ventricular assist device explantation

None of the 47 weaned CCM patients was lost to follow-up after VAD removal as long as they were alive. At the time of evaluation, the fate of all 47 patients included in the study was well known. The median follow-up after VAD removal was 5.7 years (range 0.1−14.8 years). Figure 1 shows a diagram giving the number of weaned CCM patients at time points and their outcome, starting from the time of VAD explantation.

Patient survival after ventricular assist device explantation

At the time of evaluation, 33 (70.2%) of the 47 patients with end-stage CCM before VAD implantation, who were weaned since March 1995 from their VADs after different degrees of cardiac recovery, were alive. Kaplan−Meier estimates of overall survival after VAD removal (including post-HTx survival for those with HF recurrence) revealed probabilities of 71.4 ± 7.1 and 65.7 ± 7.6% for 5 and 10 year survival, respectively (Figure 2A). Of 14 patients who have died to date, 9 (64.3%) died due to different causes not related to VAD removal. The vast majority of patients with HF recurrence underwent HTx and thus, the assessment of post-weaning survival from HF recurrence or weaning-related complications by Kaplan−Meier estimates revealed high probabilities for 5 and 10 year survival, reaching 88.4 ± 5.7 and 85.8 ± 6.0%, respectively (Figure 2B). There was no between-group difference in the Kaplan−Meier estimates of overall survival for patients with and without HF recurrence after VAD removal (10 year survival 64.7 ± 11.6 and 67.1 ± 9.7%, respectively; $P = 0.76$). Kaplan−Meier estimates of transplant-free survival after VAD removal revealed probabilities of 68.9 ± 7.6 and 61.6 ± 8.6% for 5 and 10 year survival, respectively.

The complications related to VAD removal were uncommon. Infection was a major problem in five patients, but in four of these, it was already present before VAD removal. Bleeding

Table 2 Weaned patient characteristics at the time of ventricular assist device implantation: comparison of patients who exhibited long-lasting cardiac stability with those showing heart failure recurrence during the first 5 years after ventricular assist device removal

Main characteristics	All chronic HF patients weaned from VADs[a] (*n* = 47)	Patients evaluated for long-lasting recovery after VAD removal[a] (*n* = 33[b])		
		Long-lasting cardiac improvement (>5 years) (*n* = 19)	Post-weaning recurrence of HF (in ≤5 years) (*n* = 14)	*P*-value
Age (years)	42.4 ± 14.4	40.1 ± 12.1	47.6 ± 9.7	0.03[c]
Sex [*n* (%)]				
Male	42 (95.5)	18 (94.7)	14 (100)	1.0
Female	2 (4.5)	1 (5.3)	0	
Diagnosis [*n* (%)]				
Non-ischaemic chronic CM	42 (95.5)	17 (89.5)	14 (100)	0.9
Ischaemic chronic CM	2 (4.5)	2 (10.5)	0	
History of HF (years)	4.1 ± 3.8	2.4 ± 1.5	6.4 ± 4.5	0.01[c]
Patients with LVADs [*n* (%)]	42 (95.5)	18 (94.7)	13 (92.9)	1
Patients with BVADs [*n* (%)]	2 (4.5)	1 (5.3)	1 (7.1)	
Heart rhythm [*n* (%)]				
Sinus rhythm	43 (97.7)	19 (100)	13 (92.9)	0.42
Atrial fibrillation	1 (2.3)	0	1 (7.1)	
LVEF (%)	15.4 ± 3.4	15.0 ± 2.6	15.3 ± 3.4	0.79
LVEDD (mm)	74.3 ± 7.5	73.1 ± 4.3	78.4 ± 4.1	0.09
Fibrosis (%)	12.1 ± 9.6	9.8 ± 5.2	16.0 ± 10.5	0.08
Serum A-β_1-AABs (LU)	5.4 ± 2.1	5.2 ± 1.7	5.4 ± 1.9	0.95

LU, laboratory units.
[a]Values are means ± SD.
[b]Only 33 of the 47 weaned patients with CCM could be used for comparison. Patients with stable cardiac function who died during the first 5 post-weaning years due to different causes not related to VAD removal and patients who were weaned <5 years before this evaluation were not included.
[c]Statistically significant.

complications occurred in only one patient (lethal pulmonary bleeding 4 months after LVED removal). None of the patients with the residual apical conduit left in place after LVAD removal had stroke or extracerebral embolic complications arising from the LV.

Of the 31 patients who were weaned before March 2002, 5 (16.1%) died due to complications related to VAD removal or recurrence of HF, 2 (6.5%) died due to causes not related to VAD removal, and 3 (9.6%) died after HTx. Of the 16 patients with CCM who were weaned thereafter, when we used the modified weaning protocol, 2 (12.5%) died during the first 3 years after weaning due to causes not related to VAD explantation and 2 (12.5%) died after HF recurrence beyond the fifth post-weaning (one before HTx, the other early after HTx).
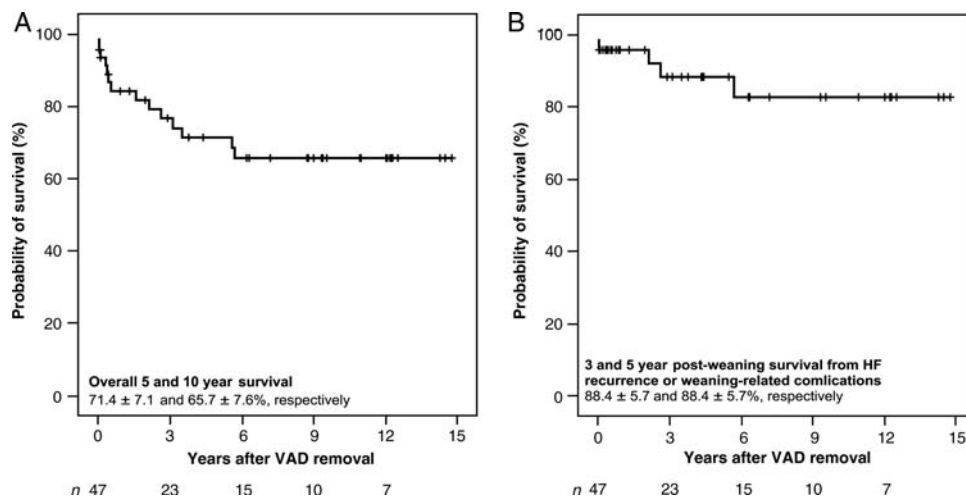
Heart function after ventricular assist device removal

To date, post-weaning recurrence of HF occurred in 17 (36.2%) of the evaluated patients suffering from CCM before VAD implantation (*Figure 1*). Myocardial dysfunction with progressive LV dilation but not the new appearance or aggravation of pre-existing mitral regurgitation appeared to be the cause for the recurrence of HF symptoms. Kaplan–Meier estimates revealed a probability of 66.0 ± 8.2% for 5 year freedom from HF recurrence after VAD removal (*Figure 3A*). In the patient group that underwent VAD removal before March 2002, HF recurred in 14 (45.2%) of 31 patients. Of these HF recurrences, nine (64.3%) occurred during the first year after weaning. In the group weaned thereafter, only 3 (18.8%) of the 16 patients showed HF recurrences, which all arose late, beyond the fourth post-weaning year. There were no significant differences in post-weaning cardiac stability between patients who were weaned from continuous flow LVADs and those weaned from pulsatile LVADs.

Of the 17 patients with HF recurrence, 15 underwent HTx, 1 patient (>65 years of age at HF recurrence) received another LVAD designed as a chronic mechanical circulatory support, and 2 patients died suddenly 2.1 and 5.7 years after LVAD removal, respectively.
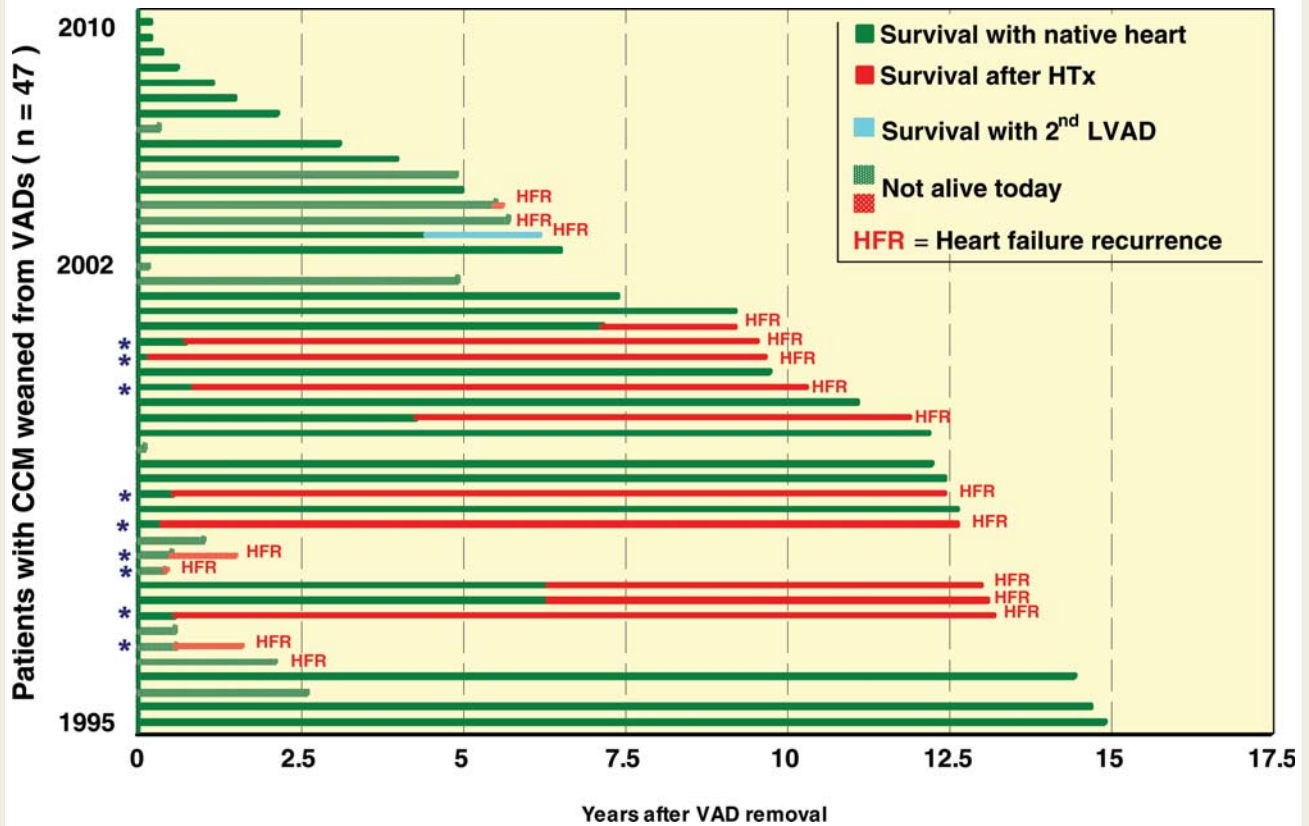
Figure 1 Outcome after ventricular assist device (VAD) removal. Between 1995 and 2002, of the 31 weaned patients, 9 (marked with asterisk) had left ventricular ejection fraction values of between 30 and 44% at left ventricular end-diastolic diameter values of between 55 and 66 mm before VAD removal. All nine patients showed heart failure recurrence during the first 10 post-weaning months. Therefore, thereafter weaning was restricted to patients with left ventricular end-diastolic diameter ≤55 mm and left ventricular ejection fraction ≥45%.

Figure 2 Kaplan–Meier estimates of patient survival after ventricular assist device (VAD) removal. (*A*) Probability of overall post-weaning survival with the inclusion of post-transplant survival for patients with recurrence of heart failure (HF). (*B*) Probability of post-weaning survival from heart failure recurrence or weaning-related complications.
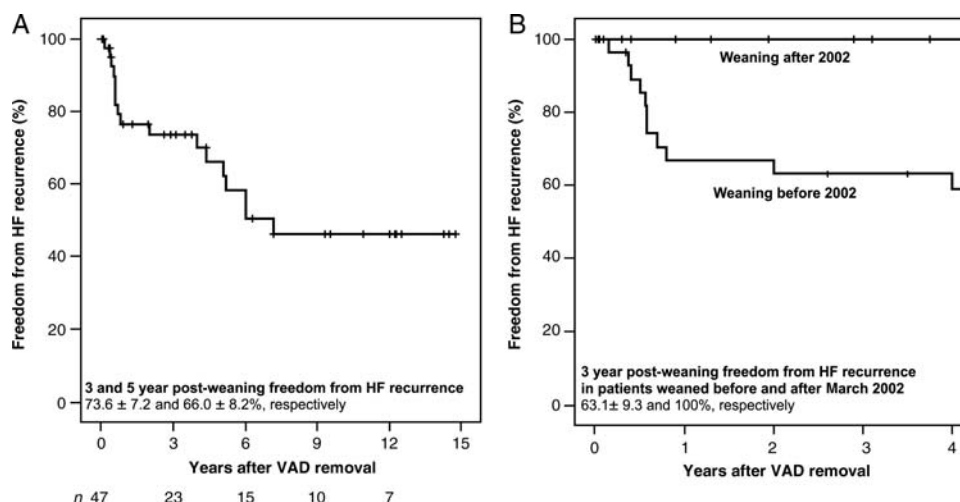
Figure 3 Kaplan–Meier estimates of freedom from heart failure (HF) recurrence after ventricular assist device (VAD) removal. (*A*) Post-weaning freedom from heart failure recurrence for all evaluated patients. (*B*) Comparison of 3 year post-weaning freedom from heart failure recurrence between patients who were weaned from ventricular assist devices before and after March 2002.

Among the 19 patients without HF recurrence during the first 5 post-weaning years, 16 (84.2%) were in functional NYHA class $\leq$II at the end of the fifth post-weaning year. Another two patients, who also showed good cardiac function, were not capable of physical activities because of neurological sequels after cerebral vascular accidents which occurred before VAD removal, and one patient oscillated between NYHA class II and III. In these patients, exercise testing performed between the third and fourth year (3.5 $\pm$ 0.5 years) after weaning revealed only slightly or moderately reduced exercise tolerance. Expressed as a percentage of the predictive values, the maximum oxygen uptake reached 77.3 $\pm$ 4.5%, and the ventilatory equivalent for CO_2 was 29.7 $\pm$ 3.5 in these patients. Patients with >3 year cardiac stability after VAD removal showed only slightly elevated NT-proBNP levels even late after weaning (159.8 $\pm$ 91.7 pg/mL at 6.5 $\pm$ 2.3 years after weaning).

Comparison of patients with and without recurrence of heart failure

Heart failure recurrence vs. cardiac stability during the first 5 post-weaning years

Data obtained from 33 patients who could be evaluated for long-term (>5 years) post-weaning cardiac stability (weaning since $\geq$5 years and no deaths before the fifth post-weaning year due to causes other than HF recurrence) show that in patients with HF recurrence during the first 5 post-weaning years, the duration of VAD support necessary for recovery was longer than in those with post-weaning cardiac stability for >5 years (*Table 3*). In patients with post-weaning cardiac stability for >5 years, the LVEF was higher and the LVEDD smaller before VAD removal than in the patients with HF recurrence during the first 5 post-weaning years (*P* < 0.01). There were no differences in Doppler parameters or Doppler-derived indices of diastolic function measured at final off-pump trials in patients with and without HF recurrence after weaning. However, wall motion peak systolic velocities (S_m)

measured during the final off-pump trials by pulsed-wave TDI were higher in patients with stable post-weaning cardiac function (*Table 3*). Patients with long-lasting post-weaning cardiac stability also showed higher stability of S_m values before VAD removal (no or <10% reduction after maximum improvement and $\leq$10% reduction during the final off-pump trials in comparison with the S_m measured with the working pump).

Between patients with and without HF recurrence during the first 5 post-weaning years, there were no differences for the disappearance time of A-β_1-AABs during VAD support (*Table 3*). There were also no differences in PAP values (measured at the time of VAD removal) between these two groups.

Comparison between patients weaned before and after weaning protocol changes

In the patient group that underwent VAD removal before March 2002, 11 (78.6%) of the 14 HF recurrences were during the first 5 years, whereas in the group with removal thereafter according to a modified weaning protocol (no weaning if LVEF <45% and/or LVEDD >55%), there was no HF recurrence during the first 3 post-weaning years and only one patient showed HF recurrence before the end of the fifth post-weaning year (*Figure 3B*).

Predictability of cardiac stability after ventricular assist device removal

None of our weaned CCM patients with history lengths of HF $\leq$5 years before VAD implantation who at the time of VAD removal had off-pump LVEF and LVEDD values of $\geq$45% and $\leq$55 mm, respectively, showed recurrence of HF during the first 3 post-weaning years and even cardiac stability beyond the fifth post-weaning year appeared predictable by these parameters. Thus, pre-explantation off-pump LVEF of $\geq$50% appeared highly predictive (91.7%) for cardiac stability lasting $\geq$5 years after VAD

Table 3 Patient characteristics at the time of ventricular assist device explantation: comparison of patients who exhibited long-lasting cardiac stability with those showing heart failure recurrence during the first 5 years after ventricular assist device removal

Patient characteristics	All chronic HF patients weaned from VADs[a] (n = 47)	Patients evaluated for long-lasting recovery after VAD removal[a] (n = 33[b])		
		Long-lasting cardiac improvement (>5 years) (n = 19)	Post-weaning recurrence of HF (in ≤5 years) (n = 14)	P-value
LVEF (%)	47.2 ± 6.8	49.2 ± 2.6	42.4 ± 3.4	<0.01
LVEF change (% of best value)	−7.7 ± 9.6	−4.2 ± 4.4	−16.2 ± 19.5	<0.001
LVEDD (mm)	52.2 ± 7.5	49.2 ± 3.9	56.2 ± 5.9	<0.01
LVEDD change (% of best value)	9.0 ± 9.6	4.7 ± 3.5	16.9 ± 6.3	<0.001
RWT	0.39 ± 0.07	0.42 ± 0.04	0.35 ± 0.04	<0.001
S_m (cm/s) posterior wall, radial	8.5 ± 1.3	9.5 ± 2.2	7.0 ± 1.9	<0.01
S_m (cm/s) posterior wall, longitudinal	8.8 ± 1.4	9.8 ± 2.6	7.3 ± 1.5	<0.01
RWT change during off-pump trials (%)	8.6 ± 6.9	−5.5 ± 3.5	−15.8 ± 0.4	<0.001
LV sphericity Index (short-/long-axis ratio)	0.66 ± 0.07	0.64 ± 0.09	0.72 ± 0.07	0.05
Duration of LVAD support (months)	4.9 ± 2.8	3.5 ± 2.1	6.7 ± 5.2	0.02
Time (months) to disappearance of serum A-β_1-AABs[c]	2.6 ± 0.3	2.5 ± 1.7	2.6 ± 1.9	0.90[d]

[a]Values are means ± SD.
[b]Only 33 of the 47 weaned patients with CCM could be used for comparison. The six patients with stable cardiac function who died during the first 5 post-weaning years due to different causes not related to VAD removal and patients who were weaned <5 years before this evaluation were not included.
[c]Anti-β1-adrenoceptor auto-antibodies.
[d]Statistically not significant.

removal and if the LVEDD and duration of HF were considered in addition, high predictive values (up to 80%) were also obtained for cardiac stability lasting ≥7 years after weaning (*Table 4*). Pre-explantation off-pump LVEF of ≥45% also appeared predictive for long-term post-weaning stability, especially in relation to LV size, duration of HF, and stability of cardiac improvement before VAD explantation. The highest predictive values for stability lasting a minimum of 7 years after VAD removal in patients with off-pump LVEF ≥ 45% were obtained in patients with history lengths of HF of ≤5 years and stable LVEDD of ≤55 mm as well as in patients with off-pump LVEF ≥45% who showed no LVEF alterations during the first month after VAD removal (positive predictive value 78.6 and 80%, respectively). A cut-off value of ≥40% for pre-explantation off-pump LVEF showed relatively low predictability for ≥5 year cardiac stability after LVAD removal even in relation to other parameters such as LV size, LV relative wall thickness (RWT), duration of HF, or pre-weaning stability of cardiac improvement (predictive values ≤74%).

Radial or longitudinal off-pump S_m values ≥8 cm/s showed a positive predictive value of 86.7% for post-weaning cardiac stability during the first 5 post-weaning years.

Major risk factors for recurrence of heart failure after ventricular assist device explantation

Patients with ≥5 year cardiac stability after VAD removal were younger, and their duration of HF before VAD implantation was

shorter. The predictive value for HF recurrence during the first 5 post-weaning years for HF duration of >5 years reached 88.9%. Although patients with post-weaning cardiac stability showed less fibrosis in myocardial specimens collected during VAD implantation, the differences between stable and unstable patients during the first 5 post-weaning years were not statistically significant (*Table 2*).

At the time of VAD removal, patients with and without HF recurrence during the first 5 post-weaning years also showed differences in LV size, geometry, and systolic function (*Table 3*). Thus, in those with HF recurrence, the LV had larger end-diastolic diameters, was more spherical, and showed lower RWT and EF. There were also differences between patients with long-term post-weaning stability and those with HF recurrence in the time course of LVEDD and LVEF during mechanical unloading. Thus, patients with post-weaning HF recurrence required longer mechanical support for recovery and already showed partial reversibility of cardiac improvement (LVEDD increase and/or LVEF worsening) before LVAD removal. Patients with post-weaning HF recurrence also had more RWT alterations (LVEDD increase and end-diastolic wall thinning) during final off-pump trials (*Table 3*). During the first month after LVAD removal, the time course of LVEF and LVEDD was different between patients with and without cardiac stability during the first 3 post-weaning years. At the end of the first post-weaning month, all patients with HF recurrence during the first 3 post-weaning years already had >10% lower LVEF values in comparison with the values measured at the time of VAD removal. Left ventricular ejection fraction reduction during the first month of

Table 4 Echocardiographic prediction of post-weaning cardiac stability in patients with chronic cardiomyopathy as the underlying cause for ventricular assist device implantation

Selected parameters and cut-off values	Prediction of freedom from HF recurrence					
	For ≥5 years			For ≥7 years		
	Sensitivity (%)	Specificity (%)	Predictive value (%)	Sensitivity (%)	Specificity (%)	Predictive value (%)
Final[a] off-pump LVEF ≥50%	55.0	92.3	91.7	57.1	77.8	66.7
at LVEDD ≤55 mm	55.0	100	100	57.1	83.3	72.7
plus history of HF ≤5 years	50.0	100	100	57.1	88.9	80.00
Final[a] off-pump LVEF 45%	95.0	61.5	79.4	100	50.00	60.9
plus pre-weaning LVEF stability[b]	90.0	76.9	85.7	92.9	61.1	65.00
at LVEDD ≤55 mm	95.0	76.9	86.4	100	61.1	66.7
at LVEDD ≤55 mm plus pre-weaning LVEDD stability[b]	80.0	92.3	94.1	78.6	72.2	68.8
at LVEDD ≤55 mm plus pre-weaning LVEF and LVEDD stability[b]	80.0	92.3	94.1	78.6	71.4	73.3
plus history of HF ≤5 years	90.0	76.9	85.7	100	72.2	73.7
at LVEDD ≤55 mm with pre-weaning stability[b] plus history of HF ≤5 years	85.0	100	100	78.6	83.3	78.6
without alteration during the first post-weaning month[c]	90.0	84.6	90.0	92.9	61.1	65.0

[a]Last pump-stop before VAD explantation.
[b]Not more than 10% alteration in comparison with the best of all off-pump values until VAD removal.
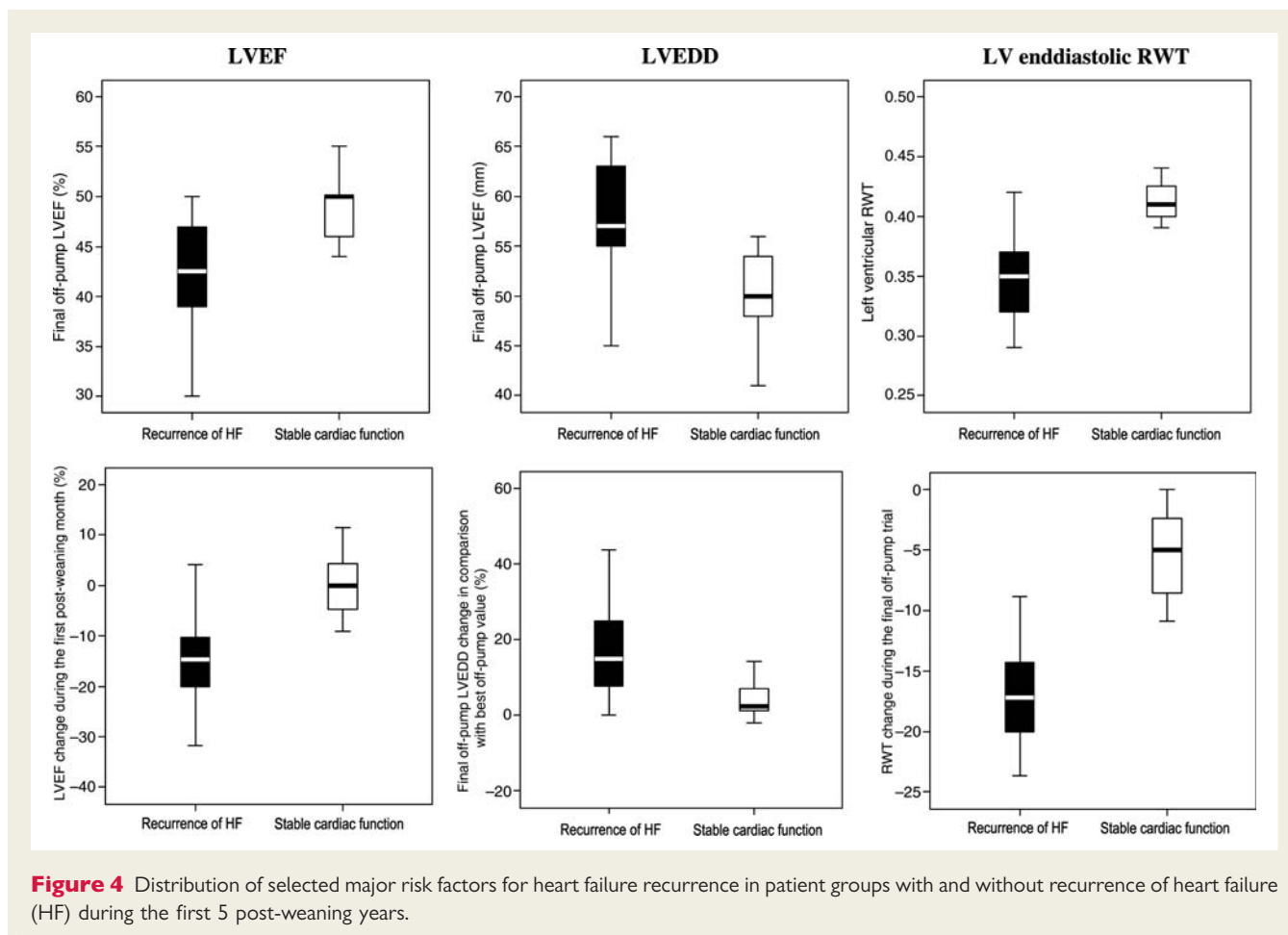[c]Not more than 10% alteration in comparison with LVEF at VAD removal.

>10% of pre-weaning values showed a predictive value of 84.6 and 91.7% for HF recurrence during the first 3 and 5 years, respectively.

Our data revealed several risk factors for HF recurrence (*Table 4*; *Figure 4*). At certain cut-off values which provide the best-balanced sensitivity and specificity, the presence of these risk factors appeared associated with high probabilities for HF recurrence. Pre-explantation off-pump LVEF <45%, LVEDD >55 mm, and LV end-diastolic RWT <0.37, as well as end-diastolic RWT decrease of >10% during the final off-pump trials revealed high predictive values for HF recurrence (*Table 5*). Also, LVEF and/or LVEDD alterations of >10% of the best off-pump value (i.e. off-pump LVEF reduction and/or LVEDD increase after their improvement has reached the optimal values, at the time of VAD removal already showing alterations of >10% in comparison with their best values), as well as history lengths of HF >5 years appeared to be risk factors for weaning. In our patient cohort, LV sphericity indexes of >0.67 or prolonged VAD support time of ≥6 months also revealed relevant positive predictive value for HF recurrence during the first 5 post-weaning years of 84.6 and 72.7%, respectively. Left ventricular ejection fraction of <40% showed a 100% predictive value for HF recurrence already during the first 3 post-weaning years. Univariate logistic regression analysis (*Table 6*) confirmed the relevance of several risk factors for HF recurrence. Thus, with each unit of LVEF reduction, the risk for HF recurrence became 1.49 times higher, and with each year of longer history of heart disease before VAD implantation, the risk for post-weaning HF recurrence appeared to be 1.62 times

higher. Also with each unit of early post-weaning alteration of LVEF during the first month after VAD removal, the risk for HF recurrence was 1.31 times higher. Cox regression analysis also confirmed the importance of these risk factors yielding for the duration of HF before VAD implantation, the final off-pump LVEF and LVEDD measured before VAD removal, and the pre-VAD-explantation instability of LVEF and LVEDD (alterations of >10% in comparison with the best off-pump values) *P*-values of ≤0.001.

Discussion

To date, published studies have reported only small numbers of patients with chronic HF who underwent VAD removal after different degrees of cardiac improvement.[2,5,13,19] Beside the low rate of relevant improvement, which might in principle allow patients to be weaned from VADs, the limited long-term outcome data after weaning and the lack of data on predictability of weaning results are major contributors to the low number of VAD explantations performed in patients with chronic HF. Our data confirm previous observations that unloading-induced cardiac improvement occurs more frequently in patients with non-ischaemic CCM and only occasionally in those with ischaemic CCM.[2,13] The proportion of our patients with non-ischaemic CCM who were weaned from VADs reached 18%, whereas that of patients with ischaemic CCM who were weaned from VADs was <1%. The impact of the VAD type, i.e. pulsatile or continuous flow pumps, on the rate of unloading-induced myocardial recovery

Figure 4 Distribution of selected major risk factors for heart failure recurrence in patient groups with and without recurrence of heart failure (HF) during the first 5 post-weaning years.

is unclear. In our patient cohort with non-ischaemic CCM, we weaned 24.4% of those who had pulsatile LVADs and only 9.2% of those who had continuous flow LVADs. This relatively low incidence of relevant myocardial recovery in patients with non-pulsatile LVADs is similar to that reported by other groups who investigated only patients with rotary pumps.[13] In our patients, the great differences in recovery rates are in part induced by the more restrictive weaning criteria which were introduced after the current use of non-pulsatile devices. However, even without the nine patients with insufficient recovery (LVEF <45% and/or LVEDD >55 mm) who were weaned from pulsatile LVADs, the prevalence of non-ischaemic CCM patients with unloading-induced recovery remained relatively high (17.5%). Despite these differences in recovery rates, the post-weaning cardiac stability appeared not related to the type of VAD which promoted the ventricular recovery.

Post-weaning 5 year freedom from HF recurrence in our CCM patients reached 66%, although only four (8.7%) of these patients had pre-explantation off-pump LVEF of >50%. Of the three patients with post-weaning cardiac stability of >14 years, two had pre-explantation LVEF of only 45 and 46%, respectively. Only few patients died due to HF recurrence or VAD explantation-related complications. With the option of HTx, 24 of 33 (72.7%) patients who were weaned from VADs before 2004 were alive at the end of the fifth post-weaning year (79.2%

of them with their native hearts). This survival rate is better than that expected after HTx.[24] All these data support the supposition that complete cardiac recovery is not indispensable for VAD explantation and that weaning is feasible without normalization of cardiac function.[2,9,11,16]

Heart failure recurrence appeared to be the most frequent complication after VAD removal and therefore, further improvement of post-weaning patients' outcome will depend mainly on better prediction of post-weaning cardiac stability. To improve future weaning decisions in patients with CCM as the underlying cause of VAD insertion, the present study also focused on the potential prediction of post-weaning cardiac stability. We identified several risk factors for post-weaning HF recurrence and found that certain cut-off values for some pre-explantation off-pump parameters related to LV size, geometry, and function, as well as the duration of HF before VAD implantation allow the distinction between patients with and without the potential to maintain cardiac stability for more than 5 or even more than 7 years after weaning. Altered LV geometry appeared to be a potential risk factor for HF recurrence even in patients with pre-weaning LVEF ≥45%. Also, LV end-diastolic RWT decrease of >10% during pre-explantation off-pump trials appeared to be a risk factor for HF recurrence. This is not surprising because RWT reduction is associated with wall stress increase.[25] According to our data, duration of HF of >5 years and to a lesser extent also the duration of

Table 5 Risk factors for heart failure recurrence after ventricular assist device removal in patients with chronic cardiomyopathy who showed myocardial improvement during ventricular unloading

| Major risk factors | HF recurrence after weaning | | | | | | | | |
| | During first 3 years | | | During first 5 years | | | During first 7 years | | |
	Events with risk factors	Number of events with risk factors	Predictive value (%)	Events with risk factors	Number of events with risk factors	Predictive value (%)	Events with risk factors	Number of events with risk factors	Predictive value (%)
Off-pump LVEF <45%	8	1	88.9	8	1	88.9	9	0	100
Off-pump LVEF <45% plus history of HF >5 years	7	0	100	7	0	100	7	0	100
Off-pump LVEF <50 and >10% alteration to the best off-pump value	7	1	88.0	8	0	100	8	0	100
Off-pump LVEF ≤50% at LVEDD >55 mm plus history of HF >5 years	8	0	100	8	0	100	8	0	100
Off-pump LVEF ≤50% at LVEDD >55 mm	9	1	90.0	9	1	90.00	10	0	100
Off-pump LVEF ≤50% plus RWT ≤0.37	10	2	83.3	11	1	91.7	12	0	100
Off-pump LVEF ≤50% with RWT decrease with >10% during off-pump trials	10	2	83.3	11	1	91.7	11	1	91.7
Early post-weaning LVEF alteration with >10%	11	2	84.6	11	2	91.7	11	1	91.7

Table 6 Relevance of main risk factors for heart failure recurrence

Selected risk factors for HF recurrence	Odds ratio[a]	95% CI	P-value
Final off-pump LVEF	1.49	1.12–1.98	0.007
Pre-weaning LVEF stability[b]	1.18	1.04–1.35	0.014
Final off-pump LVEDD	1.26	1.06–1.50	0.010
Pre-weaning LVEDD stability[b]	1.19	1.05–1.34	0.006
Duration of HF before VAD support	1.62	1.09–2.41	0.016

[a]Risk for HF with alteration by one unit.
[b]Not more than 10% alteration in comparison with the best of all off-pump values until VAD removal.

mechanical support of >6 months until maximum cardiac improvement are potential risk factors for HF recurrence, but these parameters appeared not to be a contraindication for VAD removal if pre-weaning LVEF and LVEDD are $\geq45\%$ and ≤55 mm, respectively. Also the early instability of unloading-induced cardiac improvement appeared to be a relevant risk factor for HF recurrence after VAD removal. Thus, if after maximum improvement further unloading is followed by LVEF alteration and/or LVEDD increase of $>10\%$ of best value, the risk of HF recurrence is high.

Pre-explantation off-pump LVEF $<40\%$, regardless of the presence or absence of any other additional risk factor, appeared to be 100% predictive for early recurrence of HF. The same 100% predictive value for early HF recurrence was found for off-pump LVEF $<45\%$ in patients with a history of HF >5 years and also for off-pump LVEF $\leq50\%$ with LVEDD >55 mm plus a history of HF >5 years. The importance of LVEF and LVEDD for the post-weaning outcome was confirmed by the fact that in our patients who underwent VAD removal after March 2002, when the new weaning protocol meant that only patients with off-pump LVEF $\geq45\%$ and LVEDD ≤55 mm were selected for VAD explantation, there was no HF recurrence during the first 3 years after VAD removal and only one patient showed HF recurrence before the end of the fifth post-weaning year. However, to date, only 50% of the patients weaned after 2002 reached post-weaning times of ≥3 years and therefore at present there is no certainty that our weaning criteria used after 2002 can protect all patients from early recurrence of HF.

Prediction of post-weaning long-term cardiac stability also became possible. The highest predictive values for >5 year cardiac stability were found for pre-explantation off-pump LVEF $\geq50\%$ either with LVEDD ≤55 mm or with a history of HF ≤5 years and also for LVEF $\geq45\%$ accompanied by LVEDD ≤55 mm with pre-weaning stability plus a history of HF ≤5 years (*Table 4*). The highest predictability for >7 year cardiac stability was found for pre-explantation off-pump LVEF $\geq50\%$ with LVEDD ≤55 mm. However, cardiac stability beyond the seventh post-weaning year appeared less predictable at the time of VAD removal.

All patients without HF recurrence after weaning showed systolic wall motion peak velocities (S_m) of >8 cm/s at the basal posterior wall. S_m values of ≥8 cm/s showed 86.7% predictive value for cardiac stability during the first 5 post-weaning years. The relatively high predictive value of S_m for cardiac stability after weaning is not surprising. Because the final part of ejection occurs by inertial effects after myocyte contraction is finished, S_m, 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 S_m than by EF measurements.[26,27] Nevertheless, our data available at present are insufficient for reliable conclusions and the predictive value of tissue Doppler parameters remains to be finally established by future studies.

The time course of LVEDD and LVEF early after weaning showed important prognostic value. Therefore, more frequent follow-up examinations during the first weeks after weaning are paramount.

Before VAD implantation, we found no parameters which might be able to predict the reversibility of myocardial damage and the improvement of heart function during mechanical unloading. Unloading-induced normalization of LV diameters and improvement of LVEF up to 50% were uncommon in patients with a history of HF of >5 years and/or large amount of interstitial fibrosis ($>22\%$) at the time of VAD implantation. Nevertheless, according to our observations, even in such patients relevant and stable cardiac improvement is not impossible. The use of new immuno-histochemistry techniques for the analysis of collagen content and evaluation of different collagen components, gene expression analyses, distribution of myocyte adrenoreceptors, and more sensitive methods for the evaluation of LV function like strain and strain rate imaging might help predict the reversibility of myocardial alterations during mechanical unloading.[2,26,28]

Limitations

Data were obtained from a single-centre retrospective study of prospectively gathered information. The still relatively small cohort and the lack of randomization also limited our study. However, these limitations were unavoidable because weaning is not possible in patients without relevant myocardial improvement. Also, the small number of patients with recurrence of HF after VAD removal restricted the possibilities for additional statistical evaluation like reliable multivariate analysis.

Conclusions

Weaning from VADs is a clinical option with potentially successful results for >15 years in patients with CCM even with incomplete cardiac regeneration during unloading. Off pump echocardiographic data are reliable for the assessment of cardiac improvement and for weaning decisions. Pre-explantation LVEF, LV systolic wall motion peak velocity (S_m), end-diastolic LV diameter and RWT, pre-weaning stability of unloading-induced cardiac improvement, and duration of HF before VAD implantation allow the distinction between patients with and without the potential to maintain cardiac stability for >5 years and even >7 years after weaning.

The early post-weaning time course of LVEF is helpful in prognostic assessment.

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