DISSERTATION

Predictors of feasibility of ventricular assist device explantation with stable myocardial recovery in chronic non-ischemic cardiomyopathy: a meta-analysis

Prädiktoren für die Durchführbarkeit der Explantation von ventrikulären Unterstützungssystemen mit stabiler Myokarderholung bei chronischer nicht- ischämischer Kardiomyopathie: eine Metaanalyse

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Mariano Francisco del Maria Delmo Javier

Erstbetreuung: PD Dr. Eva Maria Javier Delmo

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Foreword

An abstract of this monography was accepted for presentation during the 36th Annual Meeting of the European Association for Cardiothoracic Surgery in Milan, Italy on 8 October, 2022, and a similar modified abstract was accepted for presentation at the 43rd Annual Meeting & Scientific Sessions of the International Society of Heart and Lung Transplantation (ISHLT), which was held from 19-22 April, 2023 at the Colorado Convention Center in Denver, CO USA. The findings of this meta-analysis were presented in the form of an invited lecture at the 31st Annual Meeting of the Asian Society for Cardiovascular and Thoracic Surgery, which took place from 31 May to 3 June, 2023 in Busan, Korea.

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List of Abbreviations

AV	aortic valve
ACE-I	angiotensin converting enzyme inhibitors
ARB	angiotensin receptor blocker
BVAD	biventricular assist device
CI	cardiac index
DCMP	dilative cardiomyopathy
EF	ejection fraction
HF	heart failure
HR	hazard ratio
IGF-1	insulin-like growth factor I
INR	international normalized ratio
IQR	interquartile range
IVS	interventricular septum
IVSd	interventricular septum diastolic diameter
LV	left ventricle
LVAD	left ventricular assist device
LVEDD	left ventricle end-diastolic dimension
LVEF	left ventricle ejection fraction
MAP	mean arterial pressure
MMP	matrix metalloproteinases
MV	mitral valve
OHT	orthotopic heart transplantation
PCWP	pulmonary capillary wedge pressure
PRF	predictive risk factors
PW	posterior wall
PWd	posterior wall diameter
PWT	posterior wall thickness
RA	right atrium
RHC	right heart catheterization
RWT	relative wall thickness
RV	right ventricle
RVEDD	right ventricle end-diastolic diameter
SE	standard error
S/L_{ED}	short/long axis ratio at end-diastole
S/L_{LV}	left ventricle short/long-axis ratio
S/L_{RV}	right ventricle short/long-axis ratio

SV	stroke volume
TAPSE	tricuspid annulus peak systolic excursion
TIMP	tissue inhibitors of metalloproteinases
TTE	transthoracic echocardiography
TR	tricuspid regurgitation
TV	tricuspid valve
VAD	ventricular assist device

Abstract

Background

Myocardial recovery after ventricular assist device explantation is a field yet to be explored, despite enormous potential to shape therapeutic trajectories in heart failure management. This meta-analysis evaluates the use of clinical and echocardiographic parameters including Clenbuterol administration as potential predictors of sustained myocardial recovery. The goal is to aid in determining ventricular assist device explantation feasibility without necessitating heart transplantation.

Methods

Medline (PubMed) studies concerning patients with non-ischemic dilative cardiomyopathy weaned from ventricular assist devices were searched. Controlled trials, and prospective, retrospective and cross-sectional studies, primarily describing outcomes of ventricular assist device implantation were included. Literature describing individual patients with non-ischemic dilative cardiomyopathy supported with a ventricular assist device and eventually weaned, with sufficient echocardiographic data and at least one-year follow-up were included. The end points assessed using stepwise Cox regression were myocardial recovery, heart failure recurrence and death from any cause. A multistate analysis estimated time-related patient status fractions after ventricular assist device weaning.

Results

Ninety-eight (98) patients in 11 studies were included, with data on age, gender, pre-explantation left ventricular end-diastolic dimension/ejection fraction, exercise/dobutamine stress tests and off-pump trials available in 83 patients (Group 1) as well as heart failure duration, pre-explant left ventricular end-diastolic dimension stability, geometry (i.e., sphericity index, relative wall thickness), ejection fraction and reduced off-pump arterial diastolic pressure <50 mmHg additionally available in 51 patients (Group 2). Age at implantation (hazard ratio 2.986, p=0.002), heart failure duration (hazard ratio 1.438, p=0.001) and pre-explant instability of left ventricular geometry (hazard ratio 1.541, p=0.000) were identified as significant **heart failure recurrence predictors** in Group 2, and pre-explantation left ventricular end-diastolic dimension (hazard ratio 1.126, p=0.031) and ejection fraction (hazard ratio 0.080, p=0.007) as **stability of recovery predictors** in Group 1. **Overall freedom from heart failure recurrence** was 82%, 78%, 58% and 42% at 1, 5, 10 and 15

years, and **survival** was 100%, 80% 78% and 78% at 30-days, and 5, 10 and 15 years after weaning, respectively.

Conclusions

From the gathered data, we identified higher age at implantation, non-spheric left ventricular morphology (sphericity index stability), a sufficiently high end-diastolic pressure, high left ventricular ejection fractions and low end-diastolic dimensions as significant predictors of sustained myocardial recovery or survival after weaning. The results of this study clearly demonstrate existing potential in using the aforementioned factors as management criteria in determining the feasibility of ventricular assist device explantation with the aim of sustained myocardial recovery.

Zusammenfassung

Aufgrund des noch geringen Forschungsstandes evaluiert diese Metaanalyse klinische und echokardiographische Präexplantationsparameter sowie die Verabreichung von Clenbuterol als prädiktive Faktoren für Myokarderholung nach Explantation eines ventrikulären Unterstützungssystems. Perspektivisch soll somit die Durchführbarkeit eines elektiven Weanings ohne Herztransplantation besser abgeschätzt werden können.

Methoden

Studien der PubMed Datenbank, kontrollierte, prospektive, retrospektive und Querschnittsstudien, als auch case studies und series mit herzinsuffizienten Patienten mit nicht-ischämischer Kardiomyopathie, die ein ventrikuläres Unterstützungssystem erhalten und im Verlauf explantiert bekommen haben, wurden inkludiert. Studien wurden anhand ausreichender echokardiographischer Daten und einem Follow-up von mindestens einem Jahr selektiert. Mittels schrittweiser Cox-Regression wurden die myokardiale Erholung, das Herzinsuffizienzrezidiv und der Tod aus beliebiger Ursache als Endpunkte untersucht und in einer Multi-state Analyse ihr zeitbezogenener Kontext geschätzt.

Ergebnisse

Elf (11) Studien mit 98 Patienten wurden inkludiert. Alter, Geschlecht, linksventrikuläre enddiastolische Diameter und Auswurfsfraktion vor Explantation, Off-Pump-Versuche und Informationen über In- und Exklusion von Belastungsuntersuchungen lagen bei 83 Patienten vor (Gruppe 1). Herzinsuffizienzdauer, Stabilität der maximalen Verbesserung der linksventrikulären enddiastolischen Dimensionen, Geometrie (Sphärizitätsindex, relative Wanddicke) und Auswurfsfraktionen, sowie reduzierte off-pump arterielle diastolische Druckwerte < 50 mmHg waren bei 51 Patienten zusätzlich vorhanden (Gruppe 2). Alter (Hazard-Ratio 2,986, p=0,002), Herzinsuffizienzdauer (Hazard-Ratio 1,438, p=0,001) und eine Instabilität der linksventrikulären Geometrie (Hazard Ratio 1,541, p=0,000), wurden als signifikante prädiktive Faktoren für ein Herzinsuffizienzrezidiv in Gruppe 2 identifiziert. Die linksventrikuläre enddiastolische Dimension (Hazard Ratio 1,126, p=0,031) und Auswurfsfraktion (Hazard Ratio 0,080, p=0,007) waren prädiktive Faktoren für die Stabilität der myokardialen Erholung in Gruppe 1. Freiheit von Herzinsuffizienzrezidiven waren 82%, 78%, 58% und 42% nach 1, 5, 10 und 15 Jahren und Überleben war 100%, 80% 78% and 78% nach 1 Monat, 5, 10 und 15 Jahren.

Schlussfolgerung

Ein höheres Alter bei VAD-Implantation, eine nicht sphärische linksventrikuläre Morphologie (Sphärizitätsindex-Stabilität), hohe linksventrikuläre Auswurffraktionen, niedrige enddiastolische Diameter und ein ausreichender diastolischer Druck wurden als signifikante Prädiktoren für eine erfolgreiche Entwöhnung und eine nachhaltige Erholung des Myokards identifiziert. Die Ergebnisse dieser Studie haben deutlich gezeigt, dass bei gegebenen Voraussetzungen die Explantation eines ventrikulären Unterstützungssystems mit einer nachhaltigen myokardialen Erholung möglich ist.

Introduction

Heart failure (HF) arising from non-ischemic dilative cardiomyopathy (DCMP) is a clinical condition characterized by progressive cardiac disability to uphold and maintain adequate perfusion. Known to arise from cellular adaptations[1,2] that in turn drive functional changes[2] such as ventricular enlargement and a decline in contractility, this decompensative remodeling is widely considered irreversible once begun. Once set in motion, the cellular adaptations include myocyte hypertrophy[3], slippage[4], lengthening[3] and interstitial growth.[2,3] Although recognized to be preceded by an event causing myocardial injury, the molecular initiating factors of this remodeling process remain uncertain.

Treatment strategies applied in aiding the reverse-remodeling process have undergone historical evolution. Ranging from extended total bed rest[5] accompanied by conventional forms of therapy such as a balanced diet, and avoidance of alcohol, pregnancy and infection, to multi-pharmacological treatments, these strategies are aimed to promote cardiac unloading, thereby permitting recovery and normalization of cardiac geometry.[6,7]

The rise in ventricular assist device (VAD) implantations[8] as a bridge to transplantation and observations of their outcomes are beginning to destabilize the idea of the irreversibility of remodeling. Their application has demonstrated the possibility of structural and functional recovery as a notable trajectory[9] in HF management, which, in turn, may be propagated by the underlying hypothesis that ventricular unloading promotes the restitution of the heart's viable structural morphology.[10] Despite small groups of patients who take a course towards functional cardiac improvement under mechanical circulatory support that allows for VAD removal without necessitating transplantation, the demonstrability of such occurrences not only raises the question of whether VADs can be used as a target therapy but also lights the stage for the idea of myocardial recovery. The medical and scientific community has begun to elaborate histopathological changes associated with the remodeling process and its reversal,[11] and discussions remain ongoing as to the search for clinical predictors of sustained recovery after VAD explantation.[9,10,12,13] However, research in this field must be continued, as a positive result may entail not only reduced morbidity and mortality during the wait for a suitable heart, but also a reduction in transplantation-related complications.

It is theorized that younger age, normalization of left ventricular (LV) morphology and pre-explant stability of hemodynamic and echocardiographic parameters may reflect effective reverse remodeling and lead to sustained cardiac recovery after VAD explantation. On the other hand, it surmises that pre-explant left ventricular ejection fractions (LVEF) of below 45%, longer durations of HF before VAD support and instability of echocardiographic parameters may forebode a recurrence of HF after VAD explantation.

Objectives

This meta-analysis focuses on outcomes of patients with HF secondary to chronic non-ischemic dilative cardiomyopathy supported with and weaned off VAD. It aims to evaluate potential clinical parameters positively affecting reverse remodeling, such as age at VAD implantation, gender, HF time span preceding VAD-implantation, duration of support and type of VAD, and pharmacologic interventions during support. Furthermore, it intends to evaluate the reliability of using echocardiographic parameters such as left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), sphericity index, relative wall tension (RWT) and cardiac functional stability during off-pump trials as predictors of sustained myocardial recovery. These potential predictors are relevant in deciding the feasibility of VAD explantation without necessitating orthotopic heart transplantation (OHT).

Lastly, the study aims to assess the pharmacologic administration of Clenbuterol, a ß-2 adrenergic agonist, regarding the potential advantages of its application in promoting the stability of myocardial recovery in patients post-weaning off VAD. It is endeavored that the findings may contribute to the search for better weaning protocols and a greater clinical confidence in determining projected outcomes in patients with dilative non-ischemic cardiomyopathy under VAD support.

Materials and Methods

This study was approved on 16. March 2021 by the Doctoral Board of Charité – Universitätsmedizin Berlin. Consents of patients were waived.

Data sources

The electronic database of Medline (PubMed) from its inception through 1 July 2021 was systematically searched. The following Medical Subject Headings and keywords were used: heart failure; cardiomyopathy; non-ischemic cardiomyopathy; mechanical circulatory support; ventricular assist device; LVAD; and VAD explantation. Citations were limited to those published in English. A complete search of the health-related grey literature through manual searches of pertinent conference proceedings from related conferences and abstracts over the previous 25 years was performed. The included references were manually reviewed for other potentially relevant records. Information collected from each study included author, year of publication, study design, duration of follow−up, sample size, type of LVAD, pertinent patient characteristics and data on the relevant outcomes.

Search strategy

The search strategy included **retrieval** of the majority of the studies and assessment for appropriateness to the topic and inclusion. Specific **keywords** (see above) to broaden results were specified and searched for in journal titles, author names, article titles, and article abstracts, which were also tagged to search all text. **Index/subject terms** were used to appropriately focus on topics relevant to the search. A typical database search filter to narrow results for retrieval of articles that are most relevant to the research questions was employed.

Data Collection

A comprehensive review of all available existing literature focusing on (1) ventricular assist device (VAD) implantation in heart failure, (2) data on ventricular assist device explantation in heart failure secondary to a chronic non-ischemic dilated cardiomyopathy, and (3) weaning criteria and/or protocol in patients with ventricular assist device support and myocardial recovery after ventricular assist device support indexed in PubMed with key words, namely **ventricular assist device implantation** (n= 1162), **ventricular assist device explantation** (n= 36), **myocardial recovery** (n=917), **chronic non-ischemic dilated cardiomyopathy**

(n=95), **weaning criteria for VAD explantation** (n=4), **survival in VAD** (n=2217), **death in VAD** (n=2092), **echocardiographic data in VAD support** (n=15) was performed.

Study review

Four clinical study researchers independently reviewed all potentially relevant articles in a parallel manner by using pre-defined inclusion criteria. Studies describing VAD implantation and explantation on patients with HF secondary to non-ischemic cardiomyopathy were identified. Controlled trials, before and after, prospective, retrospective and cross-sectional studies, primarily describing outcomes of left, right and biventricular assist devices were included. Pediatric studies were also included, as the indications and use of VADs in adult and pediatric populations are distinct. Studies were included if they met the following criteria, whereby they: (i) enrolled human subjects in an original investigation, (ii) comprised either children (0-<18 years old), adult patients (>18 years of age) or both with advanced HF receiving mechanical circulatory support with an LVAD, and (iii) reported data on changes in the desired outcomes after LVAD implantation. In studies that reported outcomes on patients with VAD implantation, no differentiation was made between those with LVAD or biventricular assist device (BVAD). Individual case reports, review articles, basic science papers, animal studies, case-control studies (as our outcomes of interest are clinical outcomes) or studies primarily describing outcomes of pneumatic total artificial hearts, editorials and non-English publications were excluded. Other exclusion criteria were (1) duplicate reports failing to report additional or extended clinical outcomes and (2) ongoing studies or irretrievable data. When a study was reported as both a preliminary and final analysis, preliminary analyses were excluded. For studies in which there was substantial secondary data analysis reported separately for new outcomes, the results were combined for reporting purposes to minimize duplication.

Study selection

After a thorough deliberation, 11 articles were deemed appropriate for this meta-analysis, according to both the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14] and the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[15] PubMed, Web of Science, CINAHL, and Cochrane Library databases were separately searched for studies assessing the effect. The articles published by Hetzer et al.[13] (n=1), Dandel et al.[16,17,18,19,20] (n=5), Müller[21] (n=1), Mancini et

al.[22] (n=1), Frazier et al.[23] (n=1) and Birks et al.[24,25] (n=2) met the search criteria. The number of patients extracted from each publication is detailed in Table 1a.

Table 1a. Overview of selected published articles, year of publication and number of patients from each study considered in the meta-analysis

Number	Selected published articles	Year of publication	Number of patients
1	Hetzer R, Müller J, Weng Y, Wallukat G, et.al. Cardiac recovery in dilated cardiomyopathy by unloading with a left ventricular assist device. Ann Thorac Surg. 1999 Aug;68(2):742-9. [13]	1999	19
2	Dandel M, Weng Y, Siniawski H, et.al. Long term results in patients with idiopathic dilated cardiomyopathy after weaning from left ventricular assist devices. Circulation. 2005 Aug 30;112(9 Suppl):I37-45. [16]	2005	42*
3	Dandel M, Weng Y, Siniawski H, Potapov E, et.al. Long-term results in patients with idiopathic dilated cardiomyopathy after weaning from left ventricular assist devices. Circulation. 2005 Aug 30;112(9 Suppl):I37-45. [17]	2005	
4	Dandel M, Potapov E, Krabatsch T, et.al. Load dependency of right ventricular performance is a major factor to be considered in decision making before ventricular assist device implantation. Circulation. 2013 Sep 10;128(11 Suppl 1):S14-23. [18]	2013	
5	.Dandel M,Weng Y, Siniawski H, et al. Heart failure reversal by ventricular unloading in patients with chronic cardiomyopathy: criteria for weaning from ventricular assist devices. Eur Heart J. 2011 May;32(9):1148-60. [19]	2011	
6	Dandel M, Weng Y, Siniawski H, et.al. Prediction of cardiac stability after weaning from left ventricular assist devices in patients with idiopathic dilated cardiomyopathy. Circulation. 2008 Sep 30;118(14 Suppl):S94-105. [20]	2008	
7	Müller J, Wallukat G, Weng YG,et.al.Weaning from mechanical cardiac support in patients with idiopathic dilated cardiomyopathy. Circulation. 1997 Jul 15;96(2):542-9. [21]	1997	17
8	Mancini DM, Beniaminovitz A, Levin H, et.al. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. Circulation. 1998 Dec 1;98(22):2383-9. [22]	1998	4
9	Frazier OH, Myers TJ. Left ventricular assist system as a bridge to myocardial recovery. Ann Thorac Surg. 1999 Aug;68(2):734-41. 23	1999	5
10	Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med. 2006 Nov 2;355(18):1873-84. [24]	2006	11**
11	Birks EJ, George RS, Hedger M, et.al. . Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: a prospective study. Circulation. 2011 Feb 1;123(4):381-90. [25]	2011	

** Number of patients included in this meta-analysis among a total of 167 patients reported in the 5 published articles of the same first author to avoid data overlap*
***Number of patients included in this meta-analaysis among a total of 31 patients reported in the 2 published articles of the same first author to avoid data overlap*

Outcomes of Interest

Freedom from heart failure recurrence and **survival** after weaning from VAD support were the outcomes of interest in this study. Data regarding patient-level outcomes of weaning, i.e., stability of myocardial recovery (freedom from heart failure recurrence) and survival (freedom from death from any cause after weaning off VAD) were abstracted. After extensive discussion, attempts to define a patient group who died from weaning-related causes were abandoned and replaced by a detailed description of death causes. Most patients died for more than one reason, making any classification of weaning-related and non-weaning related deaths too arbitrary.

Patients

The overall adult patient population comprised **98** patients who were weaned from LVAD. These patients were included in Kaplan-Meier curves showing overall freedom from the two outcomes of interest, which are HF recurrence and death from any cause on follow-up post-weaning off VAD, as well as curves stratified by gender, pump type (pulsatile, n=65 and continuous, n=33) and Clenbuterol administration (n=23).

In **83 patients (Group 1)**, complete data sets comprising age at VAD implantation, gender, pre-explantation LVEDD, pre-explantation LVEF, off-pump trials and pre-explantation exercise or dobutamine stress test were available.

In **51 patients (Group 2, subgroup of Group 1)**, six additional variables, i.e., data on duration of HF before VAD implantation, maximum change of LVEF, maximum change of LVEDD, off-pump arterial diastolic pressure of 50 mmHg, change of relative wall thickness (RWT) at off-pump trial and maximum change of sphericity index were available.

Distributions of these parameters in the entire study population and the two patient groups are detailed in Table 1b.

Selection scheme of potential risk factors (PRF) for successful VAD explantation

To understand the underlying reason why such parameters were chosen regarding their potential to predict successful weaning off VAD and the stability of myocardial recovery thereafter, the consensual VAD explantation process, including the transthoracic echocardiographic (TTE) routine examination parameters (echocardiographic assessment of

cardiac dimensions, geometry and function), the indications and criteria for weaning and the VAD explantation procedure, which was mostly performed by the Berlin group,[13,17,26] is synopsized as follows:

Strategy of VAD explantation and VAD weaning scheme

a. Echocardiographic assessment of cardiac dimensions, geometry and function

Daily transthoracic echocardiography (TTE) routinely performed in an inpatient and outpatient setting is the most important tool to monitor cardiac function and to screen for potential weaning candidates. Echocardiographic reports were reviewed to determine changes in native ventricular dimensions, geometry and function while on VAD support. Cardiac parameters considered to assess cardiac recovery included: (1) LVEDD measured in the parasternal long-axis view in the antero-posterior plane as the maximal diastolic diameter between the septal to posterior wall endocardium at or immediately below the level of the mitral valve (MV) leaflet tips, (2) interventricular septum (IVS) posterior wall thickness (PWT) measured in diastole in the same view and also at or immediately below the level of the MV leaflet tips, (3) LVED relative wall thickness (RWT) measured in the parasternal long-axis view at the base of the LV using the formula RWT=–(IVSd + PWd) / LVEDD (where IVSd is the diastolic IVS diameter and PWd the posterior wall diameter), (4) LV short/long-axis ratio (S/L_{LV}), (5) stroke volume (SV) measured by the PW-Doppler at the LV outflow tract, and (6) LVEF (using the modified Simpson's rule). Other important parameters are the right ventricular (RV) end-diastolic diameter (RVEDD), the RV short/long axis ratio (S/L_{RV}) and the tricuspid annulus peak systolic excursion (TAPSE) continuous-wave Doppler-derived maximal tricuspid regurgitation (TR) velocity.

b. Selection of weaning candidates and criteria for weaning off VAD

Appropriate selection of potential weaning candidates marks the first step in the VAD weaning process. Among the clinically stable patients with adequate renal, hepatic, pulmonary and neurologic functions and with unremarkable laboratory tests (particularly *B-type* natriuretic peptide, troponin I and T levels, levels of electrolytes, blood cell count and platelet), those with acceptable basic cardiac parameters (sinus rhythm, regression of LV dilation towards normalization of LVEDD, improvement of LV wall motion with a fractional shortening > 15%), none or ≤ grade 1 mitral and / or aortic valve (AV) regurgitation, no RV dilation and no or less than grade 2 TR during full LVAD support are considered as potential weaning candidates. Progressive increase in duration and frequency of AV openings during unchanged pump rate indicate improvement of LV contractile function.

Pump flow reduction test phases: In patients who fulfill the above-mentioned criteria and before evaluating cardiac recovery during short-term complete interruptions of the VAD support, it is useful to perform TTE-guided stepwise pump rate/flow reductions in order to verify whether complete VAD interruption trials are possible and reasonable.

Complete VAD-support interruption trials are possible only if moderate speed reduction is tolerated without the development of clinical symptoms due to hemodynamic changes. These adverse clinical reactions indicate that LVAD explantation is too risky or even impossible (at least currently). If stepwise pump rate/flow reductions provoke symptoms (dizziness, sweating, etc.) and/or significant cardiac arrhythmia, LVEDD increases beyond the normal range, and/or morphological and functional instability of the RV associated with increased RV stress, and/or increasing TR, loading trials are considered not indicated and weaning infeasible.

Provided that there is no derailment in coagulation, such as bleeding or recent thromboembolic event, and the international normalized ratio (INR) is within target parameters, 30–50 IU/kg of unfractionated heparin is administered prior to VAD stops. Echocardiographic assessment of recovery is mostly based on data obtained at rest during repeated (2-4) short-term interruptions (≈ 5-10 min) of LVAD support (off-pump or pump flow reduction trials, depending on the type of the VAD). Because complete stops of axial-flow pumps lead to retrograde flow into the LV followed by a reduction of the diastolic aortic pressure, which in turn, through reduction of LV afterload, can generate overestimations of LV systolic function, rotor-speed reduction (pump-flow reduction trials) to values resulting in close-to-zero flow in one cardiac cycle (3000-6000 rpm) is preferred over complete pump stop.[16, 27, 28]

c. Specific VAD interruption parameters

LVEDD change during pump stops: This describes the difference between the smallest LVEDD measured during the pre-explant LVAD support interruption trials and the LVEDD before LVAD explantation. An increase beyond 15% suggests an unstable left ventricular morphology and may indicate a higher risk of HF recurrence.

Off-pump arterial diastolic pressure < 50 mmHg: A diastolic pressure markedly below usual daily levels eases LV ejection, whereas, under normal conditions and higher arterial diastolic pressures, ejection might well be lower. Therefore, a low arterial diastolic pressure can lead to

overestimation of LV systolic function (higher LVEF) as previously mentioned by means of reducing LV afterload, which in turn may act as a risk factor regarding heart failure recurrence and/or premature weaning.

Maximal sphericity index change: Reduced left ventricular contractility is associated with a more spherical LV geometry. An increase of the LV long axis to short axis ratio during reduced VAD support may reflect inability of the native LV to uphold hemodynamic stability, possibly favouring increased HF recurrence rates.

Relative wall thickness (RWT) change at off-pump trial: Thinning occurs if the left ventricle requires more tension (more intraventricular volume) to produce the necessary pressure to overcome aortic diastolic pressure. Hence, thinning of the ventricular wall during the course of VAD support, that can be seen during pump reduction tests, may indicate less stable recovery.

*d. **Duration of VAD support reduction test***

During an off-pump or pump reduction trial, stepwise TTE assessments in the course of repeated short-term (~5 minutes) unloading interruptions are deemed safer for the patient than one or two longer-lasting (15-20 minutes) interruptions.

Right heart catheterization (RHC) is also useful as soon as there is echocardiographic evidence of LV reverse remodeling and functional improvement. Normal (or at least borderline normal) and stable RHC-derived measurements obtained during LV unloading interruption trials are the basic prerequisites for preliminary decisions in favor of a possible LVAD explantation. It is particularly important to ensure that the pulmonary capillary wedge pressure (PCWP) does not increase during the interruptions of LVAD support. A cardiac index (CI) >2.6 L/min/m^2 at rest, which does not drop significantly and remains stable during LV support interruption trials, is additionally an essential consideration. In patients with borderline normal off-pump echocardiographic data, the CI becomes more important and CI values ≥2.8 L/min/m^2 would be desirable. Other hemodynamic requirements for a possible LVAD explantation appeared to be off-pump PCWP <12 mmHg and RA pressure <10 mmHg.

For the final evaluation of LVAD explantation feasibility and the decision in favor or against explantation, a 15-20-minute complete interruption of the LVAD support in the operating theatre (without inotropic support or ventricular pre- and afterload reduction) concomitant with a continuous TTE monitoring of cardiac function and invasive hemodynamic monitoring is mandatory.

e. Weaning patients with biventricular assist device support

Weaning from long-term biventricular assist devices (BVADs) appeared limited, possibly due to more advanced myocardial damages which necessitated BVAD implantation.[19] However, when possible, BVAD explantation can provide outcomes quite comparable to those achieved after LVAD removal.[19] Assessment of myocardial recovery with BVAD support is similar to that after LVAD implantation, but often more challenging due to the necessity of isolated right and left VAD stops before concomitant stops are possible. Given the high susceptibility of the RV to sudden increases in loading conditions, assessment of recovery is started with gradual RV pump flow reduction followed by complete interruption of RV unloading at least 30 seconds prior to reduction of the LV pump, which in turn should only occur if the RV appears unaffected during unloading. During the interruption of RV support with concomitant full LVAD support, special attention is paid to the RV size, geometry and strain, as well as to the tricuspid valve. Paradox septal shift, increase in RV end-diastolic diameter (RVEDD) and S/L_{RV} new or augmented TR, increase in right atrium (RA) size and pressure (RA >10 mmHg),

as well as decrease in LVAD-index are indicative of RV strain, necessitating the interruption of the loading trial and a return to full RV support.

If the RV size, geometry and function as well as the RA size remain stable under reduced support, without new or augmented TR, LV support can be reduced concomitantly. LV support can eventually be stopped if moderate reduction of the LVAD support is well tolerated without reduction in systemic arterial blood pressure or relevant alterations in cardiac anatomy and function.[17, 26]

Weaning from BVAD appears possible if during complete interruption of ventricular support, biventricular size and geometry remained normal and stable, without any increase in mitral and/or tricuspid valve regurgitation, LVEF reached ≥ 45% and SV reached the normal range. [17, 26]

Precautions: Complete interruption of ventricular support (i.e., ±0 flow) must be carefully considered in patients with a history of stroke, recent transient ischemic attack, hemolysis or problems with anticoagulation therapy (relative contraindications), and is not indicated in patients suspected of pump thrombosis (even in the absence of LVAD dysfunction).[29]

f. Optimal timing for weaning off VAD

Optimal duration of VAD support allowing for maximum possible improvement varies widely among patients. Even in those with appropriate recovery, it appears useful to explant VADs only after ensuring that no further improvement has been recorded during the next 2-4 weeks (maximum recovery).[17] Stability of ventricular size, geometry and function, between and during ≥2 follow-up off-pump tests, as well as normal and stable hemodynamic parameters measured during the off-pump RHC trials appears useful in weaning decisions.[17,19] If a relevant LVEF reduction (>10% from maximal value) and/or LV enlargement occurs during the 2-4 weeks after maximum cardiac recovery, explantation is considered risky, even if the LVEF does not fall below 45% and the LVEDD does not increase beyond 55mm.[19]

g. VAD explantation

In patients whom VAD explantation appears appropriate (after at least 2 off-pump/near-zero flow trials before reaching this stage), another complete interruption of VAD support in the operating theatre with simultaneous transesophageal and invasive hemodynamic measurements (preferably without the use of inotropic agents or medication for adjustment of ventricular pre-

and afterload, neither before nor during the off-pump trial) is mandatory for the final decision to explant the VAD.

Explantation is performed after a pump stop of 20 minutes if the following criteria are achieved, both in patients with LVAD or BVAD support:
(a) LVEDD < 55 mm or 55-60 mm at BSA ≥1.8 m
(b) LVEF ≥45% (i.e., no more than mild LV dysfunction)
(c) normotensive without inotropic support
(d) LV end-diastolic pressure <12 mmHg
(e) resting CI of >2.8 l/min/m^2
(f) RWT ≥ 0.38 and
(g) no RV dilatation, absence or mild aortic, mitral and tricuspid valve insufficiency.

When hemodynamics and all the aforementioned parameters remain stable after maximum cardiac recovery and during the final off-pump trial, VAD explantation is carried out.

Based on this protocol,[13,15,17,19,26] the potential predictive risk factors for weaning patients off VAD were collected from the specified literature and analysed.[30]

Statistical analysis

a. Software

Data was analyzed using IBM SPSS Statistics for Windows version 27.0 software (IBM Armonk, New York) for descriptive statistics and to form Cox regression models and related graphics.

For the multistate analyses, R (version 4.0.4 (2021-02-15, The R Foundation for Statistical Computing)) and mstate: An R Package for the Analysis of Competing Risks and Multi-State Models (2011)[30] were applied.

For Kaplan-Meier curves, the R, RStudio (Version 1.4.1717, © 2009-2021 RStudio, PBC, Boston, MA 02210, USA) and the package 'survminer' version 0.4.9 were utilized. A *p*-value < 0.05 was considered statistically significant.

Remarks: A special focus was set on offering the clinician an easily applicable tool to estimate a patient's chance for successful weaning without cumbersome calculations: for regressions where at least two independent significant risk factors were found, we calculated hazard ratio nomograms as well as model-based stratified freedom from event expectation curves and showed the observed results in patients stratified by hazard ratio groups.

b. Demographics

The Kolmogorov-Smirnov/ Shapiro-Wilk tests were used to assess normal distribution of the numerical factors and describe the distribution of the non-categorical variables for the two patient groups in percentiles. For categorial factors and outcomes, frequencies and percentages are used.

c. Overall outcome

Kaplan-Meier curves show time-dependent freedom rates from the two outcomes of interest, which were HF recurrence and survival from any cause after weaning off VAD.

d. Analyses of potential predictive risk factors

Due to the presence of two groups with varying extents of information, stepwise Cox regression models for both end points in both groups were formed.

After identifying a list of significant risk factors for a terminal event, the pertinent regression equation was formulated. If this list consisted of only 2 factors, the regression equation to calculate hazard rates for a series of factor combinations was used within the limits of observed values. If 3 factors were independent significant predictors, either the two most significant ones or the most easily available pair were chosen. Based on the resultant Cox regression equation (calculated with 2 variables), the hazard ratio (HR) was predicted based on the earliest onset of the end point. Since a hazard rate does not offer a very clear perspective - neither for the physician nor for a patient, a two-step graphical illustration was drawn: first, HRs were calculated for factor combinations, wherein coloured dots represent HR groups for the factor combinations. Second, model-based freedom-from-event estimation curves were shown. To verify the estimations, the patients were grouped according to their estimated risks and the observed freedom rates from the target events were plotted in a third series of graphs.

Event-free percentages were calculated and shown as Kaplan-Meier estimates with 95% confidence interval in stripes as well as tabulations of freedom from event rates and confidence limits at certain time points.

Various Cox proportional hazard regression models were developed to offer support for different combinations of available potential predictive risk factors.

e. Multistate analysis

To illustrate the frequencies (percentages) of patients in a certain state at a given time during the follow-up period after weaning off VAD, a multistate model of the included 98 patients with HF secondary to non-ischemic cardiomyopathy supported with and weaned off VAD was calculated. R version 4.0.4 (2021-02-15, The R Foundation for Statistical Computing) and mstate: An R Package for the Analysis of Competing Risks and Multi-State Models (2011)[30] were utilized.

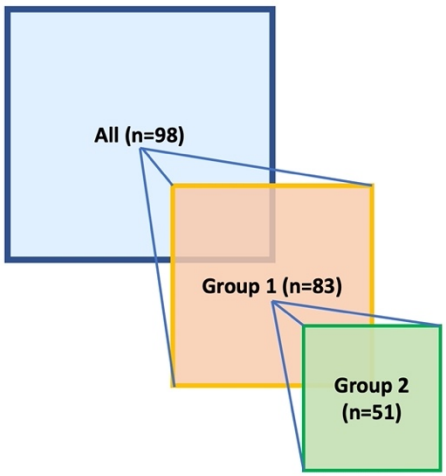
f. Pharmacologic therapy - Clenbuterol administration

Furthermore, possible advantages of administering Clenbuterol were examined by including its use as a potentially predictive risk factor. Information on Clenbuterol administration was available for all patients, of which 83 belonged to Group 1, in which 6 other factors were recorded. Consistently focusing on the two end points, a potentially significant influence of this medication with multivariate Cox regression models was evaluated. Unadjusted Kaplan-Meier curves for the 2 endpoints, stratified by Clenbuterol administration, are presented in the Results section.

g. Overview

Figure 1 illustrates an overview on patient groups, the analysed end points, the identified potential predictive risk factors and the methods of analysis applied.

Fig. 1. Overview of patient groups, end points, identified and analyzed potential predictive risk factors and the analytical methods applied. The area of the rectangles on the left side represents the total numbers of included patients and the subgroups.



Patients	Analyzed available potential predictive risk factors	Statistical analysis method used to analyze endpoints	
		Heart failure recurrence	Survival
All (n=98)[a]		Kaplan Meier	Kaplan Meier
	Age at VAD Implantation	Cox regression (Group 2)	Cox regression (Group 2)
	Gender	Kaplan Meier[b]	Kaplan Meier[b]
	Clenbuterol	Kaplan Meier[b]	
	Type of VAD (pulsatile/continuous)	Kaplan Meier[b]	Kaplan Meier[b]
Group 1 (n=83), all above factors plus pre-explantation values:			
	Left ventricular ejection fraction (LVEF)	Cox regression (Group 1)	
	Left ventricular end diastolic diameter (LVEDD)	Cox regression (Group 1)	
	Exercise/Dobutamine stress test		
	Off-pump trials		
Group 2 (n=51)			
	Duration of heart failure pre-VAD implantation	Cox regression (Group 2)	
	Maximal change (%) of LVEF during VAD pump stop		
	LVEDD increase during VAD pump stop		
	Arterial diastolic pressure <50mmHg during VAD pump stop		Cox regression* (Group 2)
	Relative wall thickness (%) during VAD pump stop		
	Maximal sphericity index change (%) during VAD pump stop	Cox regression (Group 2)	

[a]Group 1 and Group 2 patients are part of all 98 patients. [b]Unstratified Kaplan-Meier analysis, Cox = Cox regression. Clenbuterol and VAD pulsatility are placed in brackets because their use is analysed separately. In the illustrated table on the right side, the two left columns describe patient groups and examined potential predictive risk factors. The two right columns denote the analysis method and the patient group (in brackets) in which the factor listed in the left column remained statistically significant ($p<0.05$) in a stepwise Cox regression model; one factor with significance level above 0.05 is marked by an asterisk.

Results

Patients and potential predictive risk factors considered and analyzed for myocardial recovery and stability in weaning patients off VAD

A total of 11 studies involving 98 patients (Berlin = 78; others = 20) were included in the final synthesis.

Amongst the 98 patients included, 12 potential predictive risk factors (PRF) for HF recurrence and death were available, namely (1) age at VAD implantation, (2) gender, (3) off pump trial – [*a*. no flow, *b.* flow at 6000 rpm, *c.* pump further reduction, *d.* pump stop, and *e.* pump stop with exercise], (4) pre-VAD explantation dobutamine or exercise stress test, (5) pre-VAD explantation LVEF, (6) pre-VAD explantation LVEDD, (7) duration of HF before VAD implantation, (8) LVEF maximal percentile change/decrease during VAD pump stop, (9) LVEDD increase during VAD pump stop, (10) arterial diastolic pressure < 50 mmHg during VAD pump stop, (11) relative wall thickness (RWT) decrease (%) during VAD pump stop, and (12) maximal sphericity index change [S/LED change (%)] during VAD pump stop. The first six PRFs were common in 83 patients (Group 1) and all 12 PRFs were available in 51 patients (Group 2). The frequencies and distribution of these potential predictive risk factors in the two patient groups to attain the outcome of interest (HF recurrence and death) are detailed in Table 1b.

Table 1b. Frequencies of outcomes of interest and distribution of the analyzed potential clinical, echocardiographic and pharmacologic predictive risk factors in the two patient groups

	Patients		
	All (n=98)	**Group 1 (n=83)**	**Group 2 (n=51)**
Outcomes of interest			
Heart failure recurrence, n (%)	25 (25.5)	21 (25.3)	18 (35.3)
Death, n (%)	18 (18.4)	15 (18.1)	12 (23.5)
Potential predictive risk factors			
Clinical data			
Age at VAD implantation, median (interquartile range – 25 and 75 percentile), years	36 (25;49)	39 (30;53)	42 (35;56)
Gender (male), n (%)	76 (77)	71 (85.5)	46 (90.2)
Duration of heart failure before VAD implantation, median (interquartile range – 25 and 75 percentile), years	n.a.	n.a.	3 (1;5)
Echocardiographic data			
Off pump trial, n (%) *a.* no flow *b.* flow at 6000 rpm *c.* pump further reduction *d.* pump stop *e.* pump stop with exercise	 18 (21.7) 12 (14.5) 4 (4.1) 61 (62.2) 3 (3.1)	 18 (21.7) 12 (14.5) 50 (60.2) 3 (3.6)	 17 (33.3) 34 (66.7)
Pre-VAD explantation dobutamine or exercise stress test, n (%)		18 (21.7)	0
Pre-VAD explantation LVEF, median % (IQR)		50 (47;60)	48 (45;50)
Pre-VAD explantation LVEDD, median mm (IQR)		52 (48;55)	52 (48;55)
LVEF maximal percentile change/decrease during VAD pump stop – off pump, median % (IQR)			-4.2 (-9.2;0)
LVEDD increase during VAD pump stop, median mm (IQR)			4.5 (2.2;9.1)
Arterial diastolic pressure < 50 mmHg during VAD pump stop, n (%)			15 (29.4)
Relative wall thickness decrease during VAD pump stop, median mm (IQR)			-7 (-11.5; -2.4)
Maximal sphericity index [LV long axis to short axis ratio] change during VAD pump stop, median % (IQR)			3.7 (1.8; 10.3)
Pharmacologic therapy			
Clenbuterol, n (%)	23 (23.4)	21(25.2)	0

LV =left ventricle; LVEDD=left ventricular end-diastolic dimension;
LVEF = left ventricular ejection fraction; n.a.= not available; VAD = ventricular assist device.
Single values (in brackets) describe group fractions, whereas double values separated by semicolon are interquartile ranges (IQR, 25th and 75th percentile).

Non-normal distribution of each of the analyzed potential predictive risk factors is present in at least one of both applied tests as shown in Table 1c and their detailed percentile groups are shown in Table 1d, wherein numbers are listed as exactly as indicated in the source papers.

Table 1c. Distribution and numerical assessment of each of the analyzed potential predictive risk factors

Potential risk factors	*p-value*	
	Kolmogorov-Smirnov	Shapiro-Wilk
Age at VAD implantation	0.200	0.029
Pre-VAD explantation LVEF	<0.001	<0.001
Pre-VAD explantation LVEDD	0.038	0.180
Duration of heart failure pre-VAD implantation	<0.001	<0.001
LVEF maximal percentile change/decrease during VAD pump stop – off pump	<0.001	<0.001
LVEDD increase during VAD pump stop	<0.001	<0.001
Relative wall thickness decrease (%) during VAD pump stop	0.013	0.001

LV =left ventricle; LVEDD=left ventricular end-diastolic dimension;
LVEF = left ventricular ejection fraction; VAD = ventricular assist device

Table 1d. Detailed percentile distribution of the analyzed potential predictive risk factors

Patient group	Potential predictive risk factors	Percentile						
		5	10	25	50	75	90	95
6 factors available in Group 1 (n=83)	Age at VAD implantation	15.2	18.8	30	39	53	59	61.9
	Pre-VAD explantation LVEF	39.2	42.2	47	50	60	69.6	74.8
	Pre-VAD explantation LVEDD	43.2	45	48	52	55	60	63
12 factors available in Group 2 (n=51)	Age at VAD implantation	17.6	22.6	35	42	56	61.4	62.8
	Pre-VAD explantation LVEF	38	40	45	48	50	52	58.8
	Pre-VAD explantation LVEDD	41	43.4	48	52	55	60	64
	Duration of heart failure pre-VAD implantation	0.1	0.13	0.5	2	4	7.5	11
	LVEF maximal percentage change during VAD pump stop – off pump	-22	-18	-9.2	-4	0	0	0
	LVEDD increase during VAD pump stop	0	0	2	4.4	9.1	20	26
	Relative wall thickness change (%) during VAD pump stop	-22	-22	-11	-7	-2.4	-2.1	0
	Maximal sphericity index (LV long axis to short axis ratio) change (%) during VAD pump stop	0	1.3	1.8	3.7	10	21	22

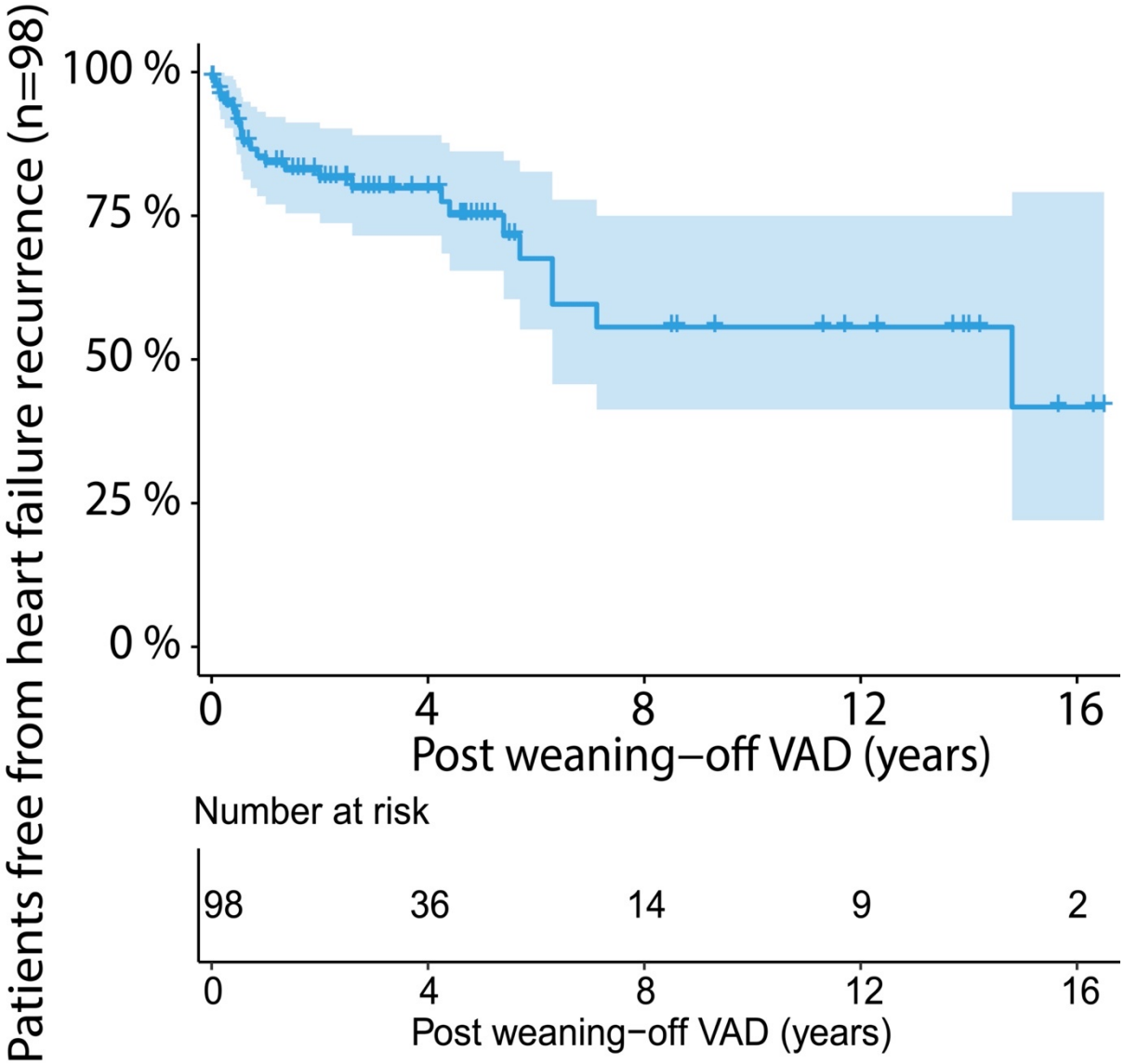
LV =left ventricle; LVEDD=left ventricular end-diastolic dimension;
LVEF = left ventricular ejection fraction; VAD = ventricular assist device

Outcome of VAD explantation and weaning

a. Overall heart failure recurrence

To assess the stability of myocardial recovery, the time to HF recurrence was evaluated. Based on Kaplan-Meier estimates at 95% confidence interval, unadjusted overall freedom from recurrence of HF after weaning off VAD in the entire patient population was 84%, 79.8%, 75.1%, 56% and 42% at 1, 3, 5, 10 and 15 years of follow-up, respectively (Fig. 2). Details are enumerated in Table 2.

Fig. 2. Observed overall freedom from heart failure recurrence. Percentages and standard errors are detailed in Table 2.



VAD = ventricular assist device

Table 2. Observed overall freedom from heart failure recurrence stratified by follow-up years, as illustrated in Fig. 2.

Follow-up years	Observed freedom from heart failure recurrence	Standard error
1	0.842	0.039
3	0.798	0.045
5	0.751	0.053
10	0.556	0.085
15	0.417	0.138

Potential predictive risk factors for HF recurrence (Group 1, n=83 patients)

An overview of the Cox regression models that were calculated in relation to HF recurrence is shown in Table 3a. Analysis of **6 potential PRFs** in this group showed that **LVEDD** and **passing a stress test with a VAD pump speed of 6000 rpm** were clinically significant PRFs for HF recurrence in the forward selection model.

However, since VAD pump speed is more of a technical option than a disease state indicator, a prediction model with LVEDD and LVEF as a commonly available combination of independently significant risk factors (significant if considered either alone or together with LVEDD in a Cox regression model) was pursued.

Table 3a. Detailed description of Cox regression modelling to predict heart failure recurrence, as illustrated in Fig. 3.

End point: Heart failure recurrence, 6 factors available in Group 1 (n=83)					
Method: Enter → coefficients did not converge					
	Variables in the equation	**B**	**SE**	**Sig.**	**Exp(B)**
	Age at VAD implantation	0.035	0.022	0.107	1.035
	Gender (M_1/W_0)	11.847	455.321	0.979	139595.570
	Off-Pump Trial (reference)			0.013	
	Off-Pump Trial (variant 1)	5.772	1.790	0.001	321.052
	Off-Pump Trial (variant 2)	1.197	1.085	0.270	3.311
	Off-Pump Trial (variant 3)	-11.17	911.133	0.990	0
	Pre-VAD explantation exercise or Dobutamine stress test	-1.148	1.201	0.339	0.317
	Pre-VAD explantation LVEF	-0.128	0.047	0.007	0.880
	Pre-VAD explantation LVEDD	0.119	0.055	0.031	1.126
Method: Forward					
Step 1	Pre-VAD explantation LVEDD	0.118	0.034	<.001	1.126
Step 2	Pre-VAD explantation exercise or Dobutamine stress test	-2.982	1.157	0.010	0.051
	Pre-VAD explantation LVEDD	0.200	0.049	<.001	1.221
Method: Backward → coefficients did not converge					
LVEDD and LVEF (replacement for pre-explantation stress test)					
Method: Enter					
	Pre-VAD explantation LVEF	-0.087	0.034	0.011	0.917
	Pre-VAD explantation LVEDD	0.107	0.040	0.007	1.113
Method: Forward					
Step 1	Pre-VAD explantation LVEDD	0.118	0.034	<.001	1.126
Step 2	Pre-VAD explantation LVEF	-0.087	0.034	0.011	0.917
	Pre-VAD explantation LVEDD	0.107	0.040	0.007	1.113
Method: Backward					
Step 1	Pre-VAD explantation LVEF	-0.087	0.034	0.011	0.917
	Pre-VAD explantation LVEDD	0.107	0.040	0.007	1.113
Covariate means		**Mean**			
	Pre-VAD explantation LVEF	52.952			
	Pre-VAD explantation LVEDD	51.687			

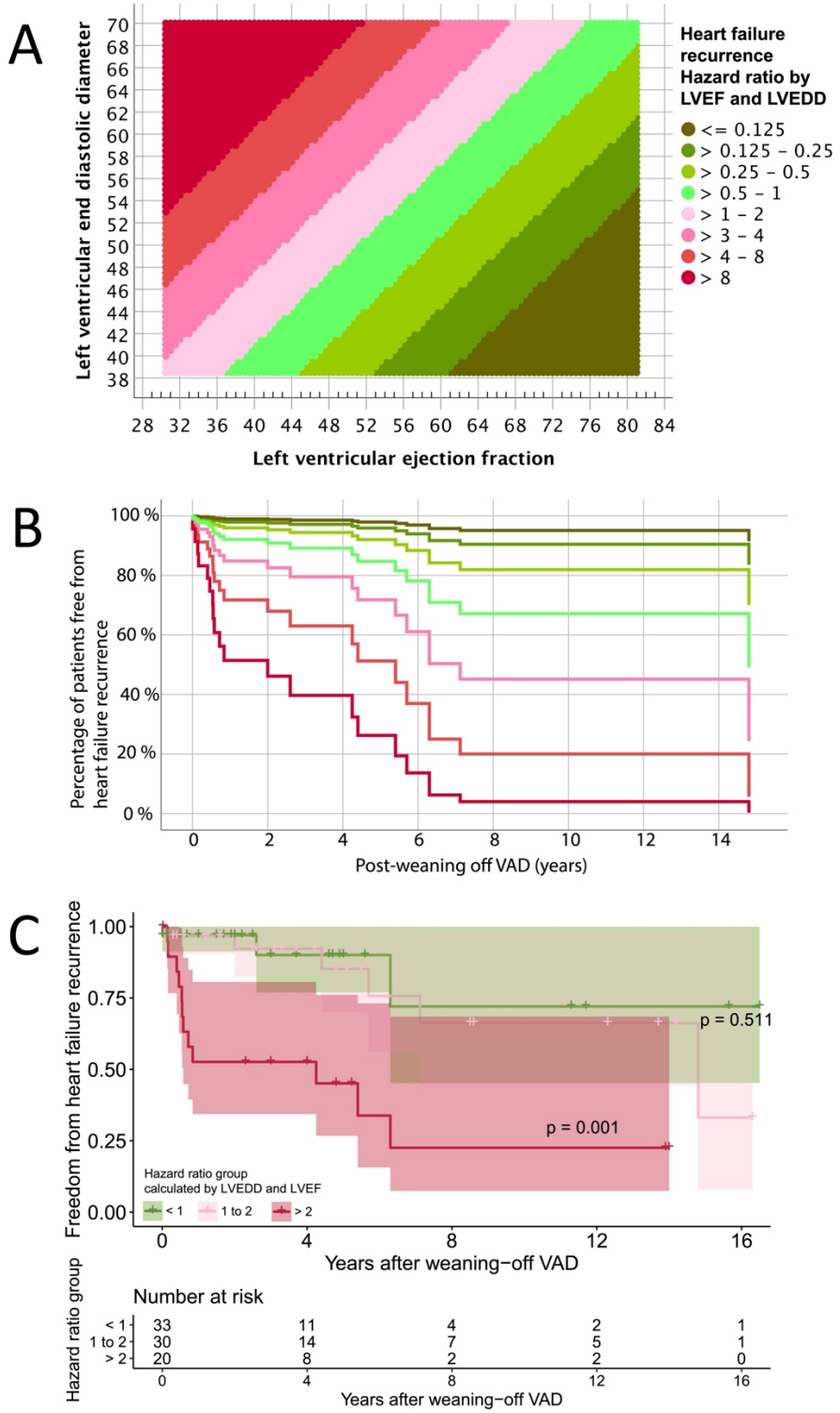
B = coefficient ß; Exp (B) = hazard ratio; SE = standard error; Sig.= significance; VAD=ventricular assist device

The HR analysis of 6 potential PRFs in Group 1 showed that LVEDD (p=0.001) and LVEF (p=0.007) are clinically significant predictive risk factors for heart failure recurrence as shown in Table 3a and stratified in Table 3b.

The HR range is shown in stripes of different colors in Fig. 3A. This figure illustrates that the HR for HF recurrence is inversely correlated with LVEF and positively correlated with LVEDD, i.e., when LVEF is <52 % and LVEDD is >53 mm, the HR is >8. Likewise, when the LVEF is >61% and the LVEDD is <54 mm, the HR is <0.125.

The pertaining regression equation is: HR = 2.718281 ^ ((LVEDF [%] – 52.952) * -0.087 + (LVEDD [mm] – 51.687) * 0.107).

Fig. 3. Heart failure recurrence prediction by 2 potential predictive risk factors in Group 1 (n=83). Hazard rate is based on left ventricular end diastolic diameter and ejection fraction.



A. Hazard rate estimated by LVEF and LVEDD at weaning off VAD
B. Hazard rate-based estimations of freedom from heart failure recurrence
C. Observed freedom from heart failure recurrence according to hazard ratio group

The rates of HF recurrence for patients with certain hazard rates are displayed in Figure 3B. It illustrates that at 7-14 years post-VAD explantation, <5% of patients with hazard ratio >8 are expected to experience freedom from HF recurrence. The study revealed that freedom from HF recurrence is 22% at 10 years post-VAD explantation (p=0.001) in patients with HR of >2, 33% at 15 years in those with HR of 1-2 (p=0.511) and 72% at 15 years in those patients with a hazard ratio of 0-1 (Fig. 3C). Further details of these HR-based Kaplan-Meier estimations are available in Table 3b.

Table 3b. Observed freedom from heart failure recurrence at certain time intervals after weaning off VAD according to hazard ratio groups calculated by LVEF and LVEDD and as shown in Fig. 3C.

Hazard ratio group	Years after weaning off VAD	Observed freedom from heart failure recurrence	SE
0 to 1	1	1	
	3	0.900	0.072
	5	0.900	0.072
	10	0.720	0.171
	15	0.720	0.171
1 to 2	1	0.967	0.033
	3	0.923	0.053
	5	0.852	0.084
	10	0.662	0.135
	15	0.331	0.244
>2	1	0.526	0.115
	3	0.526	0.115
	5	0.451	0.120
	10	0.226	0.128

LVEDD=left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; SE = standard error

Potential predictive risk factors for HF recurrence (Group 2, n=51 patients)

Analysis of the aforementioned **12 potential PRFs** by multivariate stepwise Cox regression in Group 2 (49 of them with observation times beyond the first event) revealed **age at VAD** (p= 0.012), **duration of HF (**p= 0.001) and maximal improvement of **sphericity index** (short/long axis ratio at end-diastole, S/L_{ED}, $p < 0.001$) as significant PRFs for HF recurrence at the time of weaning off VAD (Table 4A). A summary of Cox regression models is shown in Table 4a.

The Cox model regression equation indicating the HR considering these 3 factors is:

HR *(HF recurrence)* = 2.718281 ^ ((age [years] – 42.898) * 0.090 +
(HF duration before VAD implantation [years] – 3.510) * 0.363 +
(maximum sphericity index change [%] – 7.161) * 0.432)

For a quick bedside orientation, a regression equation was calculated and transformed into a nomogram for the two most significant factors, which were *age at VAD implantation* and *maximum sphericity index change*. The nomogram to estimate the hazard ratio is shown in Figure 4A: 40-year-old patients with a maximum sphericity index change of 10 have an HR for heart failure recurrence between 1 and 3.

The time dependent occurrence expectations of HF recurrence for patients with certain hazard ratio groups are displayed in Figure 4B. It illustrates model-based expectations for freedom from HF recurrence depending on several HRs: our example patient, with an HR between 1-3, has an estimated freedom from HF recurrence at 4 years of about 85%. Likewise, it is shown that at 4 years post-VAD explantation, all patients with an HR of 0.4-1 have a 98% freedom from HF recurrence.

Fig. 4C depicts the observations from patient subgroups in comparable HR ranges: patients with an HR from 1 to 3 had about 86 % freedom from HF recurrence at 4 years. Likewise, the regression estimation suggests that freedom from HF recurrence is 100% at 5 years and 70% at 15 years post-VAD explantation (p<0.001) in patients with an HR of 0.2-1, 86% at 5 years in those with HR of 1-3 (p=0.040) and 21% at 5 years in those patients with a hazard ratio of 3-50 (p=0.002) (Fig. 4C).

Cox regression models for these observations are listed in Table 4a. Further details of the HR-based Kaplan-Meier estimations are available in Table 4b.

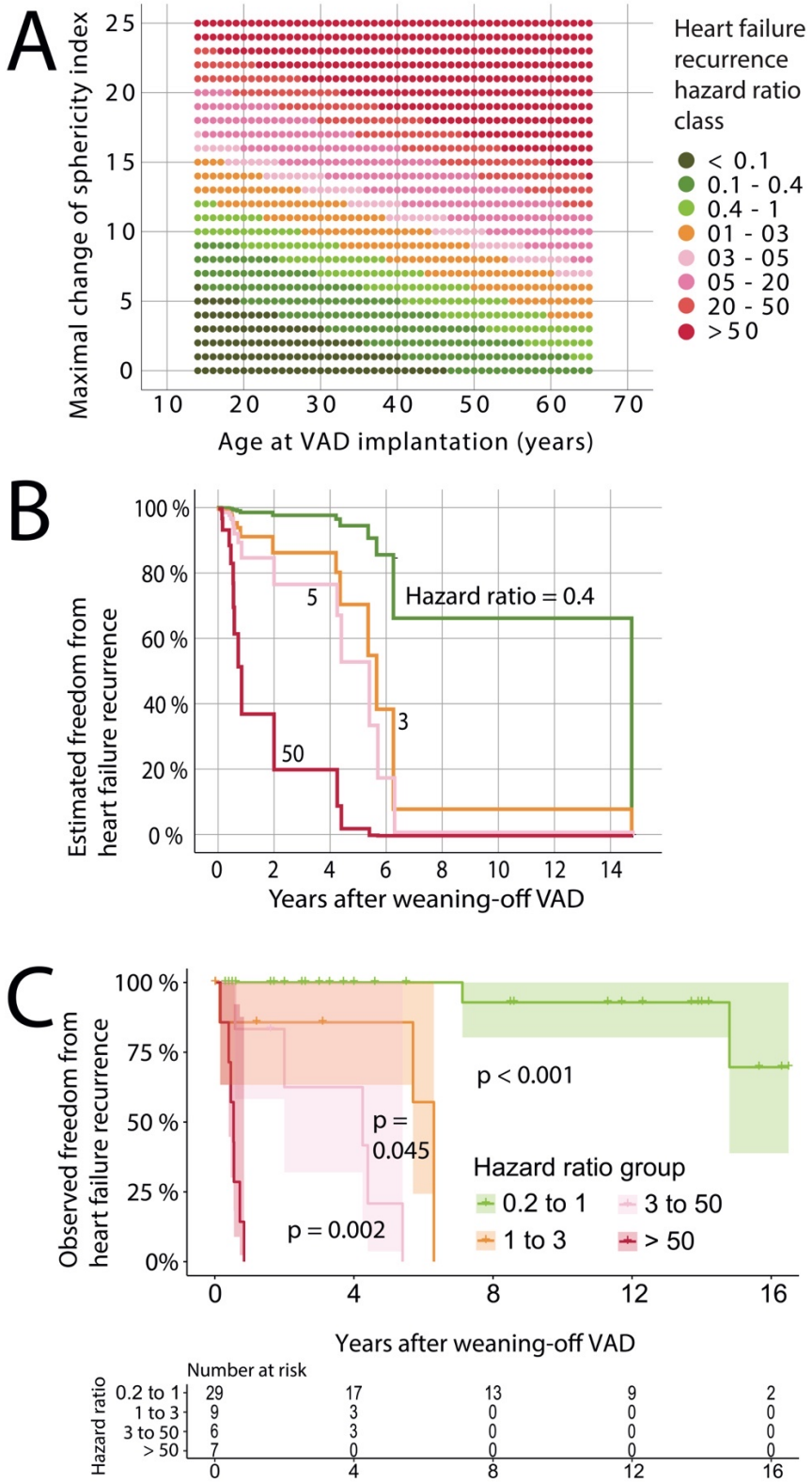
The corresponding HR regression, which uses 2 variables only, is:
$HR_{(HF\ recurrence)}$ = 2.718281 ^ ((age [years] - 42.898) * 0.067 + (maximum sphericity index change – 7.161) * 0.360).

Table 4a. Cox regression model summary for prediction of heart failure recurrence (12 factors available in 51 patients). First triple method includes all factors; second triple method includes 3 significant factors and third triple method includes the two variables chosen as shown in Fig. 4A.

Method: Enter → coefficients did not converge					
Method: Forward					
	Variables in the Equation	**B**	**SE**	**Sig.**	**Exp(B)**
Step 1	Maximum change of sphericity index	0.323	0.063	< 0.001	1.381
Step 2	Duration of HF pre-VAD implantation	0.293	0.089	0.001	1.345
	Maximum change of sphericity index	0.372	0.079	< 0.001	1.454
Step 3	Age at VAD implantation	0.090	0.036	0.012	1.094
	Duration of HF pre-VAD implantation	0.363	0.114	0.001	1.438
	Maximum change of sphericity index	0.432	0.097	< 0.001	1.541
Method: Backwards stepwise → coefficients did not converge					
3 of 12 significant factors					
Method: Enter					
	Maximum change of sphericity index	0.432	0.097	< 0.001	1.541
	Age at VAD implantation	0.096	0.036	0.012	1.094
	Duration of HF pre-VAD implantation	0.363	0.114	0.001	1.438
Method: Forward					
Step 1	Maximum change of sphericity index	0.323	0.063	< 0.001	1.381
Step 2	Maximum change of sphericity index	0.372	0.079	< 0.001	1.450
	Duration of HF pre-VAD implantation	0.293	0.089	0.001	1.340
Step 3	Maximum change of sphericity index	0.432	0.097	< 0.001	1.541
	Age at VAD implantation	0.098	0.036	0.012	1.094
	Duration of HF pre-VAD implantation	0.363	0.114	0.001	1.438
Method: Backward					
Step 1	Maximum change of sphericity index	0.432	0.097	< 0.001	1.541
	Age at VAD implantation	0.0912	0.036	0.012	1.094
	Duration of HF pre-VAD implantation	0.363	0.114	0.001	1.438
Covariate means	Maximum change of sphericity index	7.161			
	Age at VAD implantation	42.898			
	Duration of HF pre-VAD implantation	3.51			
2 of 12 significant factors					
Method: Enter					
	Maximum change of sphericity index	0.360	0.072	< 0.001	1.433
	Age at VAD implantation	0.067	0.028	0.015	1.069
Method: Forward					
Step 1	Maximum change of sphericity index	0.323	0.063	< 0.001	1.381
Step 2	Maximum change of sphericity index	0.360	0.072	< 0.001	1.433
	Age at VAD implantation	0.067	0.028	0.015	1.069
Method: Backward					
Step 1	Maximum change of sphericity index	0.360	0.072	< 0.001	1.433
	Age at VAD implantation	0.067	0.028	0.015	1.069
Covariate means	Maximum change of sphericity index	7.161			
	Age at VAD implantation	42.898			

B= coefficient ß; Exp(B)= hazard ratio; HF= heart failure; SE= standard error; Sig.= significance; VAD= ventricular assist device

Fig. 4. Heart failure recurrence based on hazard ratio calculation of maximal sphericity index change and age at VAD implantation



A. Hazard rate estimated by maximal sphericity index change and age at VAD implantation
B. Hazard rate-based estimations of freedom from heart failure recurrence
C. Observed freedom from heart failure recurrence by hazard ratio group (p-values show results of pairwise log-rank test comparisons). Details are shown in Table 4b

Table 4b. Observed freedom from heart failure recurrence at certain time intervals after weaning off VAD according to hazard ratio calculated by age at VAD implantation and maximum sphericity index change as shown in Fig. 4C.

Hazard ratio group	Years after weaning off VAD	Observed freedom from heart failure recurrence	SE
0.2 to 1	1	1	
	3	1	
	5	1	
	10	0.929	0.069
	15	0.696	0.208
1 to 3	1	0.857	0.132
	3	0.857	0.132
	5	0.857	0.132
3 to 50	1	0.833	0.152
	3	0.625	0.213
	5	0.208	0.184
50+	0.5	0.571	0.187

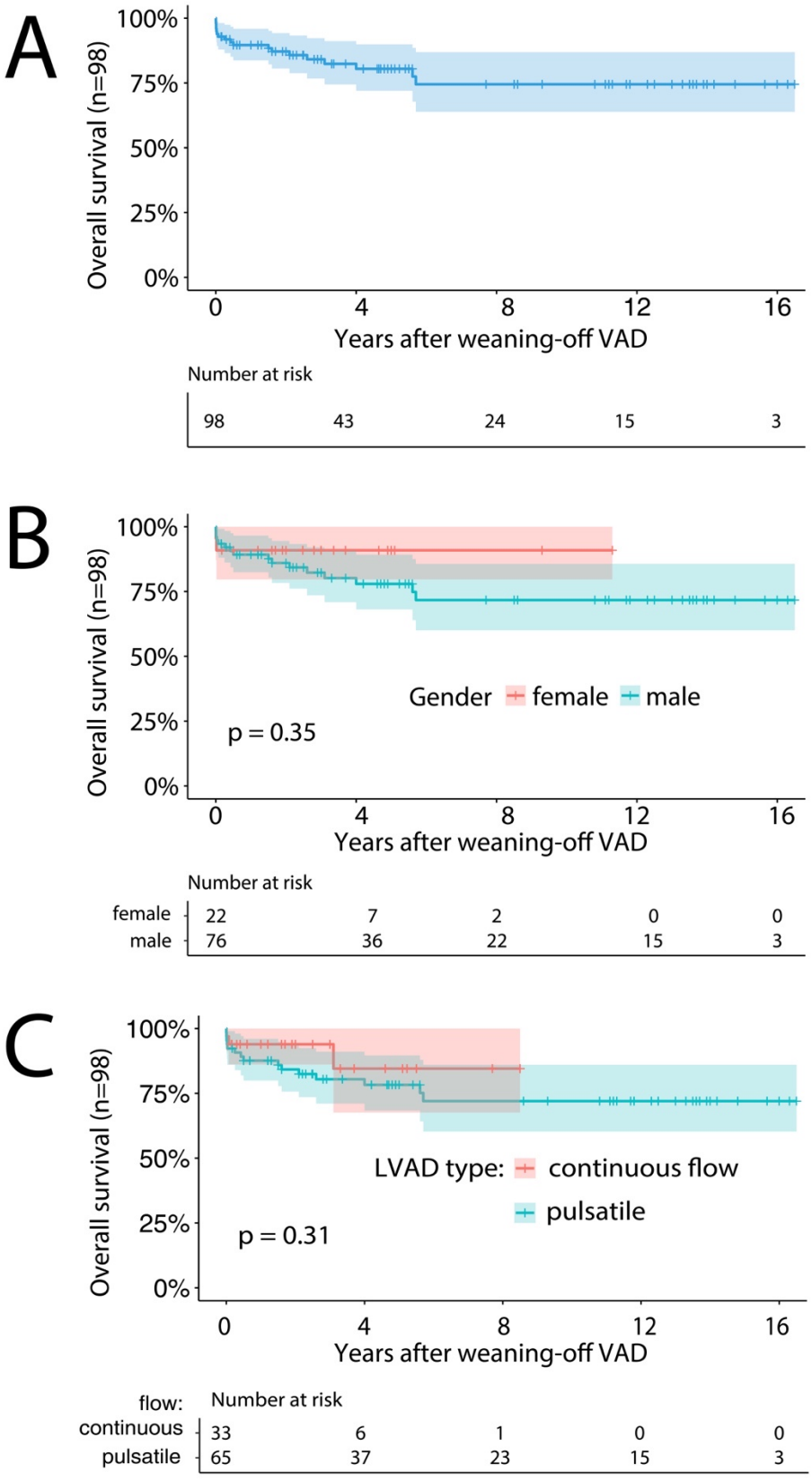
LVEDD=left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; SE = standard error

b. Overall survival after VAD explantation and weaning off VAD

Overall survival after weaning off VAD is 100% at 30-day, 80% at 5-year and 74% at both 10- and 15-year follow-up (Fig. 5A).

Stratification according to gender (Fig. 5B) and type of VAD (pulsatile and continuous flow) (Fig. 5C) revealed no statistical significance (p=0.35 and p=0.31, respectively). Table 5a details survival rates with standard errors.

Fig. 5. Observed overall survival after weaning off VAD for all patients and stratified by gender and type of VAD



Survival rates: A. overall B. by gender C. by type of VAD

Table 5a. Survival rates with standard errors on follow-up after weaning off VAD based on gender and type of VAD, as illustrated in Fig. 5 A-C.

Figure	Group	Years after weaning off VAD	Observed freedom from death from any cause	SE
5A	all	1	0.896	0.031
		3	0.841	0.040
		5	0.805	0.046
		10	0.745	0.059
		15	0.745	0.059
5B	female	1	0.909	0.061
		3	0.909	0.061
		5	0.909	0.061
		10	0.909	0.061
	male	1	0.892	0.036
		3	0.823	0.047
		5	0.780	0.054
		10	0.717	0.065
		15	0.717	0.065
5C	Continuous flow VAD	1	0.939	0.042
		3	0.939	0.042
		5	0.845	0.097
	Pulsatile VAD	1	0.876	0.041
		3	0.804	0.051
		5	0.783	0.054
		10	0.720	0.065
		15	0.720	0.065

SE= standard error; VAD= ventricular assist device

Risk factor analysis for survival (Group 1, n=83)

The analysis of the 6 potential PRFs in this group revealed no statistically significant risk factors for overall survival.

Risk factor analysis for survival (Group 2, n=51)

Among the 51 patients with 12 variables, **arterial diastolic pressure above 50 mmHg** during pump-flow reduction trials (p= 0.018, HR = 0.018) and **higher age (>45 years) at VAD implantation** (p= 0.006, HR = 1.089) have been found to be PRFs for overall survival. The model development is briefly shown in Table 5b. Younger aged (≤45 years) patients who achieve an arterial diastolic pressure above 50 mmHg during the VAD support reduction tests are supposed to have promising medium-term survival chances, even beyond childhood age. Further data collections might permit using the achieved arterial diastolic pressure for

prediction as a numerical value instead of the dichotomy shown in this study. The HR regression equation is:

HR$_{(Heart\ failure\ recurrence)}$ = 2.718281 ^ ((Age [years] - 42.925) * 0.047 + 0.534 [if diastolic arterial pressure ≥ 50 mmHg, if not: add + 0 instead of + 0.534])

Table 5b. Cox regression modelling summary for overall survival, based on 6 or 12 variables. Since the entire evaluation is intended as hypothesis-generating and not confirmatory, the formation of the regression equation, despite the *p-value* of 0.108 of the potential predictive risk factor, i.e. off pump arterial diastolic pressure 50 mmHg, was pursued.

Factors	Method	Result (potentially significant predictive risk factors)
6 factors		no convergence of coefficients with any applied method.
12 factors	Enter	Age at VAD implantation (p= 0.004) Off-pump arterial diastolic pressure 50 mmHg (p= 0.040) + 10 others with p > 0.05
	Forwards	Age at VAD implantation (p= 0.006) Off-pump arterial diastolic pressure 50 mmHg (p= 0.018) + 2 others with p > 0.05
	Backwards	Age at VAD implantation: no convergence of coefficients
> 2 factors	Enter	Age at VAD implantation (p= 0.045) Arterial diastolic pressure 50 mmHg (p= 0.108)

VAD = ventricular assist device

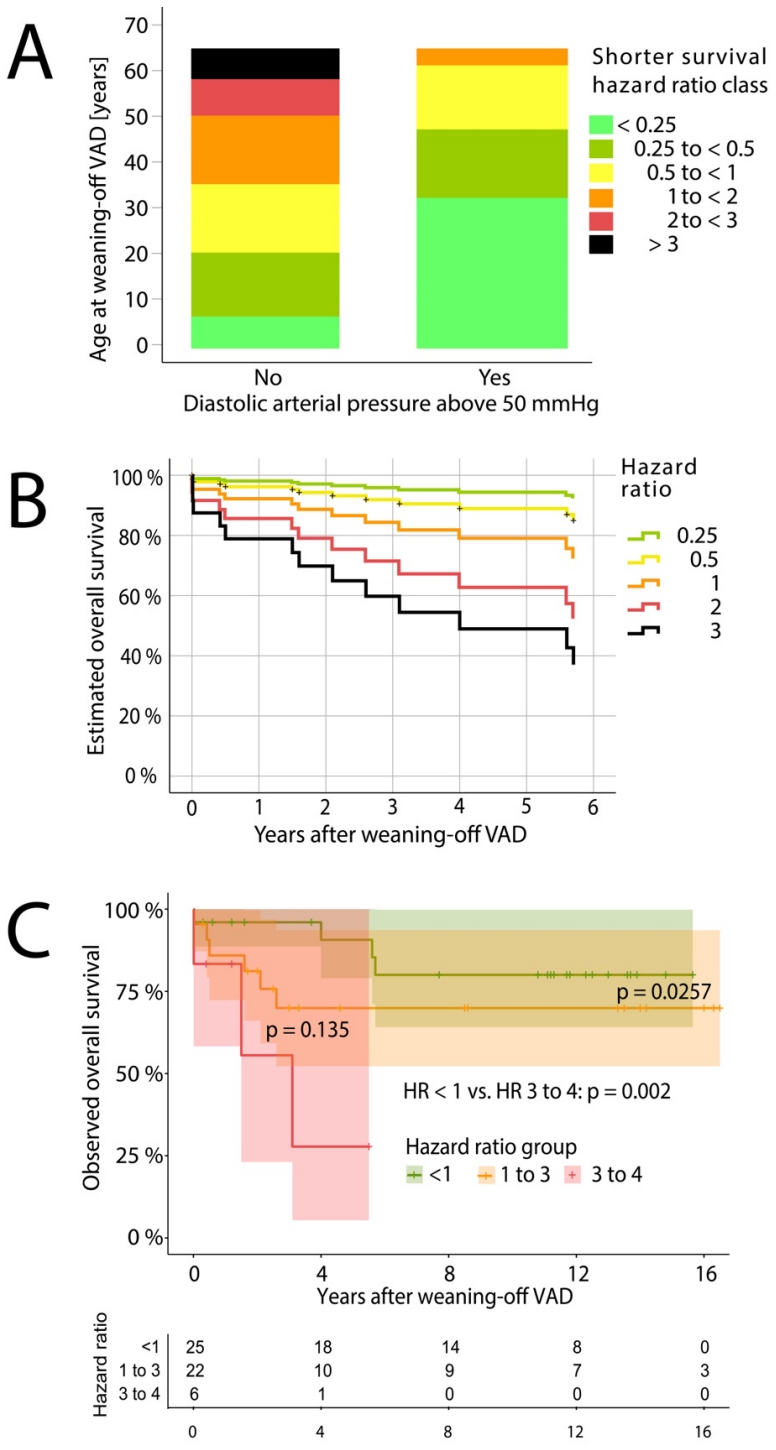
Fig. 6A shows the nomogram estimation of the all-cause death hazard ratio, which consists of two stacked bars instead of stripes since one of the factors is dichotomous. The regression equation is based on 53 patients on whom the 2 potential predictive risk factors were available.

Fig. 6B is a survival estimation plot based on HR calculated from age at VAD implantation and off-pump arterial diastolic pressure of 50 mmHg. As illustrated, a patient with HR of 3 would have a 79.9%, 61.4% and 50.8% survival chance at 1, 3 and 5 years post-VAD explantation, respectively; a patient with HR of 2 would have an 85%, 71.5% and 63.0%, survival at 1, 3 and 5 years post-VAD explantation, respectively; with HR of 1, patients would have a 92.8%, 84.9 % and 79.6% survival chance at 1, 3 and 5 years post-VAD explantation, respectively; patients with HR of 0.5 would have a 96.4%, 92.3% and 89.4% survival at 1, 3 and 5 years post-VAD explantation, respectively, and those with an HR of 0.25 would have a

98.1%, 95.9% and 94.4%, survival at 1, 3 and 5 years post-VAD explantation, respectively.

Fig. 6C shows the observed survival stratified by HR grouping derived from age at VAD implantation and off-pump arterial diastolic pressure of 50 mmHg. About 70% of the observed patients with HR between 1 and 3 survived for 16 years post-VAD explantation (p=0.0257). Among those with HR <1, 80% survived, with the longest follow-up time being 15 years (p=0.002), and 28% survived at 5 years in those with an HR of 3 to 4. Further details on observed survival are provided in Table 6.

Fig. 6. Overall survival based on hazard ratio estimation by age at VAD implantation and arterial diastolic pressure at weaning off VAD (≤ or > 50 mmHg)



A. Hazard rate (HR), estimated by arterial diastolic pressure at weaning off VAD (≤ 50 mmHg or >50 mmHg) and age at VAD implantation
*Equation: HR = e ^ ((Age [years]-42.925) * 0.047 + (arterial diastolic pressure ≤ 50 [no =0. yes = 1] - 0.283) * - 1.251)*
B. Hazard rate-based survival estimations
C. Observed survival according to hazard ratio group

Table 6. Observed survival rates (illustrated in Figure 6C) on follow-up post-weaning off VAD according to hazard ratio classes stratified by patient age and arterial diastolic pressures above 50 mmHg

Hazard ratio class	Years after weaning off VAD	Observed freedom from death from any cause	SE
<-1	1	0.960	0.039
	3	0.960	0.039
	5	0.907	0.064
	10	0.800	0.090
	15	0.800	0.090
1 to 3	1	0.859	0.075
	3	0.699	0.104
	5	0.699	0.104
	10	0.699	0.104
	15	0.699	0.104
3 to 4	1	0.833	0.152
	3	0.556	0.248
	5	0.278	0.232

SE = standard error; VAD = ventricular assist device

Post-VAD weaning death

An overview on death causes, phases, and the risk estimations of the affected patients is enumerated in Table 7. Eighteen patients died post-weaning off VAD over time during the follow-up, i.e., due to non-cardiac related causes such as infection, pulmonary bleeding, ischemic stroke, complications of immunosuppression after heart transplantation for HF recurrence or unknown cause of death without HF recurrence. These patients were analyzed for factors with regards to weaning-related death, but this event number was too low for a multivariable analysis. Furthermore, due to the complicated critical conditions of these patients, death references exclusively related to VAD weaning proved to be ambiguous.

Table 7. Heart failure recurrence and death in specified states post-weaning off VAD

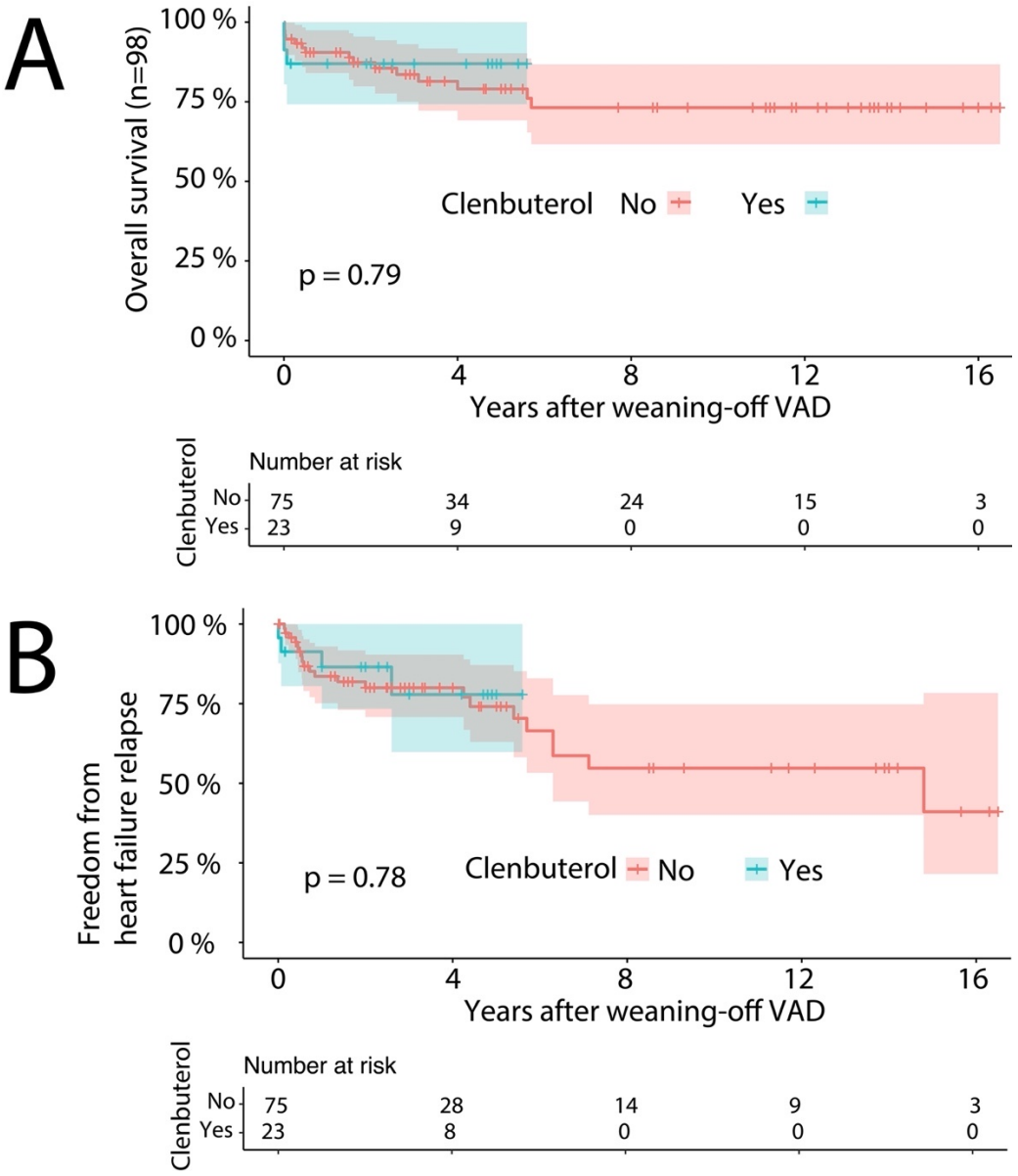
State	Pre-weaning					Pre-heart transplantation					Post-heart transplantation				
			Hazard rate for end points					Hazard rate for end points					Hazard rate for end points		
Cause of death	Patient ID	Years to event	HFR by LVEF and LVEDD	HFR by age and maximum sphericity index	Death by age & arterial diastolic pressure ≤50 mmHg*	Patient ID	Years to event	HFR by LVEF & LVEDD	HFR by age and maximum sphericity index	Death by age and arterial diastolic pressure ≤50 mmHg*	Patient ID	Years to Event	HFR by LVEEF and LVEDD	HFR by age and maximum sphericity index	Death by age and arterial diastolic pressure ≤50 mmHg*
Sepsis	63	0.01	0.98	1.00	3.05	60	2.6	1.34	0.36	3.05					
Sepsis, HFR						11		1.16							
						12	0.004	0.16	286.14						
HFR						48	2.1	1.38	4.21	2.53					
						61	0.42	8.92	286.14	2.30					
						87	0.25								
						85	0.03								
						21	0.002								
						58	5.7	1.08	1.59	0.76					
OHT adverse events											38	1.6	12.30	216.50	1.03
											51	1.5	15.53	149.46	3.36
											31	6.6	8.44	3.14	0.41
Unknown						60	0.2	1.34	0.36	2.78					
						72	0.5	0.82	0.05	1.03					
						62	4	2.19	0.14	0.98					
						28	3.1	1.28	1.16	3.52					
Stroke	24	0.1	0.16		0.44										

** The first row denotes the state in which the death cause occurred. The first column describes the cause of death. Years to event is the occurrence of a specific event after weaning off VAD; *mean arterial diastolic pressure below 50 during off-pump trial; HF = heart failure; ID – identification number; HFR = heart failure recurrence; HR = hazard ratio; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; OHT = orthotopic heart transplantation. Most non-survivors had elevated hazard rates.*

c. Pharmacologic therapy with Clenbuterol

Based on Cox regression stepwise analysis, Clenbuterol administration in patients with HF secondary to non-ischemic cardiomyopathy neither had a statistically significant impact on HF recurrence after VAD weaning nor on overall survival, as illustrated in Fig. 7A and B and detailed in Table 8. The Cox regression model series of the aforementioned analyzed end points showed no statistically significant influence of Clenbuterol administration in any regression.

Fig. 7. Influence of Clenbuterol administration in heart failure recurrence and survival after weaning off VAD



A. Overall survival

B. Freedom from heart failure recurrence

(with Clenbuterol= blue; without Clenbuterol = red)

Table 8. Impact of Clenbuterol administration on freedom from heart failure recurrence and survival on follow-up post-weaning off VAD

Figure	End point	Clenbuterol	Years	Freedom from specified end point	SE
6A	Death from any cause on follow-up post-weaning off VAD	no	1	0.905	0.034
			3	0.835	0.0346
			5	0.790	0.054
			10	0.732	0.064
			15	0.732	0.04
		yes	1	0.870	0.070
			3	0.870	0.070
			5	0.870	0.070
6B	Heart failure recurrence	no	1	0.836	0.045
			3	0.800	0.050
			5	0.741	0.061
			10	0.547	0.087
			15	0.411	0.0135
		yes	1	0.865	0.073
			3	0.778	0.105
			5	0.778	0.105

SE = standard error, VAD=ventricular assist device

Multi-state analysis

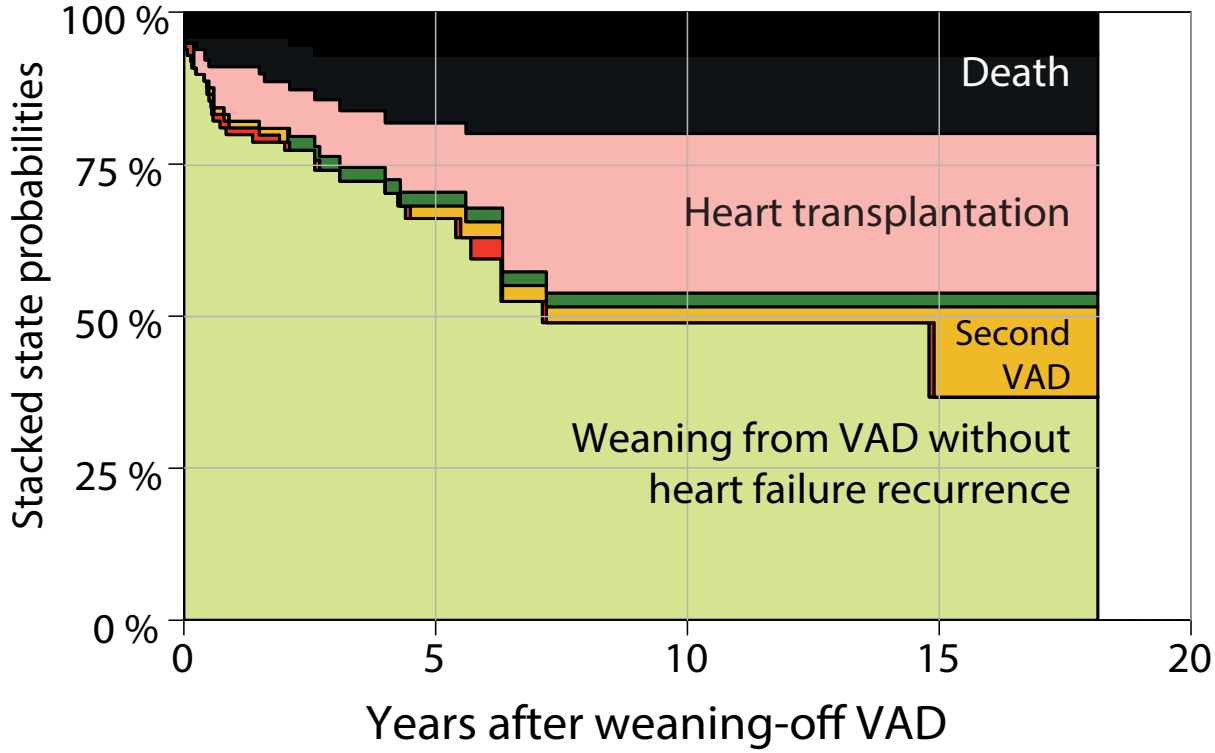
A multi-state model (Fig. 8) shows the probabilities of being in a certain state at a certain time after a start event, i.e., VAD explantation and weaning off VAD. The observed states are freedom from HF recurrence, HF recurrence, repeat VAD implantation, VAD re-explantation, heart transplantation and death. It is a model calculation, hence the numbers at risk which contribute to the estimation at a certain time correspond to those indicated in the survival curves.

Fig. 8 illustrates the various multi-state probabilities stacked in an approximately sequential order. The y-axis of the individual stripes (from the lower to the upper boundary line) reflects the proportion of patients in the respective stage in approximately chronological order. Each patient has not necessarily experienced all stages. The height of a stripe at a defined time (from

its lower to its upper border) reflects the percentage of patients in this state at the particular time. This paradigm is shown in Table 9.

It has been observed that the desired (green) state *weaning without HF recurrence* takes a predominant role for almost 15 years after primary VAD explantation, followed by *heart transplantation*. The probability of *death* from any cause post-weaning off VAD is <14.5% after 3-5 years follow-up. A quarter of all patients underwent heart transplantation after 6 years. The probability of having a repeat VAD implantation is below 5% for each time up to 14 years. The same patient fraction lives after weaning off the second VAD. Approximately half of the patients remain free from VAD implantation and heart failure recurrence for up to 10 years and approximately a third (36.7%) even beyond this interval.

Fig. 8. Multi-state model of status probabilities after weaning off VAD



**Heights of stripes indicate the estimated percentage of patients being in the described status at the time shown at the x-axis. Red areas show patients in the state of "heart failure recurrence", dark green areas show patients in the state of "second VAD explanted". Exact estimation percentages are described in Table 9.*

Table 9. Multistate probability estimations over time after weaning off VAD

Years post-weaning off VAD		0	1	3	5	10	15
Status	Weaning from VAD without heart failure recurrence [%]	100.0	79.9	74.0	66.1	48.9	36.7
	Heart failure recurrence [%]	0	1.1	0	0	0	0
	Second VAD [%]	0	1.1	0	2.1	2.6	14.8
	Second VAD explanted [%]	0	0	2.3	2.3	2.3	2.3
	Heart transplantation [%]	0	9.0	9.3	11.4	26.2	26.3
	All-cause death on follow-up post-weaning off VAD [%]	0	9.0	14.5	14.5	18.3	18.3

VAD=ventricular assist device

Discussion

As the rugged landscape of clinically described myocardial recovery is marked by a scarcity of large clinical studies that present long-term outcomes of weaning from VAD, progress in this field, despite growing interest, remains stagnant. Current medical experiences remain insufficient for creating non-arbitrary guidelines to predict the possible occurrence of heart failure recovery following circulatory unloading with VADs. The prevailing state is thus reliant on the experience and intuition of physicians to evaluate potential recovery. However, reliable identification and selection of candidates with the potential to survive and benefit from gradual cessation of circulatory support with minimal risk in suffering from HF recurrence must be treated as a vital construction point for cardiac surgeons and cardiologists alike, who aim to pursue progress in managing myocardial recovery.

Inasmuch as regular and invasive molecular diagnostics are not without risks and may be considered economically unjustified, the initial focus must additionally encompass ameliorating clinical prediction and weaning candidate selection. An initial approach to forward our search is to incorporate frequent and non-invasive monitoring methods during VAD therapy in order to gather data that reflect and allow assessment of the course of reverse remodeling and indicate the potential for sustained recovery.

Patients afflicted with non-ischemic DCMP and supported by a long-term ventricular assist device represented the majority of those in which myocardial recovery was sufficient to allow for assist device explantation.[16, 24, 31,32,33,34] With the hope of eluding OHT, predictors may be used in assessing a central crosspoint: determining the feasibility of electively weaning the patient from mechanical circulatory support and ensuring a stable myocardial recovery.

Echocardiography in determining long-term cardiac stability

As echocardiography embodies a staple procedure in cardiovascular diagnostics, optimizing its interpretation and implementation in VAD-supported HF patients is filled with potential in pre-explant evaluations, aiding in determining weaning candidates. The results of the meta-analysis allow the instilling of clinical importance onto three important echocardiographic parameters in pre-explant evaluation of LV size, geometry and function: LVEDD, LVEF and LV sphericity index.

Through quantitative assessment of long to short-axis ratios of the cardiac chambers, it comes as no surprise that the sphericity index is useful as a progress marker in dilative cardiomyopathy. A shift from spherical shapes typical of HF progression back to elliptical shapes indicates a morphological reversal of pathognomonic processes leading to dilation and kinetic deterioration. Besides regression in the pathologic cardiac morphology, a reduction in LVEDD and S/L_{ED} ratio reflects a return to normal wall tension, whilst improvement in the LVEF values shows effective functional improvement. Therefore, coupling morphological improvement with the diminution of LV dilation marked by a decrease in LVEDD and an improvement in effective contraction marked by an increase in LVEF, clinicians may be able to deduce the occurrence of a recovery process and the reversal of the HF phenotype. Positive molecular effects of mechanical unloading through VAD support have been associated with interstitial changes such as a decrease in matrix metalloproteinases (MMPs) and an increase in MMP modulators (TIMPs)[35,36,37,38] leading to an increase in collagen content of the myocardium and its cross-linking.[39] In turn, a resulting decrease in cardiac fibrosis[40] combined with increased collagen was theorized to act preventative for future re-dilation,[18,39] although this process remains a topic for discussion.[16, 39,40,41,42] The relationships between LVEDD, LVEF, sphericity indices and these molecular changes are a field that needs to be further evaluated.

However, when aiming to identify weaning guidelines, both quantitative and qualitative assessment of cardiac function must be combined in order to balance therapeutic optimism and patient safety. In potential weaning candidates with relevant improvement of echocardiographic parameters, repeated (preferentially weekly) TTE follow-up examinations with target values of LVEDD <55mm, LVEF >45%, LV peak systolic wall motion velocity at the basal posterior wall (Sm) >8cm/s, lack of RV dilation and mitral regurgitation more than grade I, CI >2.6 L/min/m2, PCWP <13mmHg, right atrial pressures of <10mmHg, heart rate <90/min with an increase of <25% during weaning trials and a mean arterial pressure (MAP) of >65mmHg have been suggested as inclusion criteria for elective LVAD explantation during the final off-pump trial.[11,12] Considerations have to be made in performing off-pump trials with respect to the VAD type used (axial, pulsatile, continuous), as complete flow cessation in patients under axial-VAD support may lead to retrograde flow over the aortic valve, leading to false evaluations of LV systolic function.[11] Thus, patients under circulatory support with axial flow pumps must undergo flow-reduction trials with near-zero flow values, in order to avoid such misevaluations. Overestimation of LV systolic function may furthermore occur when diastolic aortic pressures fall to less than 50mmHg under pump reduction or off-pump trials,

as lower transaortic gradients facilitate left ventricular ejection and therefore may inaccurately reflect recovered ventricular function.

Ventricular unloading interruption trials

Accumulation of echocardiographic data from frequent off-pump or pump-flow reduction trials at rest has shaped the foundation for the echocardiographic evaluation of myocardial recovery in potential weaning candidates. Following months of complete ventricular unloading with VAD, short-term physiological requirements may be met with hemodynamic intolerance and myocardial exhaustion.[16, 17, 21] This, in turn, may present a hurdle in the process of ongoing reverse remodeling and recovery and represents an important consideration when initiating loading trials. This rationale therefore justified that all adults weaned from long-term VADs initially intended as a bridge to transplantation or destination therapy between 1995 and 2014 by the Berlin group underwent evaluation of myocardial recovery solely at rest.[12, 17, 19] Despite associated limitations in the evaluation of recovery pertaining to the lack of conclusions with regards to inotropic reserves or hemodynamic and myocardial stress adaptation, no significant weaning result differences were seen between patients of the Berlin group and other groups in which stress echocardiography and/or exercise testing were implemented.[28, 43] It is, however, important to note that the inclusion of stress echocardiography may deliver valuable information on myocardial adaptability to stress and inotropic reserves which, in turn, may be a useful additive consideration in weaning assessments. The preservation of contractility may be reflected by an absolute increase in LVEF of 5% according to some authors.[28] In contrast and as previously mentioned, stress echocardiography with dobutamine may theoretically lead to myocardial exhaustion and thus negatively affect ongoing reverse remodeling. Hence, it is necessary to further investigate the true benefits of performing stress tests and using obtained values to guide the weaning decision.

In the creation of weaning criteria, the importance of the nature of changes of the aforementioned echocardiographic parameters must not be underestimated. After reaching relative maximal improvement of any parameter, minimal oscillations in the recorded values reflect stability and reliability in functional improvement. Therefore, the key consideration in recognizing persistent recovery after explantation is the stability of cardiac improvement in weaning candidates after reaching its maximum value. The results of this meta-analysis have transpired in favor of this hypothesis.

Myocardium and heart failure recurrence

Prediction of HF recurrence as a major post-weaning complication must be incorporated into the decision process.[19] A significant observation that we have been able to make is that age (p=0.012) seems to positively correlate with HF recurrence (p=0.015). Despite this observation suggesting a larger potential for recovery in younger demographics, there remains the necessity to fully explain the molecular changes occurring in reverse remodeling. Although patient age at VAD implantation was found as a risk factor for post-weaning HF recurrence, more advanced age (>45 years) alone should not be considered an absolute contraindication for VAD explantation. This is reflected in the gathered data - among the weaned patients, there were 4 patients aged between 59 and 64 years at the time of VAD explantation, who showed no alteration of post-weaning cardiac function throughout an observation period which ranged between 4.2 and 8.6 years.

A reversal of processes driving HF, including myocyte hypertrophy,[3] slippage,[4] interstitial growth and lengthening as well as a decline in antiapoptotic proteins,[44,45,46] are molecular changes that have been suggested as part of the reverse remodeling process.[1] VADs may facilitate myocardial recovery by propagating reversal of abnormalities of myocytes and the extracellular matrix, in turn macroscopically followed by restitution of ventricular geometry and function. A variety of modifications in myocyte structure and function, as well as ventricular structure and organization with simultaneous normalization of ventricular end-diastolic pressure-volume relationships are contributory to the beneficial functional effects. However, the specific constituents and the necessary extent of reverse remodeling responsible for clinical myocardial recovery that allow for VAD explantation are not yet sufficiently well known.[47] Moreover, further research is required to link the propensity to reverse remodel on the molecular level with a younger age. It is further important to note that molecular reversal of the changes promoting HF does not necessarily precipitate clinical recovery.[1] However, myocardial biopsy and histological examination are currently not used for weaning decisions and indicated only in patients with acute myocarditis or severe cardiac allograft rejection as the underlying cause for drug-refractory heart failure.

Similarly, a correlation can be found between HF duration before VAD implantation and HF recurrence. Whilst longer afflictions are known to be associated with lower blood pressure, increased left ventricular loads, increased wall motion score indices [48] and thus a higher risk to suffer adverse outcomes, the relationship between HF duration and the propensity to

myocardial recovery has yet to find some foundation. These observations suggest significance of myocardial injury in recovery, although oversimplification must be cautioned against in light of the vast heterogeneity and phenogroups[49] involved in HF. The fraction of viable and functional myocardium is hypothesized to influence the propensity to recover and alter the resultant trajectory [50] as, in theory, tissue viability is fundamental for reverse remodeling to be possible. Depth must be gained in understanding the interrelation between younger demographics, HF duration and the propensity to reverse remodel and sustain recovery.

HF recurrence has unfolded to be the most frequent complication post-VAD explantation, particularly in patients with long-standing myocardial alterations before VAD implantation.[16,24,33] Although the inability to sustain myocardial recovery leading to HF recurrence may have occurred due to insufficient pharmacologic therapy, other factors such as patient compliance and further improvements of the predictive power of post-explant cardiac stability may influence post-VAD explantation patient outcome.

Pharmacologic therapy with Clenbuterol administration

In light of the potential of mechanical cardiac unloading with VADs to change the course of mechanical circulatory support towards a bridge-to-recovery, optimization of VAD use to facilitate reverse remodeling is a topic of importance and must be acknowledged. One study has shown potential in the concomitant use of the ß-2 receptor agonist Clenbuterol in promoting recovery.[25] Its use is rationalized by facilitating atrophy counteraction and limiting apoptosis that may occur through complete ventricular unloading [51] by promoting the expression of insulin-like growth factor I (IGF-I).[52] A different study has shown the beneficial effects of multiple drug therapy during VAD support by implementing Clenbuterol therapy after accomplishing reverse remodeling and reverting left ventricular dilation with the use of an angiotensin converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), ß-blocker and a diuretic.[53] Its findings may point towards a possible neurohormonal involvement in the recovery process facilitated by ventricular unloading. Unfortunately, the present meta-analysis has shown that Clenbuterol administration during the duration of VAD support neither had an influence on the prevention of HF recurrence nor guarantees the stability of myocardial recovery after weaning off VAD.

However, there are other novel pharmacological approaches that may be of potential benefit, such as the use of Adrenomedullin, which has been postulated to be protective in HF patients

by inducing advantageous hemodynamic effects.[54] Although its implementation in VAD-supported HF patients has not been studied, its adjunctive therapeutic inclusion in the form of adrecizumab[55] may be considered in future studies aiming to examine pharmacologically optimized cardiac unloading with VADs.

Survival

Overall, the meta-analysis strongly suggests that a prediction of long-term post-weaning cardiac stability is achievable and can be managed and interpreted more reliably through deliberate examination and purposeful inclusion of selected echocardiographic and clinical parameters before VAD explantation. The present meta-analysis confirmed this cognizance in the largest patient cohort to date. The 74% survival rate at both 10 and 15 years revealed in this study is advocative of the feasibility in pursuing further augmentation and optimization of the VAD weaning process. Younger aged (<45 years) patients who achieve an arterial diastolic pressure above 50 mmHg during the VAD support reduction tests have promising medium- to long-term survival chances, even beyond childhood age. An eminent and compelling feature in this meta-analysis is underscored by the multi-state model to prognosticate the prospects of being in a certain state at a certain time in follow-up years after weaning off VAD, such as freedom from HF recurrence, HF recurrence, repeat VAD implantation, VAD re-explantation, heart transplantation and death. Patients who survived may not necessarily endure or go through each or all facets. Nevertheless, this multi-state model provides a deep insight on possible trajectories after weaning off VAD. Likewise, this indicates the necessity for continued management and optimized treatment of the survivors after VAD explantation.

Limitations

Data on this topic is rare. Prospective multicenter studies have not been carried out yet, despite the importance of the matter. The advantage of accumulating the experience of several centers is accompanied by the limitation of a lack of a common study protocol. Rare data weakens the reliability of estimations, leading to a predictive regression equation that includes a factor that exceeds the usual 5 % significance level, as seen in Fig. 5. This can be considered as justified in order to show the options that may result from collecting and sharing relevant data. All the presented models are to be considered not as assertions but as hypotheses that require confirmation by larger patient numbers and other centers. The figure parts 2C, 3C and 5C suggest that the regression equations might indeed be helpful.

Conclusions

This meta-analysis has focused on the parameters collected before VAD explantation and examined their effects on the outcomes of patients afflicted with heart failure secondary to non-ischemic cardiomyopathy. The absolute values as well as their evolution throughout off-pump trials were analyzed, measuring their predictive capabilities by analyzing two key trajectories: HF recurrence and overall survival. Within the frame of this study, factors such as gender and type of VAD have had no statistical influence on the HF recurrence nor the long-term survival of patients weaned off VAD. It can be hypothesized that factors such as a younger age, duration of HF, gradual normalization of LV morphology, and the stability of pre-explant echocardiographic parameters would be significant considerations in VAD-weaning management. The present findings have largely supported this hypothesis, in which the factors age at VAD implantation, stability in improvement of the cardiac sphericity index (i.e., improvement of LV geometry), LVEDD and LVEF have transpired to be significant predictors of sustained myocardial recovery after cessation of mechanical circulatory support. Although the decision whether to wean off VAD remains a clinical decision, based on a patient's condition and the balance between the optimism and experience of a physician, the results of this study have clearly demonstrated an existing potential in using the aforementioned factors as considerations to aid in determining the feasibility of VAD explantation. In light of its potential to circumvent OHT and drastically minimize the adverse effects of "conventional" surgical heart failure therapy, the continued examination of VADs and myocardial recovery can be strongly proposed, with hope resting on a more widely considered bridge-to-recovery trajectory.

We have now reached the crossroads in VAD implantation to support patients with heart failure secondary to non-ischemic dilative cardiomyopathy. A cornerstone in the foundation of the decision to wean or not to wean has been set and guidelines of how to traverse the weaning process have been laid out. However, the weaning strategy and the final decision to perform VAD explantation may merely represent the first of many steps in the management of sustaining myocardial recovery.

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Eidesstattliche Versicherung

„Ich, Mariano Francisco Del Maria Delmo Javier, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Predictors of feasibility of ventricular assist device explantation with stable myocardial recovery in chronic non-ischemic cardiomyopathy: a meta-analysis“; „Prädiktoren für die Durchführbarkeit der Explantation von ventrikulären Unterstützungssystemen mit stabiler Myokarderholung bei chronischer nicht-ischämischer Kardiomyopathie: eine Meta-Analyse“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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MyAuswertung – Statistik, Auswertung und Beratung
Wrangelstraße 22 | 10997 Berlin

Zur Vorlage bei der
Promotionskommission der
Charité – Universitätsmedizin Berlin

Kontakt:
MyAuswertung – Statistik, Auswertung und Beratung
Wrangelstraße 22 | 10997 Berlin
Mobil +49 (0) 170 231 43 98
Mail info@myauswertung.de

Berlin, den 04.04.2023

Bescheinigung nach § 8 Abs. 2a PO 2017

Sehr geehrter Herr Mariano Javier,

hiermit bestätige ich Ihnen zum Zwecke der Vorlage beim Promotionsbüro der Charité die erfolgte Beratung zu Ihrem Promotionsprojekt. Die Durchführung und Beschreibung der statistischen Methoden der mir vorgelegten Schrift ist in Art und Umfang für die Erarbeitung adäquat. Nach Einsicht in Datenbank und der mir vorgelegten Beschreibung von Methoden und Berechnungen sehe ich eine sorgfältige und detaillierte statistische Bearbeitung.

Ergänzend erfolgte eine Beratung zu deskriptiver und induktiver Statistik, Anwendung von „Cox-Regression", „Kaplan-Meier Methode" und „nicht-parametrische Testverfahren".

Ich wünsche Ihnen für die Zukunft alles Gute!

[redacted]

Murat Karaman
Akkreditierter Statistiker der Promotionskommission
MyAuswertung – Statistik Auswertung und Beratung
Wrangelstraße 22 | 10997 Berlin