

One year improvement of exercise capacity in patients with mechanical circulatory support as bridge to transplantation

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Abstract

Aims Mechanical circulatory support (MCS) results in substantial improvement of prognosis and functional capacity. Currently, duration of MCS as a bridge to transplantation (BTT) is often prolonged due to shortage of donor hearts. Because long-term results of exercise capacity after MCS are largely unknown, we studied serial cardiopulmonary exercise tests (CPETs) during the first year after MCS implantation.

Methods and results Cardiopulmonary exercise tests at 6 and 12 months after MCS implantation in BTT patients were retrospectively analysed, including clinical factors related to exercise capacity. A total of 105 MCS patients (67% male, 50 ± 12 years) underwent serial CPET at 6 and 12 months after implantation. Power (105 ± 35 to 114 ± 40 W; $P \leq 0.001$) and peak VO₂ per kilogram (pVO₂/kg) improved significantly (16.5 ± 5.0 to 17.2 ± 5.5 mL/kg/min ($P = 0.008$)). Improvement in pVO₂ between 6 and 12 months after LVAD implantation was not related to heart failure aetiology or haemodynamic severity prior to MCS. We identified maximal heart rate at exercise as an important factor for pVO₂. Younger age and lower BMI were related to further improvement. At 12 months, 25 (24%) patients had a normal exercise capacity (Weber classification A, pVO₂ > 20 mL/kg/min).

Conclusions Exercise capacity (power and pVO₂) increased significantly between 6 and 12 months after MCS independent of Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile or heart failure aetiology. Heart rate at exercise importantly relates to exercise capacity. This long-term improvement in exercise capacity is important information for the growing group of long-term MCS patients as this is critical for the quality of life of patients.

Keywords Mechanical circulatory support; Quality of life; Functional capacity; Cardiopulmonary exercise test. VO₂

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Introduction

Mechanical circulatory support (MCS) by a continuous-flow left ventricular assist device (cf-LVAD) has shown to improve survival and quality of life in selected patients with end-stage heart failure.^{1–4} The present generation of cf-LVADs consists of axial or centrifugal flow pumps operating at a fixed pump speed (RPM), thereby creating a totally different physiology than the native heart. Because of the

shortage of donor hearts, resulting in longer waiting time and the use of LVAD's as destination therapy, long-term MCS has increased substantially. In this respect, functional capacity after implantation is getting more and more important for a better quality of life and the opportunity to reintegrate into society.

Previous small studies reported improved exercise capacity after MCS compared with the situation prior to implantation, as assessed by cardiopulmonary exercise test (CPET).^{5–9}

However, information about long-term exercise capacity in MCS patients is currently sparse. Previously, lower age, aerobic training, and LVAD settings, such as pump speed, pump flow, and power, have been associated with improved exercise capacity after MCS.^{8–11} Aetiology of the cardiomyopathy was not associated with CPET results.⁸ Markers for cardiac function, such as left ventricular ejection fraction (LVEF), peak heart rate, right ventricular function, and aortic valve opening, have not consistently been associated with better CPET results.^{8–10}

At our centre, MCS patients perform a CPET, together with an echocardiogram at rest, laboratory test, and full examination, on a routine basis at 6 and 12 months after implantation. As a result, many data were collected over the years.

The aim of this study was to investigate whether exercise capacity during the first year of MCS treatment showed a long-term improvement, measured by CPET at 6 and 12 months after implantation, in a large cohort of MCS patients. Also, factors associated with exercise capacity were analysed, including aetiology of heart failure, echocardiographic parameters, markers for left ventricular unloading, heart failure medication, chronotropic (in)competence, and pre-operative Inter-agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification.¹²

Methods

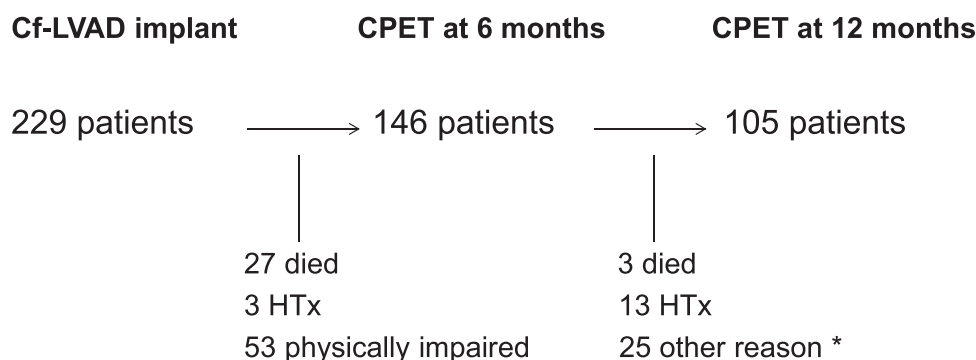
Study population

Between 2006 and 2017, 229 adult patients received MCS [HeartMate-II (HM-II, Abbott), HVAD (Heartware, Medtronic), or HeartMate3 (HM3, Abbott)] at the University Medical Center Utrecht, the Netherlands, all implanted as a bridge-to-transplantation (BTT). After MCS, patients underwent cardiac rehabilitation two times a week for 1 h per session under the supervision of a second-line physiotherapist. Outpatient rehabilitation started after discharge for a total duration of 6 weeks up to 3 months, conforming individual needs. During the training, patients improved their exercise tolerance on a treadmill/hometrainer and trained the large muscles for strength and endurance. Afterwards, patients are supported to improve or at least maintain the exercise performance achieved at the end of the rehabilitation programme. This study was approved by our institutional ethics committee.

Eighty-three patients did not perform a CPET at all in the first year following MCS implantation, because of physical impairment in 53 patients (23%), early heart transplantation in three patients (1%), and death in 27 patients (12%). At 6 months, 146 patients performed a CPET. Thereafter, 13 patients underwent a heart transplantation, three patients

Figure 1 Study population.

Study population



- * 7 admitted due to adverse event (gastro-intestinal bleeding, right heart failure, ventricular tachycardia)
 2 explanted, of whom 1 shortly thereafter urgent heart transplantation because of circulatory failure
 2 cf-LVAD replacement because of pump failure at 7 and 10 months, respectively
 11 physically impaired due to extracardiac comorbidity (e.g. stroke, severe back pain, invalidating dizziness, viral infection, inefficient pacemaker settings)
 3 logistically not possible

died, and 25 were physically unable to perform a CPET at 12 months, mainly due to extra-cardiac morbidity (Figure 1). Thus, 105 patients underwent sequential CPET both at 6 and 12 months after MCS implantation.

Routine cardiopulmonary exercise test, echocardiography, and laboratory testing

Cardiopulmonary exercise test was planned prospectively at 6 and 12 months after MCS, together with an echocardiogram at rest, blood test, and full examination. CPET was performed on a bicycle ergometer using a symptom-limited ramp protocol with an increase of workload by 10 Watt every minute. Respiratory gas analysis was analysed continuously (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany).

Peak VO₂ (pVO₂), peak VO₂ per kilogram (pVO₂/kg), percentage of predicted peak VO₂ (per kilogram) levels according to Jones,¹³ the anaerobic threshold (AT), the respiratory exchange ratio (RER), EqCO₂, maximal heart rate, and maximal workload were reported. The anaerobic threshold was defined as the oxygen uptake before the increase in the ventilatory equivalent for oxygen (VE/VO₂), without an increase in the ventilatory equivalent for carbon dioxide (VE/VCO₂), and using the V-slope method. The ventilatory response to exercise was defined as VE/VCO₂ (EqCO₂) at peak exercise.

Delta pVO₂ and delta pVO₂/kg were defined as the absolute difference between pVO₂(/kg) at 6 and 12 months. Results of CPET were reported by an independent cardiologist.

Echocardiography at rest was used to measure two-dimensional left ventricular dimensions. Furthermore, assessment of the right ventricular function by the tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler imaging (TDI-RV) and (intermittent) opening of the aortic valve were performed.

Laboratory tests included haemoglobin (g/dL), bilirubin (mg/dL), B-type natriuretic peptide (BNP) (pg/mL), and the kidney function, where the latter was divided into normal (estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m²) and moderately impaired (eGFR 30–60 mL/min/1.73 m²).

Statistical analysis

For this retrospective analysis, the results of the CPET were collected in a central database, together with baseline characteristics, results of echocardiogram at rest, laboratory results, and medication at 6 and 12 months. Data were extracted to IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) for statistical analysis.

Comparison of continuous variables between two groups was performed by a *t*-test or non-parametric test if not normally distributed. Dichotomous variables were compared by χ^2 or Fisher's exact test in unrelated variables and by McNemar in related variables. Correlation between continuous variables was tested using a Pearson or Spearman rank test. Analysis of factors related to differences between the two test moments was analysed by univariable and multivariable linear regression.

Results

Patient characteristics

A total of 105 patients (67% male, mean age 50 ± 12 years at MCS implantation) performed serial CPET in the first year following MCS implantation after a mean of 5.4 (±1.4) months and 12 (±1) months. Prior to MCS implantation 45% of patients were in INTERMACS profile 2 ('sliding on inotropes') and 29% were stable on inotropes (INTERMACS 3). Because of severe cardiogenic shock (INTERMACS 1), temporary mechanical support (Centrimag, intra-aortic balloon pump or extracorporeal membrane oxygenator) as bridge to implantation was necessary in 19% of the patients. Most patients (*n* = 75; 71%) received an HM-II, followed by HVAD in 22 patients (21%) and HM3 in eight patients (8%). The underlying aetiology of heart failure was a dilated cardiomyopathy

Table 1 Baseline characteristics of patients who performed serial CPET at 6 and 12 months after MCS (*n* = 105)

Baseline characteristics	
Gender, male (%)	70 (67%)
Age at MCS implantation (years, mean ± SD) II	50 ± 12
Device type	
HM-II (%)	75 (71.4%)
HVAD (%)	22 (21%)
HM3 (%)	8 (7.6%)
Aetiology	
Dilated	55 (52%)
Ischaemic	35 (33%)
Myocarditis	1 (1%)
Hypertrophic	1 (1%)
Peripartum	1 (1%)
Congenital	1 (1%)
Toxic	5 (5%)
Other	6 (6%)
INTERMACS profile	
1 with temporary support	20 (19%)
1 without temporary support	1 (1%)
2	47 (45%)
3	30 (29%)
4	6 (6%)
6	1 (1%)
Hospital duration, days (mean ± SD)	48 ± 22

HM-II, HeartMate-II; HM3, HeartMate 3; HVAD, HeartWare; INTERMACS, Inter-agency Registry for Mechanically Assisted Circulatory Support; II MCS, mechanical circulatory support.

(DCM) in 55 (52%) patients, and 35 (33%) patients suffered from ischaemic heart disease (IHD). Other aetiologies included myocarditis and toxic (chemotherapy-induced) cardiomyopathy (Table 1).

Cardiopulmonary exercise test

Patients achieved a maximal workload of 105 ± 35 Watt at 6 months, which increased to 114 ± 40 Watt ($P \leq 0.001$) at 12 months. The pVO₂ and pVO₂/kg at 6 months postoperatively were 1.26 ± 0.42 L/min ($53 \pm 12\%$ of predicted) and 16.5 ± 5.0 mL/kg/min ($52 \pm 12\%$ of predicted). Peak VO₂ further improved at 12 months after MCS both uncorrected (1.35 ± 0.46 L/min; $P \leq 0.001$) and corrected for body weight (17.2 ± 5.5 mL/kg/min; $P = 0.008$), corresponding to an absolute increase in pVO₂ of 7% (L/min). The percentage of the predicted pVO₂ increased to $57 \pm 12\%$ ($P \leq 0.001$) and to $55 \pm 13\%$ ($P \leq 0.001$) for pVO₂/kg. The AT increased from 10.8 ± 3.1 to 12.1 ± 3.7 mL/kg/min ($P \leq 0.001$). Both maximal heart rate (141 ± 26 bpm vs. 144 ± 26 bpm; $P = 0.178$) and EqCO₂ (36.1 ± 6.0 vs. 36.7 ± 5.8 ; $P = 0.162$) did not change

between 6 and 12 months. Interestingly, RER was significantly lower during the CPET at 12 months (1.21 ± 0.11 resp. 1.18 ± 0.11 ; $P = 0.021$), indicating lower anaerobic metabolism and/or effort (Table 2).¹⁴

At 12 months, 25 (24%) patients had a normal exercise capacity, according to the Weber classification (pVO₂ > 20 mL/kg/min, Weber A).¹⁵ This subgroup of patients (mean age 40 ± 13 years, 80% male) had a maximal work load of 158 ± 41 Watt, a pVO₂/kg of 24.6 ± 5.6 mL/kg/min, a RER of 1.18 ± 0.1 , and a peak heart rate of 164 ± 19 bpm ($91 \pm 8\%$ of maximal predicted heart rate).

Factors related to exercise capacity

Haemoglobin levels at 6 and 12 months after implantation were included in the analysis as anaemia is associated with worse CPET results due to lower oxygen-carrying capacity.¹⁴ Mean haemoglobin level at the first CPET was 12.9 ± 1.5 g/dL and increased to 13.4 ± 1.6 g/dL at the second CPET ($P \leq 0.001$), but no correlation was found between the

Table 2 Diagnostic results at serial follow-up after MCS implantation ($n = 105$)

	6 months after implant	12 months after implant	P-value
BMI (kg/m ² , mean \pm SD)	24.5 \pm 3.5	25.7 \pm 5.0	<0.001
CPET results			
Max workload (Watt, mean \pm SD)	105 \pm 35	114 \pm 40	<0.001
VO ₂ (L/min, mean \pm SD)	1.26 \pm 0.42	1.35 \pm 0.46	<0.001
VO ₂ % predicted (mean \pm SD)	53 \pm 12	57 \pm 12	<0.001
VO ₂ /kg (mL/kg/min, mean \pm SD)	16.5 \pm 5.0	17.2 \pm 5.5	0.008
VO ₂ /kg % predicted (mean \pm SD)	52 \pm 12	55 \pm 13	<0.001
Anaerobic threshold (mean \pm SD)	10.8 \pm 3.1	12.1 \pm 3.7	<0.001
Respiratory exchange ratio (mean \pm SD)	1.21 \pm 0.11	1.18 \pm 0.11	0.021
EqCO ₂ (mean \pm SD)	36.0 \pm 6.0	36.7 \pm 5.8	0.162
Max heart rate (bpm, mean \pm SD)	141 \pm 26	144 \pm 26	0.094
Percentage of max predicted heart rate (mean \pm SD)	83 \pm 14	85 \pm 14	0.055
Echocardiography			
LVEDD (mean \pm SD)	59 \pm 12	58 \pm 12	0.073
TAPSE (mean \pm SD)	12 \pm 3	13 \pm 3	0.637
TDI-RV (mean \pm SD)	6.1 \pm 1.6	6.4 \pm 2.1	0.640
Aortic valve opening (%)	18/68 (17%)	20/60 (19%)	0.302
Laboratory results			
Haemoglobin level (g/dL, mean \pm SD)	0.78 \pm 0.35	0.88 \pm 0.35	0.165
Bilirubin (mg/dL, mean \pm SD)	12.9 \pm 1.5	13.4 \pm 1.6	<0.001
BNP level (pg/mL, mean \pm SD)	151 \pm 113	190 \pm 143	0.398
Kidney function, eGFR >60 mL/min/1.73 m ² (%)	85/104 (81%)	80/104 (76%)	0.227
Kidney function, eGFR 30–60 mL/min/1.73 m ² (%)	19/104 (18%)	24/104 (23%)	0.344
Heart failure medication II			
ACE inhibitor/ARB (%)	54/97 (56%)	56/94 (60%)	0.289
Beta-blocker (%)	11/97 (11%)	17/94 (18%)	0.063
Antihypertensive (%)	6/97 (6%)	7/94 (7%)	1.000
Anti-arrhythmics (%)	44/97 (45%)	47/94 (50%)	0.727
Sildenafil (%)	24/97 (25%)	23/94 (24%)	1.000
Diuretic (%)	59/96 (62%)	52/93 (56%)	0.092

ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CPET, cardiopulmonary exercise test; eGFR, estimated glomerular filtration rate; EqCO₂, ventilatory equivalent for carbon dioxide; II ACE inhibitor, angiotensin converting enzyme inhibitor; LVEDD, two-dimensional left ventricular end-diastolic diameter, measured in parasternal long axis (mm); percentage of max predicted heart rate: predicted maximal heart rate, 220-age; TAPSE, tricuspid annular plane systolic excursion (mm); TDI-RV, peak systolic tissue Doppler value of the right ventricle (cm/s); VO₂/kg % predicted, percentage of predicted value according to Jones (mL/kg/min).

increase in haemoglobin levels and the increase (delta) in pVO₂/kg ($r = 0.183$, $P = 0.068$). BNP levels (151 ± 113 pg/mL vs. 190 ± 143 pg/mL; $P = 0.398$) and left ventricular end-diastolic diameter did not change between 6 and 12 months after MCS suggesting a similar amount of LV unloading over time (Table 2). Right ventricular function, assessed by TAPSE and TDI-RV, did not change between 6 and 12 months after MCS. Furthermore, kidney function as a marker of organ perfusion, bilirubin level as a marker for right ventricular failure, heart failure medication affecting the afterload (i.e. ACE inhibitors), and heart rate (beta-blocker) were analysed as these factors might influence the CPET results. However, no difference in kidney function, bilirubin level, and heart failure medication was noted (Table 2).

Subgroup analyses

Dilated cardiomyopathy versus ischaemic heart disease

Previous studies did not show differences in exercise capacity between patients with IHD and a non-ischaemic cardiomyopathy, probably related to small sample sizes.^{16,17} In our analysis, patients with a DCM ($n = 55$) had significant better CPET results both at 6 and 12 months after implantation compared with patients with IHD ($n = 35$). At 6 months, pVO₂ was 1.35 ± 0.46 L/min in DCM patients and 1.11 ± 0.26 L/min in patients with IHD ($P = 0.011$). This increased to 1.46 ± 0.45 L/min (DCM) versus 1.18 ± 0.36 L/min (IHD) at 12 months ($P = 0.003$). Maximal workload was also substantially higher in DCM compared with IHD patients both at 6 months (110 ± 36 Watt vs. 90 ± 25 Watt; $P = 0.014$) and 12 months (120 ± 39 Watt vs. 99 ± 33 Watt; $P = 0.015$) after implantation. Importantly, the improvement in pVO₂ (delta pVO₂) and pVO₂/kg (delta pVO₂/kg) from 6 to 12 months was similar in both groups ($P = 0.27$ and $P = 0.23$), as shown in Table 3. Age, gender, heart failure medication, BNP, and haemoglobin levels did not differ between DCM and IHD patients.

INTERMACS profile

As patients with INTERMACS profile 1 at time of implantation are in a considerably worse condition, we compared the CPET results of these patients with the results of patients in INTERMACS profile 2 and 3. At both test moments, CPET results were comparable between INTERMACS 1 ($n = 21$) and INTERMACS 2 + 3 ($n = 77$), both uncorrected and corrected for body weight. At 6 months, pVO₂ was 1.31 ± 0.52 and 1.25 ± 0.40 L/min ($P = 0.806$) and pVO₂/kg 17.4 ± 6.1 and 16.2 ± 4.8 mL/kg/min ($P = 0.556$) for INTERMACS 1 and INTERMACS 2 + 3, respectively. At 12 months, pVO₂ was 1.35 ± 0.56 and 1.37 ± 0.44 L/min ($P = 0.792$) and pVO₂/kg 17.4 ± 7.1 and 17.2 ± 5.2 mL/kg/min ($P = 0.710$), respectively. Delta pVO₂ ($P = 0.216$) and pVO₂/kg ($P = 0.188$) were also similar between INTERMACS 1 and 2 + 3.

Chronotropic (in)competence

Previous studies evaluating the chronotropic response after MCS showed a significantly lower maximal heart rate during CPET compared with healthy individuals.^{18,19} Therefore, we compared exercise capacity in patients with chronotropic incompetence (CI) versus patients without CI, defined as a peak heart rate <80% of the predicted maximal heart rate for age (220-age). At 6 months, 67 patients (46%) met the criteria for CI, and 79 (54%) patients reached a maximal heart rate above 80% of predicted (not CI). Compared with patients without CI, patients with CI had a significantly lower pVO₂ (1.07 ± 0.24 L/min vs. 1.37 ± 0.45 L/min; $P < 0.001$) and pVO₂/kg (14.1 ± 2.8 mL/kg/min vs. 18.0 ± 5.4 mL/kg/min; $P < 0.001$). Importantly, RER did not differ between the groups (1.21 ± 0.11 , $P = 0.972$). The importance of heart rate was further illustrated by the presence of a significant correlation between the percentage of predicted maximal heart rate and pVO₂/kg at both 6 months ($r = 0.299$; $P = 0.002$) and 12 months ($r = 0.310$; $P = 0.001$) after implantation as a continuous variable.

Patients with one cardiopulmonary exercise test (6 months only)

Selection bias may be introduced as 53 patients were physically not able to perform any CPET in the first year after MCS implantation and 41 only performed one CPET at 6 months (physically impaired, died, or received heart transplantation). To gain more insight into the reasons for physical impairment, the 1 year incidence of adverse events was registered. In patients who were not able to perform any CPET, the incidence of stroke (haemorrhagic or ischaemic), VAD-related infection, sepsis, and major bleeding were higher compared with patients who performed a CPET at 6 and 12 months (0.23, 0.25, 0.54, and 0.90 events per patient year vs. 0.12, 0.13, 0.16, and 0.62).

Importantly, no differences were observed in patient characteristics including age, gender, aetiology, INTERMACS profile, and duration of hospitalization in patients who performed no or only one CPET compared with patients who performed a CPET at both 6 and 12 months. Furthermore, pVO₂(/kg), echocardiographic, and laboratory results did not differ between patients who performed one CPET and patients who performed two CPETs during the first year after implantation.

Predictors for pVO₂/kg over time

Using linear regression analysis, factors contributing to the difference between pVO₂/kg at 6 and 12 months (delta pVO₂/kg, Appendix A) were identified. Multivariable linear regression analysis including CPET results at 6 months, age, and gender, resulted in a significant model; $F(7, 89) = 4.879$, $P < 0.001$, explaining 22% of the variance in delta VO₂/kg

Table 3 Diagnostic results in dilated and ischaemic cardiomyopathy (*n* = 90)

	Dilated cardiomyopathy	Ischaemic cardiomyopathy	<i>P</i> value
Baseline			
Number of patients (%)	55 (61%)	35 (39%)	
Age at implant	48.2 ± 14	53.1 ± 8.1	0.181
Male (%)	38 (69%)	23 (66%)	0.738
INTERMACS 1 with temporary support	7 (13%)	12 (34%)	0.015
INTERMACS 1 without temporary support	0 (0%)	1 (3%)	0.389
INTERMACS 2	25 (46%)	15 (43%)	0.809
INTERMACS 3	18 (33%)	5 (14%)	0.051
INTERMACS 4	4 (7%)	2 (6%)	1.000
INTERMACS 6	1 (2%)	0 (0%)	1.000
HM-II	42 (76.4%)	22 (63%)	0.168
HVAD II	10 (18.2%)	10 (26%)	0.248
HM3	3 (5.5%)	3 (9%)	0.674
Diagnostics: 6 months			
Body mass index (kg/m ² , mean ± SD)	24.4 ± 3.7	24.7 ± 3.1	0.524
Max load (Watt, mean ± SD)	110 ± 36	90 ± 25	0.014
VO ₂ (L/min, mean ± SD)	1.35 ± 0.46	1.11 ± 0.27	0.011
VO ₂ /kg (mL/kg/min, mean ± SD)	17.4 ± 5.5	15.1 ± 3.7	0.057
Anaerobic threshold (mean ± SD)	11.3 ± 3.4	10.3 ± 2.6	0.250
Respiratory exchange ratio (mean ± SD)	1.20 ± 0.11	1.22 ± 0.10	0.312
Max heart rate (bpm, mean ± SD)	142 ± 26	133 ± 26	0.127
EqCO ₂ (mean ± SD)	35.3 ± 6.2	38.1 ± 4.6	0.021
Haemoglobin (g/dL, mean ± SD)	13 ± 1.7	12.6 ± 1.3	0.444
BNP (pg/mL, mean ± SD)	186 ± 162	211 ± 100	0.061
Bilirubin (mg/dL, mean ± SD)	0.86 ± 0.44	0.71 ± 0.22	0.242
Use of beta-blocker (%)	5/50 (10%)	4/33 (12%)	1.000
Use of ACE inhibitor/ARB (%)	30/50 (60%)	16/33 (49%)	0.302
Use of antihypertensive (%)	5/50 (10%)	1/33 (3%)	0.395
Diagnostics: 12 months			
Body mass index (kg/m ² , mean ± SD)	25.3 ± 3.8	26.5 ± 6.5	0.413
Max load (Watt, mean ± SD)	120 ± 39	99 ± 33	0.015
VO ₂ (L/min, mean ± SD)	1.46 ± 0.45	1.18 ± 0.36	0.003
VO ₂ /kg (mL/kg/min, mean ± SD)	18.3 ± 5.3	15.3 ± 4.5	0.002
Anaerobic threshold (mean ± SD)	12.2 ± 3.6	11.5 ± 3.3	0.477
Respiratory exchange ratio (mean ± SD)	1.18 ± 0.09	1.17 ± 0.11	0.659
Max heart rate (bpm, mean ± SD)	147 ± 26	137 ± 26	0.166
EqCO ₂ (mean ± SD)	35.6 ± 5.0	38.9 ± 5.8	0.008
Haemoglobin (g/dL, mean ± SD)	13.6 ± 1.7	13 ± 1.6	0.137
BNP (pg/mL, mean ± SD)	115 ± 88	190 ± 126	0.390
Bilirubin (mg/dL, mean ± SD)	0.88 ± 0.4	0.8 ± 0.3	0.092
Use of beta-blocker (%)	6/51 (11%)	6/30 (17%)	0.345
Use of ACE inhibitor/ARB (%)	32/51 (63%)	16/30 (53%)	0.405
Use of antihypertensive (%)	5/51 (9%)	2/30 (6%)	1.000
Delta VO ₂ (L/min, mean ± SD)	0.1 ± 2.3	0.1 ± 3.5	0.27
Delta VO ₂ /kg (mL/kg/min, mean ± SD)	0.9 ± 2.8	0.2 ± 2.2	0.23

BNP, B-type natriuretic peptide; EqCO₂, ventilatory equivalent for carbon dioxide; HM-II, HeartMate-II; HM3, HeartMate 3; II HVAD, HeartWare; INTERMACS, Inter-agency Registry for Mechanically Assisted Circulatory Support.

(adjusted $R^2 = 0.22$). Significant predictors for a higher delta pVO₂/kg were a younger age, a lower body mass index, lower maximal work load, and anaerobic threshold during the CPET at 6 months.

An improvement of peak oxygen uptake >6% on repeated CPET, which is defined clinically important in heart failure patients, was observed in 46 (44%) of the patients.²⁰

Discussion

This single centre study is the first study to examine exercise capacity in a large cohort of MCS patients during 1 year of follow-up. It demonstrated an increase of maximal workload by

9% and pVO₂ by 7% between 6 and 12 months postoperatively. Although this increase seems only modest, a recent position paper on the role of CPET in heart failure patients showed that an increase of >6% in maximal exercise capacity is considered clinically relevant and related to improved prognosis.²⁰ This was observed in almost half of the patients. Furthermore, approximately a quarter of patients had a normal maximal exercise capacity after 1 year, defined as a pVO₂/kg > 20 mL/kg/min according to Weber.¹⁵

The improvement in exercise capacity could not be explained by increasing effort or motivation, as the respiratory exchange ratio was lower at 12 months while pVO₂ values increased. Although a considerable amount of patients were not able to perform sequential exercise testing at 6 and 12 months,

selection bias seems unlikely. No differences were observed in pVO₂ at 6 months between patients who were physically able to perform two CPETs and those who performed a CPET at 6 months only. Patient characteristics, echocardiographic, and laboratory results were also similar, and the most important reason for drop-out was extra-cardiac morbidity.

The explanation for the further improvement of exercise performance over the first year after LVAD implantation is probably multifactorial.^{21–23} As a consequence of the continuous flow, haemodynamics change dramatically with MCS. Device output is mainly determined by the pump speed and the preload and afterload of the left ventricle. During exercise, total output might be further enhanced by residual left ventricular output through the aortic valve. As mentioned earlier, in cf-LVADs, the pump speed (RPM) presently is fixed, independent of the physical activity of the patient.²³ In our study, LVAD settings during the exercise test were not changed. Earlier studies evaluating the effect of increasing pump speed also showed an increase in pVO₂.^{17,24} Although performed in a small number of patients, this might advocate the need for an algorithm to adapt speed settings during exercise in cf-LVADs.

Previous reports did not show a clear correlation between right ventricular function and exercise capacity in MCS recipients.^{10,16,17} More recently, no correlation was found between right ventricular ejection fraction (measured by four-dimensional cardiac computed tomography) and pVO₂.²⁵ In line with these data, our study observed an identical right ventricular function (TAPSE and TDI-RV) at 6 and 12 months after MCS, while maximal exercise performance increased, further negating the importance of RV function for exercise capacity in MCS patients.

On the other hand, maximal heart rate seems to play an important role in exercise capacity after MCS.^{26,27} Approximately half of the MCS recipients in our study were chronotropic incompetent, as was also observed in previous studies.^{18,19,26}

Furthermore, we demonstrated a significant correlation between maximal heart rate and pVO₂/kg, and patients who achieved a normal exercise capacity had a peak heart rate >90% of predicted during exercise. Therefore, an impaired chronotropic response might largely explain the relatively limited maximal exercise performance in the majority of MCS patients.

Nevertheless, the improvement of maximal exercise capacity between 6 and 12 months in our study did not go hand in hand with a significant additional increase in maximal heart rate. So other factors must also contribute to the improvement of pVO₂ beyond 6 months postoperatively.

Despite the significantly higher haemoglobin levels at 12 months, it is not obvious that this is an important factor because the (small) increase in haemoglobin did not correlate with delta pVO₂/kg. Unfortunately, we were not informed about the iron status (and possible iron deficiency) in these patients, as it is known that iron deficiency is associated with

reduced exercise capacity in heart failure patients, improving by intravenous iron supplementation.²⁸

Additionally, increased muscle strength may also contribute to improved exercise capacity over time, which is probably enhanced by the cardiac rehabilitation programme after MCS.²⁹

We identified that the magnitude of improvement of exercise capacity was more pronounced in younger patients and in those with a lower BMI. The fact that a lower maximal workload and AT at 6 months were predictive of further improvement at 12 months illustrates that cf-LVAD patients might benefit from prolonged cardiac rehabilitation, extending even beyond 6 months after implantation. Cardiac rehabilitation has already demonstrated to affect maximal exercise capacity in MCS patients positively, together with an increased muscle strength.²⁹ However, the effect of long-term cardiac rehabilitation on maximal exercise capacity in chronic MCS has not been studied yet.

Subgroups

In this study, patients with a DCM showed a better exercise capacity than patients with IHD at both test moments, which could not be explained by differences in age and/or gender. Hypothetically, a lower maximal exercise performance in IHD might relate to the presence of generalized atherosclerosis and a subsequent decrease in organ and muscle perfusion compared with DCM patients, in which primarily the heart is affected.

Another important finding was that maximal exercise capacity in INTERMACS 1 patients was identical to that of INTERMACS 2 + 3 patients. Although survival differs substantially, improvement in exercise capacity in patients surviving the first year is similar between INTERMACS 1 and 2 + 3. These findings illustrate that functional 'recovery' after receiving MCS is substantial, even for haemodynamically severely compromised patients.

This does not correspond to the findings of a recent study by Gustafsson *et al.*, which identified an INTERMACS profile 1 or 2 before HM 3 implantation to be predictive of a lower exercise capacity (i.e. 6 min walk distance below 300 m) at 6 months postoperatively. However, because of the relatively low number of INTERMACS 1 and 2 patients included in that study, the results may be less reliable and cannot be fully compared with our group of LVAD patients, consisting 20% INTERMACS 1 and 45% INTERMACS 2.³⁰

The detrimental effect of an impaired chronotropic response on maximal exercise capacity in MCS patients advocates the need for studies evaluating the mechanisms of chronotropic incompetence in these patients and analysis of interventions to increase maximal heart rate, for example, a

more aggressive rate response in patients with pacing devices.²⁶

Limitations

The study sample consisted of patients with MCS implanted as a bridge to transplantation. Results of CPET might not be extrapolated to implantations as destination therapy, as these patients generally are older and have a worse outcome than patients who received MCS as a bridge to transplantation. Although echocardiograms during the actual CPET were not made, resting echocardiograms showed no difference in aortic valve opening at 6 and 12 months, suggesting comparable intrinsic contractile contribution. The effect of adaptive pump speed changes during exercise was not investigated in the current study but may lead to further improvement in exercise capacity based on the study by Jung *et al.*¹⁷ This may also account for optimization of pacemaker settings, for example, rate response, as a substantial number of patients on MCS has a cardiac resynchronization device and/or implantable cardioverter defibrillator *in situ*.³¹ The improvement between 6 and 12 months was more pronounced in pVO₂ (7%) than pVO₂/kg (4%). This is likely related to the increase in body weight over time.

Conclusions

This study demonstrates a significant increase in exercise capacity between 6 and 12 months after MCS in end-stage heart failure patients. Maximal heart rate at exercise plays

an important role in this improved exercise capacity. RV function seems to be less important. DCM patients generally have a better exercise capacity after MCS than patients with IHD, irrespective of age, but improvement over time was equal in both groups. Another important finding was that patients in INTERMACS 1 at the time of LVAD implantation, meaning severe cardiogenic shock, are able to achieve the same exercise capacity after MCS as less sick patients (INTERMACS 2 and 3). The improvement of exercise capacity over time after MCS correlates with younger age and lower BMI at the time of LVAD implantation and highlights the importance of prolonged cardiac rehabilitation.

Our results are important information for the growing group of patients on long-term MCS, as improvement in exercise capacity is critical for the quality of life of patients.

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Conflict of interest

None declared.

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Appendix A: Linear regression analysis on delta VO₂/kg

Then, multivariable linear regression was performed, including the variables of the CPET at 6 months as well as age and gender, in relation to the delta VO₂/kg.

Methods

To assess the association between the results of the CPET at 6 months and the delta VO₂/kg, which was normally distributed, linear regression analysis was performed.

First, univariable analysis was performed, including the results of the CPET at 6 months and the demographic parameters, age and gender, using Pearson correlation.

Results

The assumptions for linear regression were met. Multivariable linear regression built a significant model, $F(7, 89) = 4.879$, $P < 0.001$, explaining 22% of the variance in delta VO₂/kg (adjusted $R^2 = 0.22$). Significant predictors for a higher delta VO₂/kg were a younger age and a lower body mass index, maximal work load, and anaerobic threshold during the CPET at 6 months (*Table A1*).

Table A1 Results of the multivariable linear regression analysis on the absolute difference between pVO₂/kg from 6 to 12 months

	Standardized beta coefficient	95% CI lower	Upper	P-value
Age at implant	−0.265	−0.111	−0.004	0.034
Gender	−0.105	−1.783	0.599	0.326
BMI	−0.318	−0.389	−0.089	0.002
Max workload	−0.367	0.005	0.051	0.017
Anaerobic threshold	−0.524	−0.655	−0.239	<0.001
EqCO ₂	0.128	−0.042	0.157	0.255
Percentage max HR	−0.033	−0.046	0.033	0.753