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Impact of Left Ventricular Assist Device on physical capacity in patients with end-stage heart failure

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Table of contents

Abstract

Background

The use of left ventricular assist devices (LVAD) widely increased in the past decade due to the lack of donor organs and the rising prevalence of heart failure. This therapy should lead patients in good condition to heart transplantation (bridge to transplant) or improve their quality of life (destination therapy). LVAD support is nowadays considered as an alternative to heart transplantation, however improvement in exercise performance is inconsistently demonstrated. The current study sought to quantitate physical capacity prior and subsequent LVAD implantation in order to assess the impact of this therapy.

Methods and Results

This study is a quantitative, observational, prospective, mono-centric trial which aimed to assess exercise capacity and its changes prior and subsequent LVAD implantation, using cardiopulmonary exercise testing (CPET), in patients suffering from refractory end-stage heart failure undergoing LVAD therapy with HeartMate 3 between 2017 and 2018 at the cardiac surgery department at CHUV. 21 patients underwent LVAD therapy during the study period, yet only 5 were included. CPET were completed an average of 11 months following implantation. Although VO_2^{max} improved by approximately 30% subsequent LVAD implantation, from 9,60 ± 3,88 ml/kg/min to 12,46 ± 3,16 (t-test=-2,424; ddl=4; p=0,072), it was not statistically significant and remained considerably lower than predicted values. Nonetheless, improvement by at least one NYHA class was seen in 100% of patients, with 80% improving by two classes. As a result of the limited study sample size, firm reliance lacks between patients related clinical parameters and the variability in improvement of peak VO_2.

Conclusion

Whereas VO_2^{max} improves on LVAD support, but not significantly, it provides an adequate functional capacity suitable for daily living activities. Yet, the link between peak VO_2, everyday tasks and quality of life requires further investigations in LVAD patients. Further studies should focus towards identifying predictive factors associated with lack of improvement in VO_2^{max} and exertional capabilities in order to proceed with LVAD treatment concordant with patients' values, objectives and expectations.

Introduction

Heart failure is a syndrome in which the heart fails to both provide the organism with sufficient blood flow and meet its need for oxygen in order to maintain an optimal physiological function (1)(2). This condition leads to a progressive deterioration of functional capacity and quality of life. (3) This syndrome is a major public health concern due to its dark prognosis, with a 5 year survival rate of 51,5% and 29,5% at 10 years (4), 2012 annual costs estimated to be $30.9 billions in the USA (5) and its rising incidence and prevalence. The latter being approximately 1-2% of the adult population in developed countries (1). In 2005 a study conducted by Meyer and al. demonstrated that the heart failure event rate was 64,9 per 100'000 adult inhabitants of Switzerland, with a predominant incidence in the population aged over 65 (6). This burden is likely to increase in the next decades (5), especially in the elderly group. This is probably due to the ageing population and a better management of myocardial infraction (7).

Current state of the art treatment for end-stage heart failure is heart transplantation (8) but the shortage of organ donors and the growing waiting list result in an increasing discrepancy that needs to be balanced with other alternatives. This widening gap can be observed in the Swisstransplant annual reports between 2005 and 2017 with an increase of 235% of patients on the waiting list but a minor rise in heart transplants, from 33 to 40. This makes approximately 1 graft for 2 potential recipients in 2005 and 1 graft for 4 potential recipients in 2017. Due to this tendency and the paucity of effective medical therapies (9)(10), alternative treatments are crucial to overcome this burden.

Left Ventricular Assist Device (LVAD) is a pump which aims to unload the heart by pumping blood from the apex of the left ventricle and send it directly to the ascending aorta in order to restore an adequate blood flow which should allow improvement of the function of every organ. There are two major indications for a LVAD implantation: As a Bridge To Transplant (BTT), to increase the chance of getting a heart transplantation for the patients on the waiting list and as Destination Therapy (DT), for those who are not eligible for heart transplantation (11). It is nowadays considered as an alternative to heart transplantation (12).

Since the first implantation of a LVAD by Dr. Liotta in 1963 in Houston (13), the use of this technology widely expanded as a treatment of advanced heart failure, with approximately 2500 devices implanted every year (14).
The rise in devices implantation can probably be explained by its undeniable efficacy in end-stage heart failure therapy (15), devices technical development and miniaturization throughout years.

The vast majority of recently implanted LVADs are continuous flow (CF) pumps, operating at a fixed speed, due to their life span up to 10 years (16), 1 and 2 year survival rate of 80% and 70% respectively succeeding implantation (14), as well as the substantially decreased incidence of complications compared to pulsatile pumps (17)(18). The latest generation of CF-LVAD is HeartMate 3 (Abbott Laboratories, Chicago, IL, USA), a fully magnetically levitated centrifugal-flow pump, which generates an intrinsic artificial pump pulse in order to potentially decrease systemic effects of loss of pulsatile flow (19).

LVAD support has become an effective therapy for end-stage heart failure as well as an alternative to heart transplantation but remains an invasive surgical procedure engendering significant human and economic resources investment. Existing literature emphasized the clinical benefits on physical capacity and quality of life succeeding LVAD implantation (3)(16)(20)(21), but none have been conducted in Switzerland.
One important patient-centered outcome after permanent or semi-permanent mechanical circulatory support (MCS) is that exercise capacity should be suitable for daily living activities which should be correlated with an improved quality of life. In light of the increasing use of MCS and long term support duration, it is fundamental to objectify the impact of these devices using cardio-pulmonary exercise tests in order to demonstrate its clinical benefits on exercise capacity in patients suffering from end-stage heart failure.

Research question

What are the clinical outcomes on physical capacity of LVAD implantation in patients with end-stage heart failure?

Methods

Study design

The study is a quantitative mono-centric observational prospective trial based in the cardiac surgery department at CHUV, including patients with end-stage heart failure that underwent LVAD implantation with HeartMate 3 between 2017 and 2018. The research was considered as risk category A and was conducted within the scope of the « Ordinance relative to the research on human beings » (HRO) in accordance with the Swiss law.

Patient selection

We selected patients implanted with HeartMate 3 who performed a pre-operative and a post-operative CPET. Patients who performed a CPET prior LVAD implantation only were convocated in order to perform a post-operative CPET 8 to 12 months post-procedure. The post-operative clinical exercise tests, which are included in the routine follow-up of patients implanted with a LVAD, were carried out during the iterative medical check-ups through project leader's daily clinical practice at CHUV.
Inclusion criteria were: patient with end-stage heart failure eligible for LVAD implantation as a BTT or DT or BTC at CHUV, free and informed consent to participate in this study and age ≥18 years. Exclusion criteria were: patients too hemodynamically unstable to undergo functional testing post-LVAD implantation, any other severe condition than heart failure in compromising the realization of a CPET and mobility-limited people. Every patient were ambulatory and in stable condition.

Outcomes

The primary outcome was to quantify physical capacity on patients with refractory end-stage heart failure undergoing LVAD therapy with HeartMate 3 between 2017 and 2018 at the

cardiac surgery department at CHUV, using clinical exercise tests post-surgery. The generated data was compared with the functional testing results prior LVAD implantation which allowed us to objectify and assess a potential change in participants' physical performances and analyze the impact of this therapy.
The study's secondary endpoint was to correlate participants' clinical parameters and concomitant comorbidities with the functional testing results in order to identify patient's related factors which may influence the outcome. Hopefully, this could, in the future, guide decision-making to proceed with LVAD treatment concordant with patient's values, objectives and expectations.

CPET

In order to assess exercise capacity, participants performed a symptom-limited CPET, on a treadmill ergometer (Valiant 2, Lode BV, The Netherlands) or a cyclo-ergometer (Ergoselect 200, Ergoline GmbH, Germany) with breath-by-breath ventilatory gas exchange measurement, following an individualized ramp stress protocol, pre- and post-LVAD implantation at CHUV.
CPET belongs to the standard clinical evaluation of patients with heart failure and is routinely done as part of the pre-LVAD and pre-transplant evaluation. It provides a global evaluation of the integrative exercise response involving the cardiovascular, pulmonary and musculoskeletal system (22). This clinical tool has seen an increase in its spectrum use, notably for the objective determination of functional capacity and evaluation of patient's response to specific therapeutic interventions (22)(23)(24).
Participants were encouraged to exercise until exertion which was quantified using the modified Borg Scale, during or immediately after CPET, with numeric values ranging from 0 to 10. A rating of 0 suggests no feeling of exertion, values of 7 and higher are indicative of very hard, extremely hard and maximal exertion.

Data collection and definitions

Physiological data measured throughout CPET and recovery were oxygen uptake (VO_2), ventilatory efficiency (VE/VCO_2), respiratory exchange ratio (RER: the ratio of VCO_2/VO_2), VO_2 at anaerobic threshold, electrocardiographic (ECG) tracing and heart rate (HR). The ergo-spirometry system was carefully calibrated on a regular basis.
Physical capacity, functional capacity and exercise capacity were defined by the maximal amount of exertion a subject can sustain, and was clinically quantitated by measuring maximal oxygen uptake (VO_2^{max} or peak VO_2) during CPET. VO_2^{max} is the gold standard measure to assess exercise capacity as it represents the maximal level of oxidative metabolism attainable involving large muscle groups (22). If a clear plateau was not achieved before symptom limitation of exercise, peak VO_2, the highest VO_2 achieved during the last 30 seconds of maximal exercise, was used as an estimation of VO_2^{max} and as an expression of physical capacity. The Wasserman/Hansen equation was used to calculate predicted VO_2^{max}. RER and the modified Borg rating of perceived exertion scale were used to assess the quality of the exercise effort.

Participants' baseline characteristics, concomitant co-morbidities, heart failure etiology, medication at discharge, NYHA class prior LVAD implantation, post-operative adverse events, exercise and gas-exchange variables of the pre-operative CPET were collected retrospectively

via the softwares “Soarian” and “Archimède” to create a database, while post-operative NYHA class, peri- and post-operative adverse events, post-operative CPET’s exercise variables and gas-exchange variables were collected prospectively. Baseline characteristics and medication were collected at hospital discharge. Co-morbidities were defined by physician’s diagnosis at the time of LVAD implantation. Left-ventricular ejection fraction, pulmonary hypertension and valvulopathies were recorded from transthoracic echocardiography during the pre-LVAD evaluation. Post-operative NYHA class was collected during the medical follow-up at 9 months after discharge. Pump speed was optimized at the time of implantation, before discharge and, if necessary, during the iterative ambulatory LVAD controls based on clinical events. When several CPET were performed prior to LVAD implantation, we used the most exhaustive and nearest test to the date of surgery.

Statistical analysis

Data and statistical analysis were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA, Version 16.16.5) and IBM SPSS Statistics (IBM Corporation, Armonk, NY, USA, Version 25). Dichotomous variables are presented as percentage, continuous variables are presented as mean, ± standard deviation and median. Normality was tested using Shapiro-Wilk test. Pre- and post-operative CPET results were compared using a Paired Student’s t-test in order to demonstrate whether differences in clinical exercise testing parameters occurred after LVAD implantation. Means between parameters prior and subsequent LVAD implantation were compared with a Paired Student’s t-test for normally distributed quantitative variables and a Wilcoxon signed-rank test as the non-parametric equivalent. The Pearson’s correlation, contingency coefficient, linear regression and one-way ANOVA were used to measure the association between clinical parameters and changes in peak VO2 as well as NYHA functional class. Statistical significance was defined as $p < 0,05$.

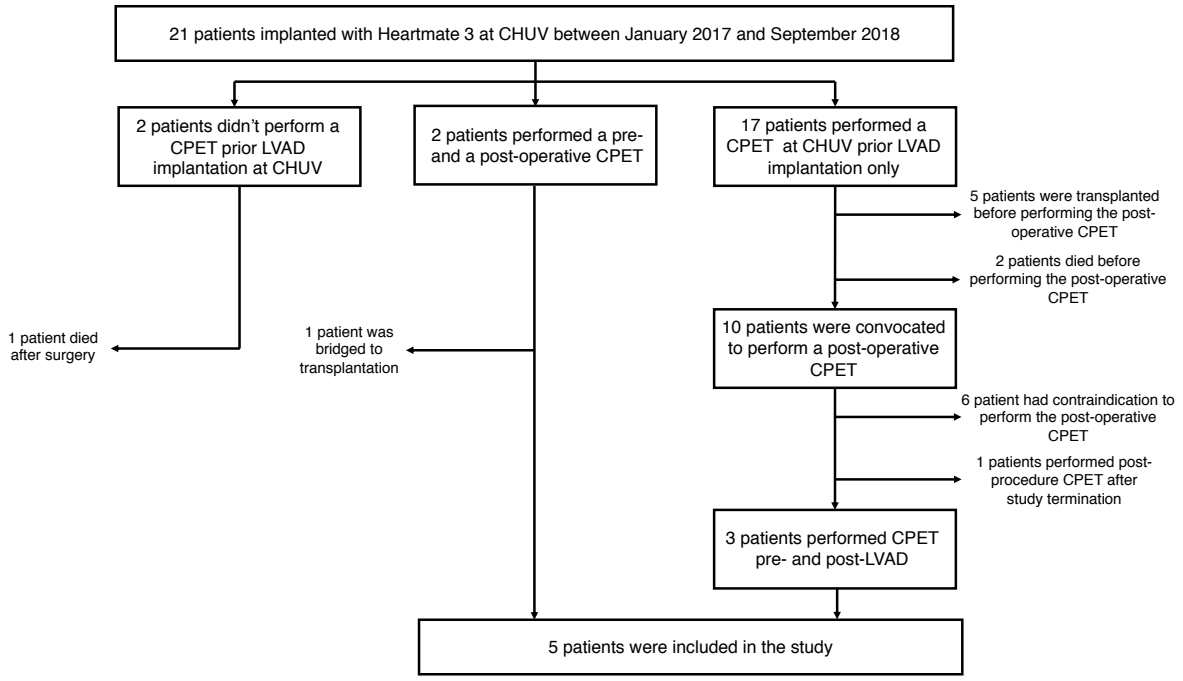
Ethical consideration

This research project was approved by the Swiss Ethics Committee on research involving humans (CER-VD) and was conducted in accordance with the Declaration of Helsinki (BASEC ID: 2017-01425). All participants signed informed consent.

Results

Between January 2017 and September 2018, 21 patients underwent LVAD implantation with HeartMate 3 at CHUV. Two patients didn’t perform a CPET at CHUV prior LVAD implantation, five patients were bridged to transplantation before undergoing the post-operative CPET, two patients died before performing the post-procedure CPET, six patients were not fit to perform the post-operative CPET, one didn’t perform the post-procedure CPET before study termination and were therefore excluded. Thus, five patients performed CPET both pre- and post-LVAD implantation, with anaerobic threshold reached, and were included in the analysis. Patient’s selection is displayed on Figure 1.

Figure 1. Patient cohort.



Study population consisted of 5 (100%) males. Average age at LVAD implantation was 56,80 ± 12,77 years. Baseline characteristics of the study cohort are presented in Table 1. All patients suffered from end-stage heart failure with a mean ejection fraction of 22,20% ± 6,35%. Heart failure etiology prior LVAD implantation was ischemic cardiopathy in 3 patients (60%) and non-ischemic in 2 patients (40%). Two patients (40%) had cardiac surgeries prior LVAD implantation, those being mitral valve replacement (n=1, 20%) and coronary artery bypass graft (n=1, 20%), moreover 80% (n=4) had a cardiac resynchronization therapy implantable cardioverter defibrillator (CRT-D). LVAD was implanted as BTT in 3 patients (60%), whereas 1 patients was implanted as DT (20%) and 1 was implanted as BTD (20%). Surgery was elective for 4 patients (80%) while 1 patient (20%) underwent emergency surgery for a cardiogenic shock. Mean operative duration was 219,60 ± 44,46 minutes and 77,80 ± 13,16 minutes for extracorporeal circulation duration. Three patients (60%) underwent concomitant cardiac procedure at time of surgery, being closure of atrial sepat defect (n=1, 20%), left atrial appendage exclusion (n=1, 20%) and extracorporeal membrane oxygenation (ECMO) implantation (n=1, 20%). Median length of hospital stay was 37 days (range: 21–131) with a median stay of 4 days (range: 2–66) in the intensive care unit (ICU). Pump settings were adjusted ambulatory, attaining mean values of 4,42 ± 0,47 L/min for pump flow, 5470 ± 139,64 RPM for pump speed, 4,40 ± 0,54 Watts for pump power and 4,44 ± 1,03 for pulsatility index by the time of the postoperative CPET. Four patients (80%) benefited from cardiac rehabilitation at a mean of 28,25 ± 10,21 days succeeding surgery and for a mean stay of 17,75 ± 3,40 days, with a program focusing on endurance, isometric training, gymnastic and calisthenics.

Table 1. Baseline characteristics	N=5
Characteristics	Values
Age (years)	56,80 ± 12,77
Male, n (%)	5 (100,00)
Weight (kg)	77,20 ± 15,06
Height (cm)	175,40 ± 10,26
Body mass index (kg/m2)	24,98 ± 4,06
Heart failure etiology, n (%)	
Ischemic	2 (40,00)
Valvular + rhythmic	1 (20,00)
Ischemic + valvular + rhythmic	1 (20,00)
Toxic	1 (20,00)
Cardiovascular risk factors, n (%)	
Tobacco use	3 (60,00)
Arterial hypertension	3 (60,00)
Dyslipidemia	4 (80,00)
Obesity	1 (20,00)
Alcohol consumption	2 (40,00)
Comorbidities, n (%)	
Atrial fibrillation	4 (80,00)
Coronary artery disease	3 (60,00)
Valvulopathy*	5 (100,00)
COPD	1 (20,00)
Obstructive sleep apnea	2 (40,00)
Kidney failure	1 (20,00)
Medical history, n (%)	
Myocardial infarction	4 (80,00)
Cardiogenic shock	3 (60,00)
Cardiopulmonary arrest	1 (20,00)
Previous cardiac surgeries	2 (40,00)
Medication at discharge, n (%)	
Angiotensin-converting enzyme inhibitor	4 (80,00)
Angiotensin II receptor antagonist	1 (20,00)
Anti-aldosterone	3 (60,00)
β-blocker	3 (60,00)
Diuretics	4 (80,00)
Anticoagulation**	5 (100,00)
Antiplatelet	3 (60,00)
Lipid-lowering drugs	4 (80,00)
Amiodarone	1 (20,00)
Echocardiographic data	
LVEF (%)	22,20 ± 6,10
Systolic pulmonary artery pressure (mmHg)	54,40 ± 15,90

Diastolic pulmonary artery pressure (mmHg)	27,40 ± 9,02	
Mean pulmonary artery pressure (mmHg)	37,60 ± 8,91	
LVAD data		
Bridge to transplant, n (%)	3	(60,00)
Destination therapy, n (%)	1	(20,00)
Bridge to decision, n (%)	1	(20,00)
Speed (rpm)	5470,00 ± 139,64	
Flow (L/min)	4,42 ± 0,47	
Power (W)	4,40 ± 0,54	
Pulsatility index	4,44 ± 1,03	

* Valvulopathy was defined by physicians' diagnose based on echocardiography's data prior LVAD implantation. 60% of patients (n=3) had a concomitant mitral regurgitation (MR) and tricuspid regurgitation (TR) while 20% (n=1) had a concomitant aortic regurgitation (AR) and TR. 20% (n=1) had a concomitant MR, TR and AR.
** One patient (20%) had dual anticoagulant therapy (vitamin K antagonist and Heparin).

Postoperative adverse events ensued in four patients (80%), with a mean of 3 ± 3,54 complications per patients during their initial hospitalization, the most common being post-surgical bleeding [5 episodes (33,34%); 2 patients (40%)], infectious events [4 episodes (26,67%); 2 patients (40%)], including 3 episodes (20%) of non-LVAD localized infection (n=2, 40%) and a septic shock (6,67%) (n=1, 20%), and supraventricular arrhythmia [2 episodes (13,34%); 2 patients (40%)]. One ischemic stroke (6,67%) occurred in 1 patient (20%) and right heart failure (6,67%) was diagnosed in 1 patient (20%). Re-hospitalization occurred in 80% of patients (n=4), with a mean of 1,50 ± 0,58 readmissions per patients, at a median time of 125,5 days (range: 32–324) succeeding LVAD implantation and for a median stay of 6 days (range: 3–56). Re-hospitalization were resulting from driveline infection [4 episodes (66,67%); 2 patients (40%)] ventricular arrhythmia [1 episodes (16,67%); 1 patients (20%)] and bleeding [1 episode (16,67%); 1 patients (20%)]. Reported postoperative adverse events and causes of readmission are listed on table 2. Two patients (40%) underwent revision surgeries at a median time of 5 days (range: 0–18) after LVAD implantation, for clot removal in the context of a iatrogenic tamponade (n=1, 20%) and ECMO withdrawal along with surgical evacuation of a retrosternal hematoma and a left hemothorax (n=1, 20%).

Table 2. Adverse events N=5

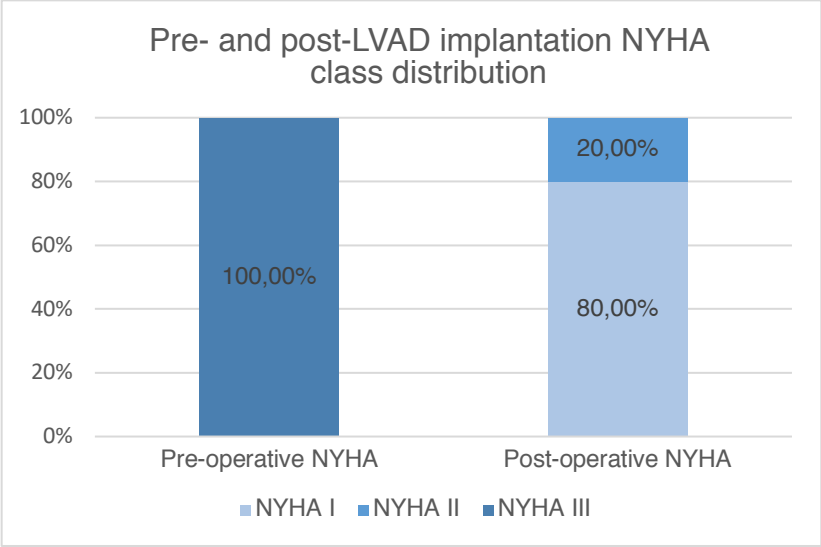
Immediate and delayed adverse events	N° of patients	% of patients	N° of events
Infection			
Non-LVAD localized infection	2	40,00	3
Driveline infection	2	40,00	4
Sepsis	1	20,00	1
Arrhythmia			
Supraventricular	2	40,00	2
Ventricular	1	20,00	1
Bleeding*	3	60,00	6
Right heart failure	1	20,00	1

Ischemic stroke	2	40,00	2
Cardiac tamponade	1	20,00	1
Pleural effusion	1	20,00	1
Kidney failure	1	20,00	1

* Post-surgical bleedings included hemopericardium [1 episode, (20%); 1 patient, (20%)], left hemothorax (2 episodes, 40%) together with retrosternal hematoma (1 episode, 20%) and gastrointestinal bleeding (1 patient; 20%). Readmission for hemorrhage included a post-traumatic acute subdural hematoma [1 episode, (100%); 1 patient (20%)].

Mean pre-operative NYHA class was 3 while mean post-operative NYHA class was 1,20 ± 0,45 (Z=-2,121; p=0,034). Hence, corresponding to an improvement of 1,80 ± 0,45 per patients in their NYHA functional class. Overall, 1 patient (20%) improved by one its NYHA functional class, while 80% of patients (n=4) improved by two NYHA classes after LVAD implantation. Comparison in NYHA class pre- and post-LVAD implantation is displayed on Figure 2. Baseline characteristics, co-morbidities, medical history, heart failure etiology, therapeutic project (BTT, DT or BTD), echocardiographic data, peri- and post-operative adverse events above-mentioned were not statistically correlated with improvement in NYHA functional class subsequent LVAD-implantation, probably due to the limited sample size.

Figure 2.



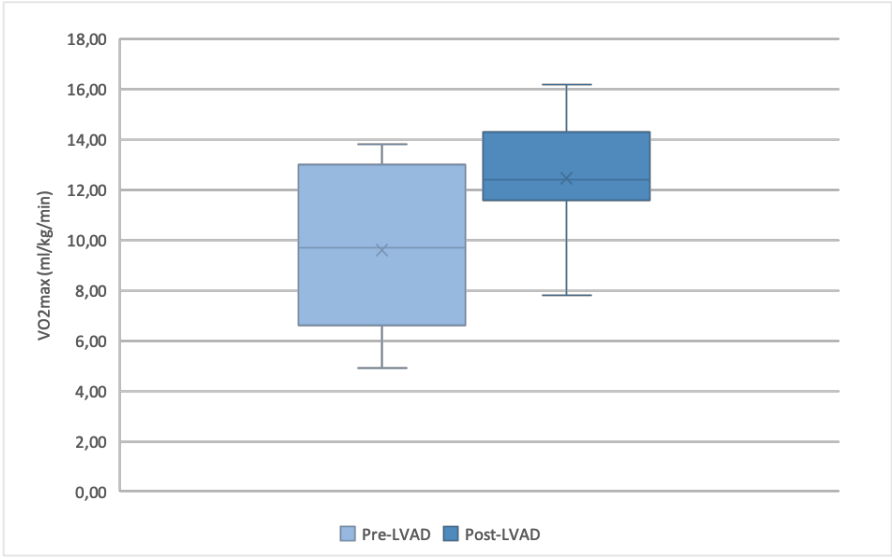
Pre-LVAD implantation NYHA class: NYHA III (n=5)
Post-LVAD implantation NYHA class: NYHA I (n=4), NYHA II (n=1)

Median time between baseline CPET and LVAD implantation was 57 days (range: 15–539). The pre-operative CPET was performed on a bicycle ergometer on 80% of patients (n=4) and on a treadmill ergometer on 20% of patients (n=1), following an individualized ramp protocol. Prior LVAD implantation, mean VO_2^{max} was 9,60 ± 3,88 ml/kg/min corresponding to approximately 36,60 ± 15,47% of the predicted VO_2^{max}. Patients were able to exercise an average of 05:54 ± 03:15 minutes and mean work load achieved was 4,98 ± 3,56 metabolic equivalents (METs). Every patient achieved adequate exercise effort as demonstrated by a

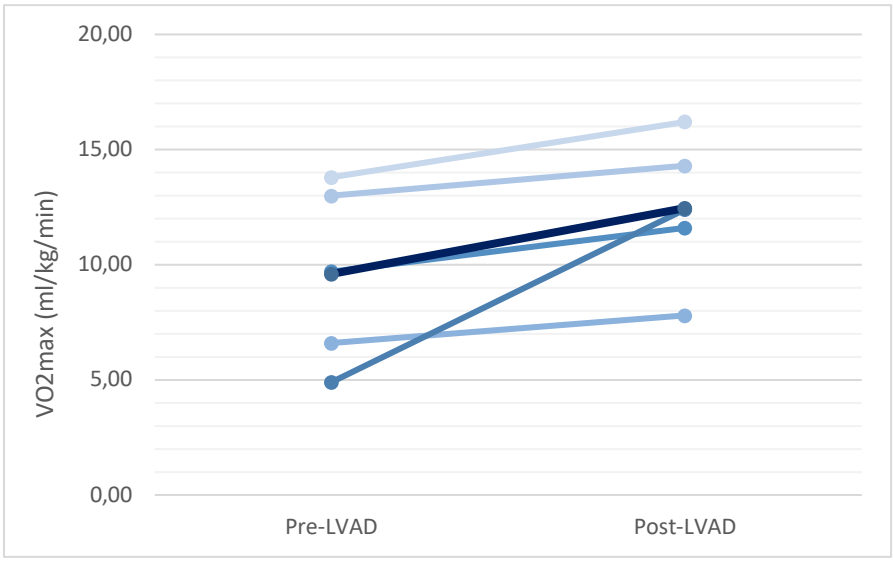
mean respiratory exchange ratio of 1,11 ± 0,16 on stress completion. Perceived exertion couldn't be assessed in 2 patients due to language barrier, however, quality of effort was rated with a mean of 7 ± 3 for dyspnea and 5 ± 4 for muscular fatigue on the modified Borg scale. Participants showed an impaired gas exchange during the pre-operative CPET as evidenced by an elevated VE/VCO2 slope (55,86 ± 36,68). Mean anaerobic threshold was reached at 27,80 ± 14,06% of predicted VO_2^{max}.

Figure 3. Pre- and post-operative VO_2^{max}.

A.



B.



Mean change in VO_2^{max} is represented by the bold dark blue line in Figure 3 B.

Post-procedure CPET was performed at a median time of 279 days (range: 194–623). A bicycle ergometer was used in 4 patients (80%) while 1 (20%) performed the post-operative CPET on a treadmill ergometer. Every patient followed a manual ramp protocol. VO_2^{max} improved subsequent LVAD implantation, from 9,60 ± 3,88 ml/kg/min to 12,46 ± 3,16 ml/kg/min, corresponding to a mean VO_2^{max} increase of 2,86 ± 2,64 ml/kg/min per patients, however without being statistically significant (t-test=-2,424; ddl=4; p=0,072). Peak oxygen

consumption remained although considerably lower than predicted values (44,80 ± 9,39%; t-test=-1,374; ddl=4; p=0,242). Mean ratio of minute ventilation to carbon dioxide production (VE/VCO_2) slope was 38,98 ± 4,29. Average test duration was 06:33 ± 02:39 minutes, which is 00:39 ± 00:88 seconds longer than pre-LVAD, and mean work load achieved was 5,30 ± 2,64 METs. Three out of five patients (60%) were able to complete the modified Borg scale of perceived exertion. Quality of exercise effort was similar to the pre-operative values, with a mean RER of 1,14 ± 0,14 and a rating of 6 ± 2 for dyspnea along with 5 ± 3 for muscular fatigue at exercise termination. Mean anaerobic threshold was reached at 29,56 ± 5,47% of predicted VO_2^{max}.Pre- and post-LVAD VO_2^{max} is displayed on figure 3 and 4. CPET results are presented in table 3.

Table 3. Cardiopulmonary exercise test result prior and succeeding LVAD implantation (N=5)

	Pre-LVAD	Post-LVAD	*p* value
Time between LVAD placement and CPET (days)	189,20 ± 231,33	346,00 ± 166,74	–
CPET modality			
Treadmill ergometry, n (%)	1 (20,00)	1 (20,00)	–
Speed (km/h)	5,80	5,10	–
Meters	742,00	602,00	–
Slope (%)	15,00	14,00	–
Bicycle ergometry, n (%)	4 (80,00)	4 (80,00)	–
Peak workload (W)	52,00 ± 18,49	71,75 ± 25,81	0,062
Predicted peak workload (W)	151,75 ± 10,56	166,25 ± 32,84	0,391
% Predicted peak workload (%)	34,25 ± 12,26	43,25 ± 12,89	0,168
Manual ramp protocol, n (%)	8 (100,00)	8 (100,00)	–
Exercise parameters			
Exercise time (min)	05:54 ± 03:15	06:33 ± 02:39	0,383
RER	1,11 ± 0,16	1,14 ± 0,14	0,255
VO2max (ml/kg/min)	9,60 ± 3,88	12,46 ± 3,16	0,072
Predicted VO2max (ml/kg/min)	26,82 ± 4,39	27,56 ± 4,29	0,727
% Predicted VO2max (%)	36,60 ± 15,47	44,80 ± 9,39	0,242
METs	4,98 ± 3,56	5,30 ± 2,64	0,602
VE/VCO2 slope	55,86 ± 36,68	38,98 ± 4,29	0,329
AT as % predicted peak VO2 (%)	27,80 ± 14,06	29,56 ± 5,47	0,784
Vital signs			
Peak heart rate (beats/min)	103,40 ± 16,07	105,20 ± 22,83	0,79
Predicted peak heart rate (beats/min)	163,80 ± 12,68	162,20 ± 12,77	0,016
% Predicted peak heart rate (%)	63,00 ± 8,54	65,00 ± 14,16	0,616
NYHA class	3,00 ± 0,00	1,20 ± 0,45	0,034

Patients with obesity (F=6,418; ddl=4; p=0,085) medical history of coronary artery disease (F=5,606; ddl=4; p=0,099), cardiogenic shock (F=5,606; ddl=4; p=0,099), ischemic HF etiology (F=5,606; ddl=4; p=0,099) and ventricular arrhythmia as cause of rehospitalization (F=6,418; ddl=4; p=0,085) tend to have lower post-operative VO_2^{max} values. Furthermore, the number of

hospital re-admission negatively correlated with improvement in VO_2^{max} subsequent LVAD implantation (r=-0,754; r-squared=0,569; p=0,141). Though, statistical significance was not observed as a result of the limited study sample, hence skewing correlation between parameters and precluding firm conclusions.

Discussion

In the present study, exercise capacity and its changes were assessed prior and after LVAD implantation, using CPET, in patients suffering from end-stage heart failure supported with a HeartMate 3. The major finding from this current study suggest that VO_2^{max} improves modestly but not significantly subsequent LVAD support. Furthermore, peak VO_2 fails to normalize to predicted values corrected for gender and age. Indeed, physical capacity improved from 9,60 ± 3,88 to 12,46 ± 3,16, corresponding to a mean VO_2^{max} increase of 2,86 ± 2,64 ml/kg/min per patients, though remained subnormal, approximately 44,80 ± 9,39% of predicted VO_2^{max}.
Divergent results were reported in previous studies assessing physical capacity prior and subsequent CF-LVAD support. Accordingly, Benton and al. established a significant increase in peak VO_2 from 11,6 ± 5,0 ml/kg/min to 15,4 ± 3,9 ml/kg/min at approximately 6 months after LVAD implantation (25). Dunlay and al. recorded a modest increase of 0,9 ml/kg/min in peak VO_2 post-LVAD (11,5 ± 2,5 ml/kg/min to 12,4 ± 2,8 ml/kg/min), but was not statistically significative (26). Leibner and al found that peak VO_2 remained constantly low throughout repeated exercise testing (11,2 ± 3,0 ml/kg/min at baseline, 12,7 ± 3,5 ml/kg/min after 3-6 months, 10,7 ± 2,7 ml/kg/min after 1 year and 11,2 ± 1,7 ml/kg/min after more than 1 year) (27). On the other hand, de Jonge and al. highlighted that peak VO_2 improves over time, with values attaining 21,3 ± 3,8 ml/kg/min at 8 months and 24,2 ± 4,8 ml/kg/min at 12 months in a younger cohort of patients (age: 37 ± 12 years) who underwent intensive training program, though didn't compare these values with pre-implantation data (21).

Though an improvement in peak VO_2 of approximately 30% has been assessed subsequent LVAD implantation, the functional impact of this value, especially throughout patients daily living activities, as its influence on quality of life remains unknown. This increase in peak VO_2 remains nevertheless higher compared to parenteral inotropic therapy, showing improvement of 11,24% after levosimendan infusion (9,8 ± 1,7 ml/kg/min to 11,0 ± 1,9 ml/kg/min; p<0,005), an inodilator agent (28). The clinical benefits of improvement in VO_2^{max} are well documented in the literature (reduced risk of all-cause and cardiovascular mortality as hospitalization in patients with chronic systolic heart failure) (29), nonetheless objective data concerning the increase in physical capacity related to this improvement is lacking. Previous studies displayed a linear correlation between six-minute walking distance (6MWD) and VO_2^{max}, we can thus extrapolate from these data that an approximate increase of 3 ml/kg/min in peak VO_2 is associated with an improvement of 100 meters in the 6MWD (30)(31). However, these estimations shall not be generalized when assessing individuals, especially in the LVAD population due to their heterogeneity and their multimorbid traits. Nevertheless, we assume that LVAD therapy provided an adequate functional capacity suitable for daily living activities. Accordingly, 80% of patients (n=4/5) in our study cohort reported no impairment in walking on a flat surface, being able to walk up a median of 3 flight of stairs without pauses (range 1–6),

60% (n=3/5) declared practicing a light physical activity, and 20% (n=1/5) reported returning to part time work (50% activity) throughout the routine follow-up around time of the post-operative CPET. Unfortunately, the absence of data on functional capacity prior LVAD implantation precludes comparisons, hence the ability to draw conclusions. Further investigations should be conducted in order to assess the improvement in functional status and quality of life related to increase in VO_2^{max} in LVAD patients.

We found no differences in post-procedure VO_2^{max} in patients supported with a LVAD as BTT, DT or BTC and when stratified by heart failure etiology. Though, patients with non-ischemic heart failure etiology (F=5,606; ddl=4; p=0,099) and higher pre-LVAD LVEF (r=-0,468; r-squared=0,219; p=0,426) tend to correlate with greater post-operative VO_2^{max} values, but not significantly. Several studies identified factors associated with improvement in VO_2^{max}. The latter being pulsatility index, pump power, pump speed, peak heart rate and exercise training (21)(32). Since our study did not aim to assess repeated CPETs over time, we cannot draw conclusions concerning the effect of training on VO_2^{max}. A mild correlation was evidenced between pump flow (r=0,455; r-squared=0,207; p=0,442), pump power (r=0,557; r-squared=0,310; p=0,329), pulsatility index (r=0,471; r-squared=0,222; p=0,424) at CPET and improvement in peak VO_2, though not statistically significant. Nonetheless, participation in cardiac rehabilitation and its duration did not correlate with improvement in VO_2^{max}.
One patient underwent CPET on a treadmill ergometer and showed higher post-implantation VO_2^{max} (16,2 ml/kg/min) compared to those who underwent bicycle ergometry (11,53 ± 2,73 ml/kg/min). These result is similar to the ones displayed by Haft and al. (peak VO_2 of 15,6 ml/kg/min on LVAD support) who tested their study group on a treadmill ergometer (33). The use of treadmill ergometry should be taken into account since it requires greater muscle mass, hence explaining these higher values.

The suboptimal oxygen consumption may be partially explained by the fixed pump speed which limits the ability to increase cardiac output during exercise, thus failing to adapt to the increasing hemodynamic needs of exercise. Nevertheless, pump-generated blood flow together with native cardiac output increase during exercise under constant pump speed (up to approximately 1L/min and 3L/min respectively at maximal effort) due to augmented preload and cardiac contractility, hence contributing to a moderate increase in total cardiac output. However this response remains insufficient to normalize VO_2^{max} (34)(35). Previous studies highlighted that higher LVAD pump speed increased cardiac output which was associated with higher peak VO_2, together with improvement in peak workload and exercise duration (36)(37). Pump speed was optimized ambulatory and at rest, in order to efficiently unload the left ventricle while averting suction events, but was not actively manipulated for the present study. Thus, conclusions could not be drawn concerning the relationship between pump speed and physical capacity. Despite the failure to normalize peak oxygen consumption to predicted levels, several studies reported that patients had improved quality of life and increased subjective exercise capacity following LVAD implantation (38). In the present study, self-reported NYHA functional class at 9 months improved significantly by one class in 20% of patients and by two classes in 80% of patients. Furthermore, Benton and al. highlighted that improvement by at least two NYHA class was achieved by 91,4% of patients, with 34,3% improving by three class (25). This marked divergence between subjective improvements in functional class and moderate increases in peak VO_2 suggest that improvement in the latter

depends upon other determinants than augmented cardiac output. Accordingly, patients' concomitant co-morbidities including obstructive and restrictive lung diseases, persistent pulmonary hypertension, right heart failure, peripheral vascular disease, endothelial dysfunction, skeletal muscle diseases and muscle deconditioning may also contribute to the inability to increase VO_2^{max} to predicted values (3)(12). In order to minimize the impact of deconditioning, post-procedure CPETs were performed 8 to 12 months subsequent LVAD implantation, hence allowing optimal postoperative convalescence.

A substantial improvement in ventilatory response to exercise (VE/VCO_2 slope) has been assessed subsequent LVAD implantation, although not statistically significant. Accordingly, VE/VCO_2 slope decreased from 55,86 ± 36,68 prior LVAD implantation to 38,98 ± 4,29 post-procedure (t-test=1,112; ddl=4; p=0,329). However, it remained elevated (VE/VCO_2 slope ≥ 34), which is associated with a poor prognostic, notably due to higher cardiac related mortality and re-hospitalizations (39).
CF-LVAD support causes considerable changes in hemodynamic physiology which leads to specific adverse events, hence frequent re-hospitalization (40). Common predominant complications stated in the literature are ischemic stroke, pump thrombosis, cardiac arrhythmia, right heart failure, driveline infection and bleeding (including surgical and gastrointestinal bleeding), the latter being the most frequent adverse event (11)(14)(17). Six unexpected re-hospitalization occurred in 80% of our discharged patients during the first year succeeding implantation. Re-admissions were owed to infection, arrhythmia and bleeding. However, our study cohort didn't experience pump thrombosis nor gastrointestinal bleeding and only one re-hospitalization was due to an hemorrhagic event at approximately 1 month post-LVAD implantation. Plausible explanations could be the inherent characteristics of the HeartMate 3, thought to decrease shear stress with larger gaps in the rotor in order to avert pump thrombosis and reduce the risk of acquired von Willebrand disease. Furthermore, the introduction of an intrinsic artificial pump pulse (approximately 25mmHg, every 2 seconds) should avert stasis in the pump and potentially prevent arteriovenous malformation in the gastrointestinal tract, which are a major cause of hemorrhage (17)(19). Two ischemic strokes occurred in 2 patients (40%) whose one was due to anticoagulation reversal in the context of a post-traumatic subdural hematoma. Considering the wide blood flow path of the HeartMate 3, an intracardiac thrombus may have embolized leaving the pump unobstructed, though a thrombosis developed within the device may unlikely embolize owing to the centrifugal flow. Current data involving HM III shows similar rates of bleeding but lower risk of pump thrombosis, lower incidence of ischemic stroke and higher survival free of disabling strokes or reoperation to replace or remove the device compared to former CF-pumps (17)(41). Furthermore, we found a strong correlation (C=0,707, p=0,025) between dual anticoagulant therapy associated with antiplatelet therapy (n=1, 20%) and the onset of non-surgical hemorrhagic events (n=1, 16,67%). Thus, the perspective of low-intensity anticoagulation protocols, which should reduce incidences of bleeding events, might be beneficial in the future when carefully balanced with the patient's risk of thrombo-embolic events.

Study limitations, Strengths and Clinical Implications

In the context of a Master's thesis, the present study was mono-centric, thus the limited sample size was defined by the local population's volume and by the time-limited research. The post-operative CPETs were performed as a routine clinical follow-up, hence time between LVAD

implantation and CPET varied from 8 to 12 months in order to allow an optimal postoperative convalescence and only a subset of patients who underwent LVAD implantation between 2017 and 2018 could be selected. The post-operative CPETs were performed by patients hemodynamically stable and in fairly good condition, which could be a selection bias as it isn't representative of the population supported with LVAD. Furthermore, only participants who underwent CPET prior LVAD implantation were selected to perform the post-operative CPET. Thus, our study cohort represents 23,81% of every patients receiving LVADs at our center during the study period. Moreover, our study was limited by a narrow statistical analysis and the possibility of confounding bias due to the low sample size, which precluded firm conclusions. The majority of patients included in our study sample (3 out of 5) underwent multiple pre-operative CPETs (mean: 2,4; SD: ± 1,67; range: 1–5) which might have influenced the post-operative exercise testing's results due to increased test familiarity. On the other hand, exercise limiting non-cardiac comorbidities may have influenced submaximal tests. CPET was performed on a bicycle ergometer by 4 patients prior LVAD implantation and post-procedure while one underwent CPET on a treadmill ergometer. Some data suggest that bicycle ergometry presents a lower peak oxygen content of approximately 6-25%, due to lower muscle mass recruitment, compared to treadmill exercise testing (22)(24), which might have induced a measurement bias. Moreover, manual stress protocols were used in order to be concordant with patients' functional capabilities, thus varied within then study group which may have affected measurement of peak VO_2.

Nevertheless, this study had several significant strength. First, time between LVAD implantation and post-procedure CPET was approximately 11,38 ± 5,48 months, hence reducing the limiting effect of skeletal muscles atrophy and diaphragm weakness on peak oxygen consumption (3)(25). Second, every subject were implanted with the latest generation of LVAD, HeartMate 3, which allowed us to assess the impact of this therapy as an homogenous LVAD system, thus avoiding biases due to intrinsic characteristics of different pump models. Furthermore, every patient had similar preoperative management procedures and almost all benefited from cardiac rehabilitation after LVAD implantation. Third, LVAD optimization together with ventricular septal position, left ventricular unloading and symptoms management were achieved as part of the iterative routine medical check-ups, which is more reflective of real-life scenarios. Moreover, our patient's collective may differ from abroad studies who used an ideal sample, due to a higher morbidity and multiple co-morbidities, which leads to a flexibility in the eligibility for LVAD implantation. Thus, being more representative of the heart failure population.

The present study provides additional data concerning LVAD's impact on physical capacity which allows to justify the direct and indirect costs of the device implantation, maintenance, and the invasive surgical procedure of this therapy. Enhancement in functional capacity shall impact on patient's daily living activities and quality of life, on life years gained and improvement in symptoms compared to medical therapy. Although improvement in physical capacity was clearly objectified, it was not statistically significant. LVAD support restores cardiac output and adequate peripheral blood flow, however remains insufficient to normalize VO_2^{max}. This suggest that other pathophysiological mechanisms underlie the incomplete recovery which LVAD therapy is unable to fully reverse. Efforts should be directed toward this concern, especially in destination therapy patients, in order to achieve satisfactory long-term

results. Moreover, this study allowed us to identify clinical parameters correlated with a poorer outcome but weren't conclusive due to the limited study sample size. Further investigations focusing on these variables should be conducted in order to guide decision-making to proceed with LVAD treatment concordant with patients' values, objectives and expectations.

Conclusion

Patients LVAD therapy have seen their NYHA functional class improve significantly, however changes in their physical capacity could not be statically assessed. By improving VO_2^{max} by approximately 30%, this therapy should lead successfully patients to heart transplantation (BTT), improve their quality of life (DT) and restore an adequate functional capacity suitable for everyday activities. Further studies should investigate the subjective improvement in exercise capacity, using standardized questionnaires, in order to correlate the results with post-procedure VO_2^{max} and to fully assess the impact of LVAD support on quality of life. No firm conclusions could be made concerning the influence of patients related clinical parameters on peak VO_2 in the present study due to the limited sample size. Further research should focus on identifying predictive factors influencing the outcome of this therapy in order to sharpen patients' selection.

Disclosure statement

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