ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 2846–2855
Published online 2 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13359

ORIGINAL RESEARCH ARTICLE

Effects of echo-optimization of left ventricular assist devices on functional capacity, a randomized controlled trial

Marzia Lilliu*, Francesco Onorati, Giovanni Battista Luciani and Giuseppe Faggian

Division of Cardiac Surgery, Department of Surgery, University of Verona, Piazzale Aristide Stefani, 1, Verona, 37126, Italy

Abstract

Aims After the implantation of a left ventricular assist device (LVAD), many patients continue to experience exercise intolerance. VAFRACT trial evaluates the additional benefit of LVAD echo-guided optimization (EO) on functional capacity (FC), measured by cardiopulmonary exercise test (CPET), and quality of life (QoL).

Methods and results Twenty-seven patients were randomized in a 1:1 ratio to EO (EO group) vs. standard settings (CONTROL group) at least after 3 months from LVAD implant procedure. The optimal device speed was defined as the one that allows an intermittent aortic valve opening and a neutral position of the interventricular septum without increasing aortic or tricuspid regurgitation and preserving right ventricular function. The primary endpoint was peak oxygen uptake (VO_2 peak) change after 3 months.

Echo-guided optimization significantly improves VO_2 peak (from 13.2 ± 2.5 to 14.2 ± 2.5 mL/kg/min; $P < 0.001$), oxygen pulse (from 9.75 ± 1.46 to 10.75 ± 2.2 mL; $P < 0.001$), CPET exercise time (from 490 ± 98 to 526 ± 116 s; $P = 0.02$), 6 min walk distance (from 363 ± 54 to 391 ± 52 m; $P = 0.04$), and QoL, using EuroQol Five Dimensions 3L (from 0.796 ± 0.1 to 0.85 ± 0.08; $P < 0.001$) and the Kansas City Cardiomyopathy Questionnaire (from 81.6 ± 6.9 to 84.6 ± 5.6; $P = 0.025$).

Conclusions Echo-guided optimization can significantly influence the FC and the QoL of LVAD patients. This procedure should represent a fundamental step in their clinical management, through the establishment of consolidated follow-up protocols. Our study may represent a starting point for a future, adequately powered clinical trial with a longer term follow-up.

Keywords LVADs; Echo-optimization; Cardiopulmonary exercise test; Functional capacity

Received: 3 January 2021; Revised: 13 March 2021; Accepted: 29 March 2021
**Correspondence to: Marzia Lilliu, Division of Cardiac Surgery, Department of Surgery, University of Verona, Piazzale Aristide Stefani, 1, 37126 Verona, Italy. Phone: +39 328 1383539. Email: marzialilliu@gmail.com*

Introduction

The evolution, not only in technologies but also in the selection of patients, and the development of competences in peri-operative and post-operative management have led to a constant improvement in the survival of left ventricular assist device (LVAD) carriers, currently estimated at around 87% after 1 year.[1]

However, after LVAD implantation, patient's functional capacity is still reduced with peak oxygen uptake (VO_2 peak) values calculated by cardiopulmonary exercise testing (CPET) ranging from 11 to 20 mL/kg/min.[2]

Various determinants have an influence on functional capacity. Only few previous reports have analysed the effects of pump speed increase on exercise performance in LVAD patients with contradictory results: an upgrade was observed in some,[3,4] but not in all reports.[5] In another case, the rise in VO_2 peak was correlated to a worsening in lung diffusion and obstructive apneas.[6]

Moreover, the role of right ventricle (RV) is often underestimated: Murninkas *et al*. found a decrease in VO_2 peak of 0.97 mL/kg/min for each ejection fraction reduction of the RV by 10%.[7] A more favourable haemodynamic profile for the RV and a probable better response in terms of

functional capacity can therefore be expected from LVAD echo-optimization (EO).

Uriel *et al*. demonstrated that EO can help patient management: in particular, the haemodynamic improvement was evident with an increase in cardiac output and a decrease in pulmonary capillary wedge pressure, confirmed by right heart catheterization.[8]

We conducted a prospective randomized trial [The Effects of Echo-optimization of Left Ventricular Assist Devices on Functional Capacity, a RAndomized Controlled Trial (VAFRACT)] to evaluate the additional benefit of an EO approach on functional capacity measured by CPET and on quality of life in LVAD carriers.

Materials and methods

Study protocol

Subjects studied were patients supported with a continuous-flow LVAD: HeartMate II (Thoratec Inc., Pleasanton, CA) and HeartMate 3™ (Abbott, North Chicago, IL). All were ambulatory patients recruited by our Day Hospital of the Division of Cardiovascular Surgery at the University Hospital of Verona, from February 2018 to August 2019.

The study protocol conforms to the Declaration of Helsinki and was approved by the local ethic committee on 19 July 2017. The trial was registered at ClinicalTrials.gov (Identifier NCT03937570). All patients gave their written informed consent.

Inclusion criteria were as follows:

- enrolment at least 3 months after LVAD implantation;
- compliance to the required follow-up schedule;
- age $\geq$ 18.

Exclusion criteria were as follows:

- distance of less than 150 m on the 6 min walking test or impossibility to perform CPET;
- poor acoustic window for echocardiographic imaging acquisition;
- recent finding of any major device-related complication (sepsis, thrombosis …).

Patients were randomized with a 1:1 allocation (using random block sizes of 4 and 6) to EO (EO group) vs. standard settings (CONTROL group) after at least 3 months from the LVAD implantation. Randomization was performed using a web-based service with secured password and protected login, managed by a doctor not involved in the trial. The ordering of blocks and their respective size was unknown to the investigators.

Patients randomized to EO treatment performed echo-guided device programming[9] at randomization. In CONTROL group, patients performed LVAD EO, but the optimal device speed was not confirmed at the end of procedure. The flow chart is specified in *Figure 1*.

The primary endpoint of our study was VO_2 peak change at 3 months after the EO. The secondary endpoints were as follows: right ventricular function (assessed by echocardiography and evaluated by fractional area change); device-related hospital admissions (complications were defined according to the Interagency Registry for Mechanically Assisted Circulatory Support[10]); *N*-terminal pro-brain natriuretic peptide (NT-proBNP) levels; CPET exercise time and changes in quality of life perceived by the EuroQol Five Dimensions 3L questionnaire (EuroQol Group, Rotterdam, the Netherlands) and the Kansas City Cardiomyopathy Questionnaire.

Kerrigan *et al*.[11] proposed a design similar to our protocol, with the intention, however, of verifying the contribution of another tool (rehabilitation) to improve the functional capacity of LVAD patients. It has been hypothesized that the EO group undergoes a variation equal to the rehabilitated group reported by Kerrigan, while the non-optimized group behaves like the control group of that study. Because the study did not report the standard deviation of the differences, it was estimated taking into account the correlation between the two measurements, according to the value of $r = 0.50$, as suggested by the Cochrane Heart Group. Therefore, a variation was obtained for the control group of 0.8 ± 2.8 and for the 'active' group of 3.1 ± 1.87. Assuming an alpha value of 0.05 and a power of 80%, an estimated sample size of 18 patients for each group was obtained.

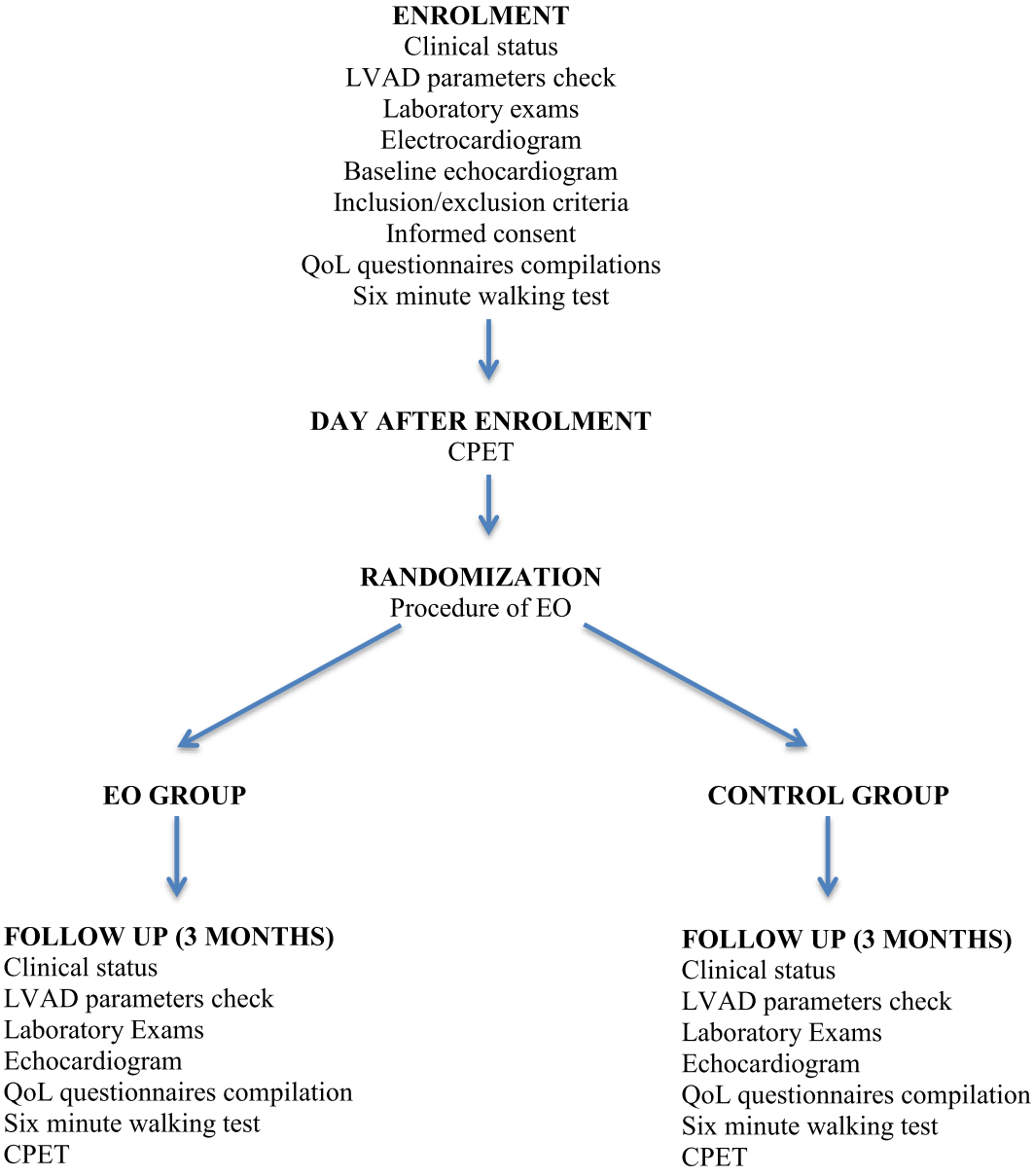
Study procedures

Measurement of blood chemistry and haematologic variables

Fasting blood samples were collected at baseline and at 3 months to assess parameters of haemolysis (lactate dehydrogenase and haptoglobin) or infection (complete blood count and high sensitivity C-reactive protein) and to investigate kidney (creatinine and blood urea) and liver function (bilirubin and alanine and aspartate aminotransferase). Lipid profile (low-density lipoprotein, high-density lipoprotein, and total cholesterol, triglycerides), blood glucose, and serum electrolytes (sodium and potassium) were also measured. Dosage of NT-proBNP, as secondary endpoint of our study, was included in the evaluation. Lastly, measurement of prothrombin time–international normalized ratio was fundamental to allow our procedure of EO in safe conditions (a value at least $>$1.8 was requested).

DOI: 10.1002/ehf2.13359

Figure 1 Study flow chart. EO, echo-guided optimization; CPET, cardiopulmonary exercise testing; LVAD, left ventricular assist device; QoL, quality of life.



Cardiopulmonary exercise test

For the exercise test, a bicycle ergometer was used (Quark CPET, COSMED, Rome, Italy). Respiratory gas exchange measurements were obtained breath-by-breath (Omnia 1.6.5, COSMED, Rome, Italy) using a face-mask as patient/metabolic cart interface.

The aim of the exercise duration was 10 ± 2 min. In all patients, the initial workload was 10 W, and it was gradually increased by a 10 W/min ramp until patients reached exhaustion. The protocol was not changed between baseline and 3 months CPET. Patients were motivated to put their maximal effort thus allowing a reliable measurement of VO_2 peak, calculated in mL/kg/min. We considered the highest 30 s average VO_2 value over the last minute of the exercise phase. Minute ventilation/CO_2 production slope was calculated as the slope of the linear relationship between minute ventilation and CO_2 production form excluding the initial part of the test (potentially influenced by hyperventilation) and the final part (from the end of the isocapnic tamponade to the end of the exercise).[12] The anaerobic threshold was measured with the V-slope analysis from the plot of CO_2 output vs. O_2 uptake on equal scales. This value was confirmed

analysing ventilatory equivalents and end-tidal pressures of CO_2 and O_2.[13] A respiratory exchange ratio >1.05 was used as an indicator of an adequate performed test.

Echo-optimization procedure

Complete transthoracic echocardiographic exams were performed in accordance with current American Society of Echocardiography guidelines,[14] using a CX-50 xMatrix Philips cardiac ultrasound system (Philips S.p.A, Milan, Italy).

Before starting the procedure, blood pressure was recorded. The patient's device speed was lowered to the minimum speed clinically recommended. After 2 min, the following parameters were documented: left ventricular (LV) end-diastolic dimension, LV end-systolic diameter, frequency of aortic valve (AV) opening, degree of aortic regurgitation, degree of mitral regurgitation, right ventricular systolic pressure, blood pressure, and heart rate. Also, the other pump parameters were recorded (power, pulsatility index, and flow).

Left ventricular end-diastolic and end-systolic dimensions were measured from the parasternal long-axis view; AV opening was assessed using M-mode over the AV in the parasternal long-axis view. Visual estimation of the severity of aortic and mitral regurgitation was performed in the parasternal long-axis view using the colour Doppler imaging technique. For the assessment of aortic and mitral regurgitation, the degree was graded from 0 to 3 (0, none; 1, mild; 2, moderate; and 3, severe). Right ventricular systolic pressure was estimated from peak tricuspid regurgitation velocity using the modified Bernoulli's equation.

The recommended speed range varies according to the indications given in the data sheet for each specific device: for the HeartMate II, the clinical recommended range is between 8800 and 10 000, and the speed can be changed by an increment or reduction of 200 rpm; for the HeartMate 3™, the allowed speed is between 4800 and 6200 rpm with possible modifications of 100.

Therefore, the device speed was increased, at 2 min intervals with repeated acquisition of all echocardiographic and device parameters at each speed step, up to the maximum clinically recommended speed.

The optimal velocity was defined as the one that allows an intermittent AV opening and a neutral position of the interventricular septum without increasing aortic and/or tricuspid regurgitation, associated or not to a dilatation of the RV.[14]

The test was stopped in case of a decrease in LV end-diastolic diameter ≤ 3 cm, suction events, ventricular arrhythmias, symptoms (palpitations, dizziness, dyspnoea, chest pain, or headache), hypertension (mean artery pressure > 100 mmHg), and hypotension (mean artery pressure < 60 mmHg). At the end of the exam, a new assessment of blood pressure was performed, and the images recorded were reviewed.

Statistical analysis

The Student's *t*-test and the χ^2 test were used to compare groups at baseline for continuous and nominal data, respectively.

A paired *t*-test was used to assess within-group changes from baseline to 3 months. Analysis of covariance was used to compare the differences in change from baseline to follow-up between the two groups. Statistical significance was defined as $P < 0.05$ (two-tailed).

Data are presented as mean ± standard deviation unless otherwise stated. All statistical analyses were performed with IBM SPSS Version 22.0 (Armonk, New York).

Results

Basal characteristics

Twenty-seven patients consented to participate in the study (*Figure 2*). No statistically significant differences were observed among groups with respect to all baseline characteristics **(** *Tables 1–4***)**. The average age of the population was 61.7 ± 8.3 years, in a predominantly male population. Time of LVAD implantation was about 674 ± 495 days. The most common indication to implant was bridge to transplant (18 patients). Average pump speed was 9222 ± 273 rpm for HeartMate II and 5250 ± 228 rpm for HeartMate 3™. At rest, average heart rate and mean artery pressure were 76 ± 12 bpm and 84 ± 9 mmHg, respectively.

Regarding LV dysfunction aetiology, ischemic was prevalent (10/27 patients; 37%); idiopathic dilated cardiomyopathy was found in seven cases (25.9%) and a dilated-hypokinetic evolution of a hypertrophic cardiomyopathy in three cases (11.1%). The remaining patients had valvular, chemotherapy-related, and post-partum cardiomyopathies.

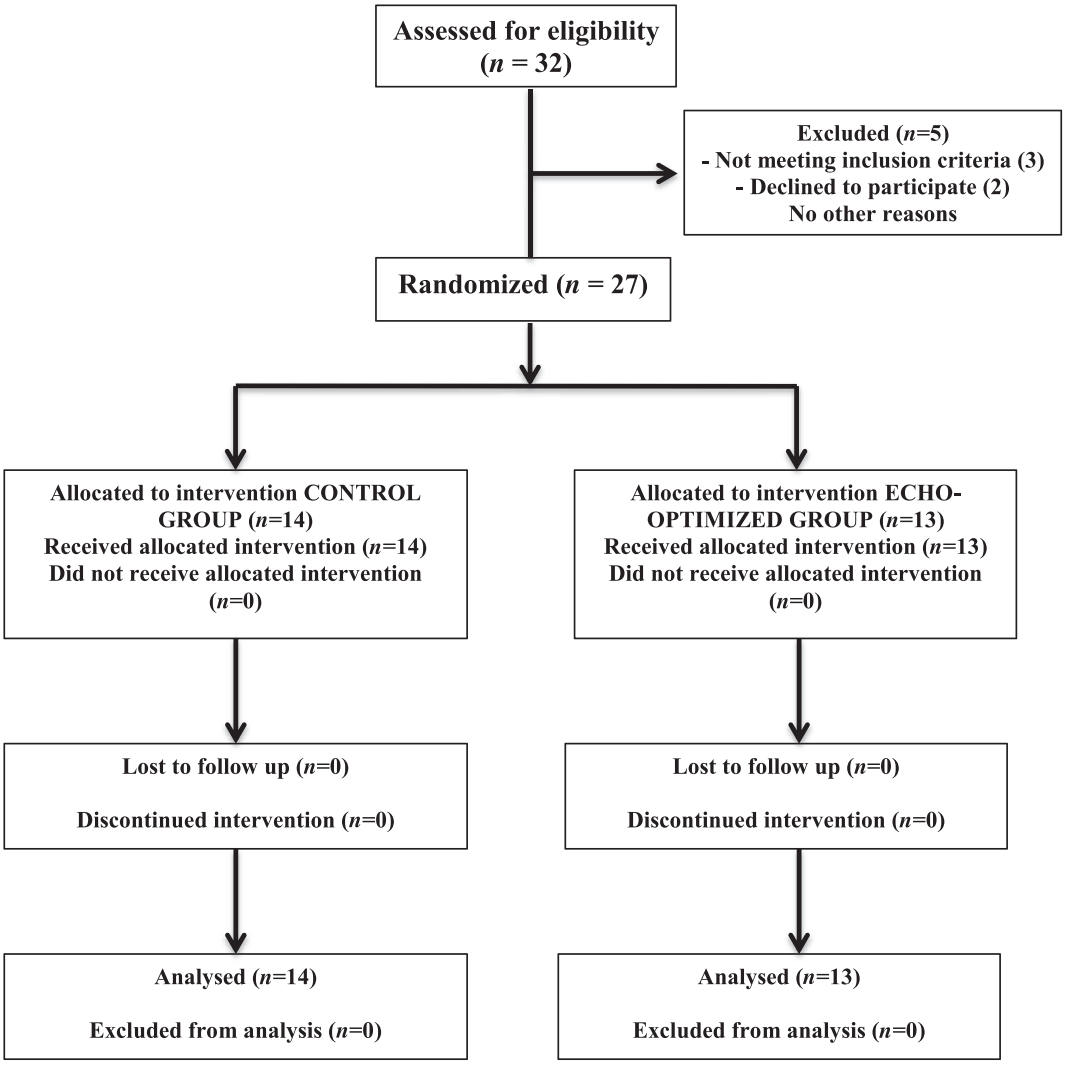
We evaluated a group of LVAD-supported patients in stable clinical conditions (4/27 declared NYHA I functional class and only two in a NYHA III) and optimized pharmacological treatment; nonetheless, they presented a severe deconditioning, with only 11/27 with a VO_2 peak at baseline >14 mL/kg/min. Two patients were on antibiotic therapy at enrolment for a superficial driveline infection.

Almost everyone was able to perform a maximal effort (respiratory exchange ratio 1.1 ± 0.06) without reporting any relevant adverse event related to the test.

The performance of a standardized EO was both safe and feasible in our patients.

At baseline pump speed, the AV was closed in 9 of 27 patients and constantly opens in other 8 patients. Aortic regurgitation was present in 15 patients: mild in 12 patients and moderate in the other 3. EO was performed in four patients with HeartMate II: in two cases, a 200 rpm speed reduction

Figure 2 Flow of participants through the trial.



was performed; in two other cases, the device speed was increased of 200 rpm. Nine patients with HeartMate 3 were echo-optimized: in five cases, device speed was reduced (by 100 rpm in four patients, by 200 rpm in one patient); in the residual four cases, an increase of 100 rpm was performed.

Endpoints

The EO group had a significant improvement (7.7%) in VO_2 peak from baseline to follow-up (EO group: from 13.2 ± 2.5 to 14.2 ± 2.5 vs. control group: from 13.8 ± 2.4 to 13.2 ± 2.6, $P < 0.001$). Graphical representation of the analysis of covariance for VO_2 peak is shown in *Figure 3*. Similarly, the increase in O_2 pulse was significant in the EO group (EO group: from 9.75 ± 1.46 to 10.75 ± 2.2 vs. control group: from 9.83 ± 1.86 to 9.76 ± 1.46, $P < 0.001$). A significant improvement was also demonstrated in exercise time (EO group: from 490 ± 98 to 526 ± 116 vs. control group: from 504 ± 103 to 499 ± 107, $P = 0.02$), a secondary endpoint of our study; for other parameters, the increase did not reach statistical significance (*Table 5*).

In the same way, the increment in the 6 min walking distance was significant in the EO group (EO group: from 363 ± 54 to 391 ± 52 vs. control group: from 364 ± 84 to 374 ± 80, $P = 0.04$), with an improvement percentage similar to that recorded for VO_2 peak.

We did not document any device-related hospitalizations in either group during the 3 months follow-up period and no significant alarms in the memory of the device in the EO group: only one event of 'low flow' was reported in one patient in the CONTROL group. We never had the clinical need to change the device speed in any of the two groups during the 3 months of the study.

Table 1 Baseline characteristics (n = 27)

	CONTROL group (N = 14)	EO group (N = 13)	P
Characteristic			
Support duration (days)	701 ± 515	645 ± 477	0.77
Type of device: Heartmate II	28.6% (4)	23.1% (3)	0.72
Type of device: Heartmate 3™	71.4% (10)	76.9% (10)	0.72
Demographics			
Age (years)	63 ± 6.4	60.3 ± 10	0.41
Female	7.1% (1)	7.7% (1)	0.91
BSA (m^2)	2 ± 0.18	1.95 ± 0.2	0.46
BMI (kg/m^2)	27 ± 2.7	26 ± 4.4	0.46
Destination therapy	28.6% (4)	30.8% (4)	0.93
Medical history			
Hypertension	28.6% (4)	30.8% (4)	0.93
Diabetes	42.8% (6)	30.8% (4)	0.52
Previous smokers	50% (7)	38.5% (5)	0.53
Ischemic heart disease	50% (7)	23.1% (3)	0.15
Chronic kidney disease	14.3% (2)	15.4% (2)	0.91
Drugs			
ACE inhibitors	64.3% (9)	61.5% (8)	0.87
Angiotensin II blockers	28.6% (4)	30.8% (4)	0.93
Loop-diuretics	92.8% (13)	84.6% (11)	0.80
MCRA antagonists	50% (7)	69.2% (9)	0.31
Beta-blockers	100% (14)	92.3% (12)	0.31
Amiodarone	64.3% (9)	61.5% (8)	0.87
Digoxin	42.8% (6)	46.1% (6)	0.94
Statins	21.4% (3)	38.5% (5)	0.35
Insulin	42.8% (6)	38.5% (5)	0.81
Antibiotics (amoxicillin clavulanate)	7.1% (1)	7.7% (1)	0.91

ACE, angiotensin-converting enzyme; BMI, body mass index; BSA, body surface area; EO, echo-guided optimization; MCRA, mineralocorticoid receptor antagonists.

Table 2 Baseline laboratory exams (n = 27)

Laboratory exam	CONTROL group (N = 14)	EO group (N = 13)	P
Leukocytes ($10^9/L$)	7.31 ± 1.8	8.16 ± 3.2	0.40
Erythrocytes ($10^{12}/L$)	4.50 ± 0.5	4.54 ± 0.6	0.87
Haemoglobin (g/L)	124.1 ± 12.9	134.4 ± 13.3	0.30
Haematocrit (L/L)	0.41 ± 0.03	0.41 ± 0.04	0.85
Platelets ($10^9/L$)	208 ± 53.4	209 ± 54.6	0.96
Prothrombin time (ratio)	2.56 ± 0.6	2.79 ± 1.03	0.50
Partial thromboplastin time (s)	1.36 ± 0.19	1.3 ± 0.17	0.37
Glycaemia (mg/dL)	113.4 ± 29.3	113.3 ± 30.2	0.99
Urea (mg/dL)	45 ± 17.4	40 ± 10.4	0.39
Creatinine (mg/dL)	1.19 ± 0.37	1.12 ± 0.27	0.58
Sodium (mmol/L)	140.1 ± 1.9	138.6 ± 2.9	0.13
Potassium (mmol/L)	4.04 ± 0.33	4.26 ± 0.39	0.11
Albumin (mg/dL)	38.5 ± 1.8	38.7 ± 1.9	0.76
Aspartate aminotransferase (U/L)	26.2 ± 10	25 ± 10.5	0.76
Alanine aminotransferase (U/L)	30.1 ± 9	32.3 ± 16.6	0.66
Bilirubin (mg/dL)	0.58 ± 0.27	0.58 ± 0.25	0.99
Total cholesterol (mg/dL)	169.5 ± 55.5	166 ± 36.1	0.85
Triglycerides (mg/dL)	147.8 ± 75.5	136.8 ± 68.7	0.70
HDL cholesterol (mg/dL)	48.2 ± 9.9	48.1 ± 11.3	0.98
LDL cholesterol (mg/dL)	99.4 ± 50.1	87.4 ± 33.1	0.49
Lactic dehydrogenase (U/L)	277.3 ± 86.8	246.2 ± 59.8	0.29
Haptoglobin (ng/L)	1 ± 0.82	1.19 ± 0.67	0.52
NT-proBNP (ng/L)	1781 ± 1505.1	1759 ± 1154.5	0.97
C-reactive protein (mg/dL)	5.1 ± 3.1	4.2 ± 2.3	0.40

EO, echo-guided optimization; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

DOI: 10.1002/ehf2.13359

Table 3 Baseline echocardiographic parameters

Parameter	CONTROL group (N = 14)	EO group (N = 13)	P
LVEF (%)	25.7 ± 2.7	26.5 ± 2.4	0.45
LVEDDI (mm/m^2)	37.6 ± 2.8	37.8 ± 3.9	0.88
LVEDVI (mL/m^2)	108 ± 16.8	106.9 ± 16.7	0.87
E/A ratio	1.49 ± 0.24	1.53 ± 0.14	0.68
LAVI (mL/m^2)	38.9 ± 6.2	38.4 ± 6.6	0.85
MR (1+)	10	9	0.73
MR (2+)	4	4	0.93
AR (1+)	5	7	0.33
AR (2+)	2	1	0.72
Basal RV diameter (mm)	36.4 ± 3.7	37.2 ± 3.2	0.52
RVOT proximal diameter (mm)	28.8 ± 3.3	29.2 ± 3.1	0.80
EDRV area index (cm^2/m^2)	10.1 ± 0.6	9.8 ± 0.5	0.74
RA area (cm^2)	16.1 ± 2.6	16.5 ± 2.9	0.72
TAPSE (mm)	15.1 ± 2.4	15.7 ± 3.4	0.58
FAC (%)	35.8 ± 4.1	36.5 ± 3.8	0.72
RV-RA gradient (mmHg)	25.4 ± 3.5	26.1 ± 4.8	0.66

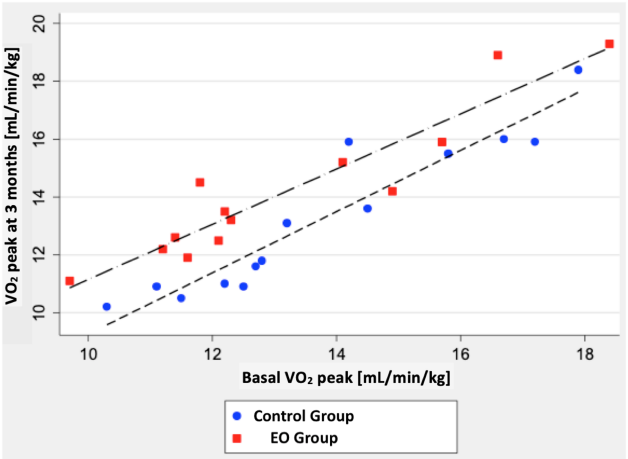
AR, aortic regurgitation; EDRV, end-diastolic right ventricular; EO, echo-optimization; FAC, fractional area change; LAVI, left atrial volume index; LVEDDI, left ventricular end-diastolic diameter index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion.

Table 4 Baseline gas exchange and exercise performance measures

Variable	CONTROL group (N = 14)	EO group (N = 13)	P
ET (s)	504 ± 103	490 ± 98	0.72
Workload (W)	86.9 ± 18.6	80.6 ± 18.1	0.38
Rest heart rate (b.p.m.)	76.5 ± 10.1	76.8 ± 14.5	0.96
Peak heart rate (b.p.m.)	111.3 ± 6.5	111.2 ± 8.4	0.97
VO_2 peak (mL/kg/min)	13.8 ± 2.4	13.2 ± 2.5	0.58
VO_2 work slope (mL/kg/min/W)	8.07 ± 0.84	8.06 ± 1.14	0.98
VE/VCO_2 slope	42.2 ± 7.7	42.5 ± 6.1	0.90
O_2 pulse (mL)	9.83 ± 1.86	9.75 ± 1.46	0.90
VO_2 AT (%)	9.5 ± 1.3	9.8 ± 1.9	0.65
VE peak (L/min)	57.1 ± 14.5	49.9 ± 12.1	0.18
RER	1.12 ± 0.06	1.07 ± 0.07	0.06
6 min walk test (m)	364 ± 84	363 ± 54	0.96

AT, anaerobic threshold; EO, echo-guided optimization; ET, exercise time; RER, respiratory exchange ratio; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen uptake.

Figure 3 Graphical representation of the analysis of covariance for VO_2 peak. EO, echo-guided optimization; VO_2, oxygen uptake.



Regarding the echocardiographic parameters, there was a significant improvement in E/A ratio in the EO group **(**EO group: from 1.52 ± 0.13 to 1.4 ± 0.15 vs. control group: from 1.49 ± 0.24 to 1.48 ± 0.2, P = 0.04). No other significant changes between the two groups were observed, particularly in the RV function data evaluated by fractional area change (EO group: from 36.5 ± 3.8 to 36.8 ± 3.2 vs. control group: from 35.8 ± 4.1 to 35.7 ± 4.2, P = 0.47).

Examining all the scores used to describe the trend in perceived quality of life, a significant enhancement was documented in the EO group: in particular, +6.8% using EuroQol Five Dimensions 3L (EO group: from 0.796 ± 0.1 to 0.85 ± 0.08 vs. control group: from 0.804 ± 0.09 to 0.8 ± 0.08, $P < 0.001$). By examining the results derived from the Kansas City Cardiomyopathy Questionnaire, we noted a statistically significant increase in the global score (EO group: from 81.6 ± 6.9 to 84.6 ± 5.6 vs. control group: from 83.3 ± 7.9 to 83.9 ± 7.2, P = 0.025) and in the following

DOI: 10.1002/ehf2.13359

Table 5 Results of analysis of covariance (ANCOVA) for gas exchange and exercise performance parameters

	EO		CONTROL			
Variable	Baseline	FU	Baseline	FU	*F*	*P*
ET (s)	490 ± 98	526 ± 116	504 ± 103	499 ± 107	6.7	0.02
VO_2 peak (mL/Kg/min)	13.2 ± 2.5	14.2 ± 2.5	13.8 ± 2.4	13.2 ± 2.6	19.5	<0.001
O_2 pulse (mL)	9.75 ± 1.46	10.75 ± 2.2	9.83 ± 1.86	9.76 ± 1.46	10	0.004
VO_2 AT (%)	9.8 ± 1.9	10.3 ± 1.4	9.5 ± 1.3	9.7 ± 1.4	1.6	0.22
VE/VCO_2	42.5 ± 6.1	43.5 ± 8.8	42.2 ± 7.7	44.4 ± 11.2	0.6	0.45

AT, anaerobic threshold; EO, echo-guided optimization; ET, exercise time; FU, follow-up; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen uptake.

domains: quality of life (EO group: +6.69 vs. control group: +2.37, $P < 0.01$), physical limitation (EO group: +4.95 vs. control group: +0.55, $P < 0.01$), social limitation (EO group: +3.01 vs. control group: +0.45, $P < 0.01$). For the others (symptom stability, symptom frequency, symptom burden, and self-efficacy), the increase in the EO group was greater than in the control group, albeit in a not statistically significant way.

To conclude, no significant changes in laboratory parameters were appreciated, particularly in NT-proBNP kinetics (EO group: from 1743 ± 1453 to 1484 ± 1251 vs. control group: from 1759 ± 1154 to 1538 ± 1020, $P = 0.87$). Furthermore, we have not documented in any patient a significant increase in parameters suggestive of haemolysis (lactate dehydrogenase and haptoglobin).

Discussion

To date, our study represents the first experience in showing the positive effects of EO in LVAD patients on the functional capacity expressed in terms of VO_2 peak and on the perceived quality of life. For this reason, a comparison with other studies is very difficult; if we consider experiences investigating the role of some actions (rehabilitation and speed increase) on functional capacity in LVAD carriers, our population is similar for age and aetiology of LV dysfunction. As in Jung *et al.*'s study,[4] our population presents relevant heterogeneity for duration in LVAD support. Not all the considered studies reported medical therapy[3,11]; in comparison with studies reporting this datum,[4,5] in our population, there were more patients in optimal medical treatment.

We evaluated a group of LVAD-supported patients in stable clinical conditions, but with a significant reduction in functional capacity. This condition is closely related to the quality of life and is associated with the risk of adverse events.[15] From this cornerstone arises the need to study reversible modifiable factors that can impact on functional capacity.

Several variables, all linked to each other, regulate cardiac output in LVAD patients, so that device speed changes cannot be converted directly into cardiac output changes. First of all, LVAD patients' cardiac output is strictly dependent on preload and afterload. Although it is not possible to predict accurately haemodynamic changes during physical exertion, EO certainly can imply more appropriate pre-load and afterload basal conditions with a consequent impact on VO_2 peak. Resting pulmonary pressures can be more predictive of exercise capacity in the LVAD patients rather than exercise pulmonary pressures.[16] On the other hand, by reducing afterload, it would be expected to generate beneficial effects on LV filling pressures and secondary pulmonary hypertension.

In our patients, we have also to consider a greater exercise-induced heart rate increase, probably caused by a major contribution of residual LV myocardial function. Native heart function may be an important determinant of functional capacity, thinking that native cardiac output can contribute an additional 3 L during effort[17] even in patients with continuous flow-LVADs. Anyway, about the role of residual myocardial function, there are no univocal results: in one study, VO_2 peak correlated with LV ejection fraction, especially at lower levels of LVAD support levels[18]; other studies have found no correlation between LV ejection fraction and VO_2 peak.[4]

Also, O_2 pulse manifests a significant trend; this parameter represents the ratio of oxygen consumption to heart rate and expresses the volume of oxygen ejected from the ventricles with each cardiac contraction. This value is clearly correlated with stroke volume.

The data on $VEVCO_2$ did not reach statistical significance, and therefore, any interpretation of it must be made with caution: we showed a worsening of this parameter in both groups, although it was less in the EO group. The impact of the patient's self-motivation on the VO_2 peak cannot be ignored: some patients felt motivated to perform longer physical exercise than the 3 months before, and these data are confirmed if we consider exercise time and respiratory exchange ratio. However, we would like to point out that the operator who carried out the CPET was not aware of which group the patient belonged to.

Regarding echocardiographic data, we found a significant amelioration only for the E/A ratio. Mitral inflow E/A ratio and deceleration time are traditionally used to identify the filling patterns. Multiple echocardiographic parameters were compared with simultaneous invasive right heart catheterization measurements in LVAD patients: an algorithm integrating E/A ratio, right atrial pressure, systolic pulmonary artery pressure, and left atrial volume index showed a 90% accuracy in distinguishing normal from elevated LV filling pressures.[19]

Actually, each medical centre uses to perform EO at its own discretion. This procedure is generally achieved in asymptomatic or minimally symptomatic patients with device alarms or other clinical measures of abnormal LVAD or cardiac function.

Some centres have chosen to include an EO protocol regularly with all LVAD surveillance echo exams. Others have decided to include the EO only with the initial surveillance echo examination and then only if a routine surveillance exam reveals a less than optimal LVAD speed.

Our experience suggests that EO has the potential of improving functional capacity and quality of live. Compared with right heart catheterization (the gold standard of haemodynamic assessment), echocardiography is readily available, non-invasive, and easily repeatable.

Limitations associated with this study should be mentioned, such as the small sample size and the consequent restriction in the findings' interpretation. Initially, this was a single-centre, prospective analysis of a relatively small cohort of patients. However, the sample size is consistent with previous research in the field of other continuous flow-LVAD monocentric, randomized clinical trials. The outbreak of the COVID-19 pandemic made it very difficult to reach the threshold of 36 patients. The analysis performed on the 27 enrolled patients has in any case provided significant data that will undoubtedly lead to the consideration of future multicentre studies.

The nature of the study precluded the possibility of a double-blind conduction, but the operators who carried out the CPET and the echocardiography were not informed of the arm of the study to which the patient was assigned. The only investigator involved in the study to be informed about the type of treatment the subject was receiving was the operator dedicated to EO. Patients were not aware of the study arm they were part of. But we cannot speak of a true 'blind' condition for the patient, considering that they are all trained in self-monitoring and they were able to see that the device speed had been changed. We tried to give to all patients, however, the impression that the LVAD setup was the best possible.

Echo-guided optimization represents a challenging procedure considering the necessity to equilibrate interventricular septum position, AV opening, mean artery pressure, and estimated filling pressures. Even after optimization of these factors at rest, the balance of these elements could change during effort. Various changes may occur in venous return, LV contractility, RV function, and peripheral resistance; the evolution of these parameters in this contest and the influence on LVAD performance remain an open debate.

We chose a 3 month timeframe to test the effects of EO, examining the average short-term follow-up in the literature's experiences, but also in order to minimize the effects of possible adverse events that cannot be correlated with EO. For our study, it was essential that the device settings remained unchanged over the 3 months; in case of need to modify the parameters for clinical reasons, the adverse event would have been reported and considered as an endpoint. Our aim was also to minimize interferences caused by physical training; in this 3 month period, we have invited patients not to change, as far as possible, their daily physical activities. Additionally, we believe that in the planning of an ideal long-term protocol of EO could be correct to execute this procedure every 3 months, considering how the patient's haemodynamics may vary also for climatic conditions and seasonality.

In addition to the role of EO, it is also necessary to consider the value of medical therapy aimed at optimizing the blood pressure values of the patients (at the aim of obtaining a mean blood pressure $\leq$ 80 mmHg) and the importance of maintaining a state of normovolemia.

The pathophysiological mechanisms responsible for severe reduction of functional capacity in LVAD patients are related not only to an impaired cardiac index and an inadequate increase in heart rate from rest to exercise but also to peripheral abnormalities (reduced skeletal muscle blood flow or endothelial dysfunction). Therefore, in these patients, the importance of physical training and treatment of comorbidities (in particular anaemia and respiratory diseases) should not be overlooked.

VO_2 peak is a relevant index of heart failure prognosis; its increase is a target of therapy, and it is associated with a survival improvement. We are not able to define whether in LVAD patients the improvement of this datum could also impact on survival. Other studies are necessary to extend the execution of CPETs in a longer period of follow-up, to understand if further improvements may occur over time.

Conclusions

The limitation in functional capacity in LVAD patients largely depends on the interface between the device and the native heart: not only the LVAD parameters (in particular, the pump speed) but also the residual function of native left ventricle and the presence of RV dysfunction and/or valves abnormalities have to be considered.

VAFRACT is the first prospective randomized trial to show the additional potential benefit of an EO approach on functional capacity and quality of live in an LVAD population. The results are encouraging, but not totally conclusive: our trial may be considered as 'hypothesis-generating' for a future, adequately powered clinical trial with a longer term outcome evaluation. Furthermore, it could be interesting to study the effects of a combined EO and long-term cardiovascular rehabilitation programme.

Acknowledgements

We would like to thank Dr Lorenzo Franceschini for his contribution and support in this study; he passed away on 25 January 2020.

Conflict of interest

None declared.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Goldstein DJ, Meyns B, Xie R, Cowger J, Pettit S, Nakatani T, Netuka I, Shaw S, Yanase M, Kirklin JK. Third annual report from ISHLT mechanically assisted circulatory support registry: a comparison of centrifugal and axial continuous-flow left ventricular assist devices. *J Heart Lung Transplant* 2019; **38**: 352–363.
2. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. *J Heart Lung Transplant* 2015; **34**: 489–496.
3. Vignati C, Apostolo A, Cattadori G, Farina S, Del Torto A, Scuri S, Gerosa G, Bottio T, Tarzia V, Bejko J, Sisillo E, Nicoli F, Sciomer S, Alamanni F, Paolillo S, Agostoni P. LVAD pump speed increase is associated with increased peak exercise cardiac output and VO_2, postponed anaerobic threshold and improved ventilatory efficiency. *Int J Cardiol* 2017; **230**: 28–32.
4. Jung MH, Houston B, Russell SD, Gustafsson F. Pump speed modulations and sub-maximal exercise tolerance in left ventricular assist device recipients: a double-blind, randomized trial. *J Heart Lung Transplant* 2017; **36**: 36–41.
5. Fresiello L, Buys R, Timmermans P, Vandersmissen K, Jacobs S, Droogne W, Ferrari G, Rega F, Meyns B. Exercise capacity in ventricular assist device patients: clinical relevance of pump speed and power. *Eur J Cardiothorac Surg* 2016; **50**: 752–757.
6. Apostolo A, Paolillo S, Contini M, Vignati C, Tarzia V, Campodonico J, Mapelli M, Massetti M, Bejko J, Righini F, Bottio T, Bonini N, Salvioni E, Gugliandolo P, Parati G, Lombardi C, Gerosa G, Salvi L, Alamanni F, Agostoni P. Comprehensive effects of left ventricular assist device speed changes on alveolar gas exchange, sleep ventilatory pattern, and exercise performance. *J Heart Lung Transplant* 2018; **37**: 1361–1371.
7. Murninkas D, Alba AC, Delgado D, McDonald M, Billia F, Chan WS, Ross HJ. Right ventricular function and prognosis in stable heart failure patients. *J Card Fail* 2014; **20**: 343–349.
8. Uriel N, Sayer G, Addetia K, Fedson S, Kim GH, Rodgers D, Kruse E, Collins K, Adatya S, Sarswat N, Jorde UP, Juricek C, Ota T, Jeevanandam V, Burkhoff D, Lang RM. Hemodynamic ramp tests in patients with left ventricular assist devices. *JACC Heart Fail* 2016; **4**: 208–217.
9. Uriel N, Morrison KA, Garan AR, Kato TS, Yuzefpolskaya M, Latif F, Restaino SW, Mancini DM, Flannery M, Takayama H, John R, Colombo PC, Naka Y, Jorde UP. Development of a novel echocardiography ramp test for optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices: the Columbia ramp study. *J Am Coll Cardiol* 2012; **60**: 1764–1775.
10. INTERMACS Executive Committee. Adverse event definitions: adult and pediatric patients. May 15, 2013. https://www.uab.edu/medicine/intermacs/intermacs-documents **(Accessed: 15 December 2019)**.
11. Kerrigan DJ, Williams CT, Ehrman JK, Saval MA, Bronsteen K, Schairer JR, Swaffer M, Brawner CA, Lanfear DE, Selektor Y, Velez M, Tita C, Keteyian SJ. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the rehab-VAD randomized controlled trial. *JACC Heart Fail* 2014; **2**: 653–659.
12. Whipp BJ, Davis JA, Wasserman K. Ventilatory control of the 'isocapnic buffering' region in rapidly-incremental exercise. *Respir Physiol* 1989; **76**: 357–367.
13. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; **60**: 2020–2027.
14. Stainback RF, Estep JD, Agler DA, Birks EJ, Bremer M, Hung J, Kirkpatrick JN, Rogers JG, Shah NR, American Society of Echocardiography. Echocardiography in the management of patients with left ventricular assist sevices: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2015; **28**: 853–909.
15. Imamura T, Kinugawa K, Nitta D, Hatano M, Kinoshita O, Nawata K, Ono M. Perioperative hypoalbuminemia affects improvement in exercise tolerance after left ventricular assist device implantation. *Circ J* 2015; **79**: 1970–1975.
16. Koshy A, Green T, Toms A, Cassidy S, Schueler S, Jakovljevic D, MacGowan GA. The role of exercise hemodynamics in assessing patients with chronic heart failure and left ventricular assist devices. *Expert Rev Med Devices* 2019; **16**: 891–898.
17. Martina J, de Jonge N, Rutten M, Kirkels JH, Klöpping C, Rodermans B, Sukkel E, Hulstein N, Mol B, Lahpor J. Exercise hemodynamics during extended continuous flow left ventricular assist device support: the response of systemic cardiovascular parameters and pump performance. *Artif Organs* 2013; **37**: 754–762.
18. Noor MR, Bowles C, Banner NR. Relationship between pump speed and exercise capacity during HeartMate II left ventricular assist device support: influence of residual left ventricular function. *Eur J Heart Fail* 2012; **14**: 613–620.
19. Estep JD, Vivo RP, Krim SR, Cordero-Reyes AM, Elias B, Loebe M, Bruckner BA, Bhimaraj A, Trachtenberg BH, Ashrith G, Torre-Amione G, Nagueh SF. Echocardiographic evaluation of hemodynamics in patients with systolic heart failure supported by a continuous-flow LVAD. *J Am Coll Cardiol* 2014; **64**: 1231–1241.