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The effects of echo-optimization of left Ventricular Assist devices on Functional capacity: a RAndomized Controlled Trial (VAFRACT)

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A mamma e papà che mi hanno insegnato il sacrificio.
A te V, che in me hai sempre creduto.

TABLE OF CONTENTS

SUMMARY

L'introduzione delle assistenze meccaniche al circolo (MCS) ha indubbiamente comportato un significativo impatto sulla sopravvivenza dei pazienti affetti da insufficienza cardiaca avanzata refrattaria alla terapia medica. Tuttavia, dopo l'impianto di un'assistenza ventricolare meccanica sinistra (LVAD), la loro capacità funzionale permane comunque ridotta con valori di VO_2 di picco al test cardiopolmonare (CPET) compresi tra 11 e 20 ml/kg/min.

E' riportato in letteratura che la procedura di ottimizzazione eco-guidata (EO) dei parametri dei LVADs migliori il profilo emodinamico di tali pazienti. Il setting ottimale del dispositivo è inteso come quello che consente di ottenere l'apertura intermittente della valvola aortica e una posizione neutrale del setto interventricolare senza incremento dell'eventuale rigurgito aortico e tricuspidale, preservando la funzione ventricolare destra.

Non esistendo invece chiare evidenze in letteratura in merito all'effetto dell'EO sulla capacità funzionale, abbiamo intrapreso uno studio prospettico, randomizzato, per valutare il beneficio addizionale della procedura su tale outcome, avvalendoci del test cardiopolmonare per una sua corretta quantificazione.

Prima di esporre in dettaglio il progetto, la tesi si propone di esplorare ampiamente il background alla base della sua ideazione.

Pertanto nell'introduzione vengono analizzati i dati relativi all'epidemiologia sullo scompenso cardiaco e alla sua classificazione. Successivamente sono esposti i dati relativi allo scompenso cardiaco avanzato, il ruolo delle terapie chirurgiche non convenzionali quali il trapianto cardiaco e i dispositivi di assistenza meccanica al circolo (MCS). Su quest'ultimi, un capitolo è dedicato alla loro storia ed alla successiva evoluzione sino ai giorni nostri. Vengono inoltre descritte le principali indicazioni cliniche al loro utilizzo, oltre che le controindicazioni e le più frequenti complicanze.

Sono poi discussi i fattori determinanti la capacità funzionale nei pazienti portatori di LVAD. A seguire, viene esplorato il ruolo dell'ecocardiografia nell'iter diagnostico-strumentale di questi pazienti; infine viene descritta la

procedura di EO soffermandosi sulla modalità di esecuzione e sui primi studi scientifici che ne hanno validato l'utilizzo.

La seconda parte dell'elaborato è ovviamente dedicata alla discussione del progetto di ricerca.

Dopo almeno 3 mesi dall'impianto di un LVAD, i pazienti che hanno accettato di partecipare allo studio sono stati sottoposti alla procedura di EO e randomizzati 1:1 in due gruppi: nel primo (gruppo EO) sono stati confermati i parametri ottimizzati; nel secondo (gruppo di CONTROLLO) è stata invece mantenuta la configurazione precedente alla procedura di EO.

Abbiamo indicato come end-point primario la variazione della VO_2 di picco a distanza di tre mesi dalla procedura di EO. Gli end-points secondari sono rappresentati da: funzione ventricolare destra valutata con la Fractional Area Change (FAC); ospedalizzazioni device correlate; i livelli di NT-pro BNP; il tempo di esercizio al test cardiopolmonare; variazioni nella qualità della vita misurate con l'EuroQol Scale e il Kansas City Cardiomyopathy Questionnaire (KCCQ).

L'arruolamento è stato effettuato tra l'Ottobre 2017 e l'Agosto 2019: 27 pazienti hanno dato il loro consenso alla partecipazione allo studio.

In riferimento alle caratteristiche di base della popolazione dei pazienti, nessuna differenza statisticamente significativa è stata osservata tra i due gruppi in esame.

L'analisi dei dati mostra dei risultati significativi per i pazienti del gruppo EO sui parametri di capacità funzionale come la VO_2 di picco, il polso di O_2, il tempo di esercizio, la distanza percorsa al test del cammino e sulla qualità della vita. Durante lo studio non abbiamo osservato alcun evento di ospedalizzazione device-correlata nei 2 gruppi.

In conclusione, si ritiene che l'EO, oltre ad essere una procedura accessibile e facilmente ripetibile in quanto non invasiva, possa avere un notevole impatto non solo sul profilo emodinamico dei pazienti portatori di LVAD, ma anche sulla loro capacità funzionale e sulla loro qualità di vita.

ABSTRACT

Background: After the implantation of a left ventricular assist device (LVAD), many patients continue to experience exercise intolerance. LVAD echo-guided optimization (EO) determines a more favourable hemodynamic profile and could provide an improvement on functional capacity (FC). VAFRACT is the first prospective randomized trial to evaluate the additional benefit of an EO approach on FC, measured by cardiopulmonary exercise test (CPET) in LVAD optimization free population.

Methods and procedures: Patients were randomized in a 1:1 ratio to EO (EO group) versus standard settings (CONTROL group) at least after 3 months from LVAD implant procedure. The optimal device speed is 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 (RV) function. The primary end-point is peak oxygen uptake (VO_2 peak) change after 3 months following the EO. The secondary end-points are: RV function (measured by fractional area change - FAC); hospital admissions device related; N-terminal brain natriuretic peptide (NT-pro BNP) levels; CPET exercise time (ET); changes in quality of life (QoL) perceived by EuroQol Scale (EQ-5D-3L™) and Kansas City Cardiomyopathy Questionnaire (KCCQ).

Results: No statistically significant differences have been found in basal characteristics of the two groups. Time of LVAD implantation was about 674 ± 495 days. The most common indication to implant was "bridge to transplant". Analysis of data shows significant results of EO for functional parameters like VO_2 peak (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 - **$p < 0.001$**), O_2 pulse (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 - **$p < 0.001$**), ET (EO group: from 490 ± 98 to 526 ± 116 vs CONTROL group: from 504 ± 103 to 499 ± 107 - **p 0.02**), 6 minute walk distance **(**EO group: from 363 ± 54 to 391 ± 52 vs CONTROL group: from 364 ± 84 to 374 ± 80 - **p 0.04)** and on quality of life, using EQ-5D-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 - **$p < 0.001$**) and considering KCCQ (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**). No device-related hospital admissions were observed in the two groups during the study.

Conclusion: Compared to right heart catheterization (the gold standard of hemodynamic assessment), LVAD EO is readily available, non-invasive and easily repeatable. Our study shows how it can significantly influence the functional capacity and the quality of life of LVAD patients. We believe that this strategy should constitute a cornerstone in the clinical management of patients with LVAD, through the establishment of consolidated follow up protocols.

INTRODUCTION

Heart failure

Epidemiology and classification

Heart failure (HF) is a global pandemic affecting at least 26 million people worldwide **[1]**.

An estimated 6.2 million Americans ≥ 20 years of age have HF and every year there are still 91,5000 new cases. The prevalence of HF increases with age for both sexes **[Figure 1]**; it is expected that by 2030 more than 8 million people will have this condition, accounting for a 46% increase in prevalence **[2]**.

Its incidence approached 21 per 1,000 after 65 years of age; data from the 2005 to 2014 community surveillance component of the ARIC study indicate that rates of hospitalizations for HF are increasing over time **[Figure 2]**. In 2016, HF was the underlying cause in 78,356 deaths **[3-5]**. HF health expenditures are considerable, with a dramatic increase in older patients. In 2012 it caused an estimated health expenditure of around $31 billion (£22.5 billion), more than 10% of the total health expenditure for cardiovascular diseases in the US **[1]**.

In Italy a recent survey reported HF prevalence of 1.44%, with rates increasing with the ageing of the population **[6]**. In 2016 it caused more than 180,000 hospitalizations **[7]**.

HF is a clinical syndrome identified by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) often associated with signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) originated by a structural and/or functional heart abnormality, leading to a reduced cardiac output and/or increased intracardiac filling pressures at rest or during stress **[8]**.

The main terminology used to describe HF is historical and is related to the ejection fraction of the left ventricle (LVEF) **[9]**. The main distinction is in patients with normal EF (LVEF ≥ 50%) that have HF with preserved EF (HFpEF) and patients with reduced EF (LVEF<40%) that have HF with reduced EF (HFrEF). EF between 40 and 49% defines a “grey condition” called HF with mid-range EF (HFmrEF) **[Table 1]**. This last definition could be misleading because

it’s not certain if it is a different entity or only a phase of transition from HFpHF to HFrEF **[10]**.

HF could also be classified in relation to its time course; patients that have had HF for some time are often said to have “chronic HF”. A treated patient with unmodified symptoms for at least one month is said to be “stable”. When a patient with a “chronic stable HF” showed a deterioration in his/her clinical situation, suddenly or slowly (often, but not always, leading to hospital admission), may be described as “decompensated”. The first appearance of HF could be defined “New-onset” (“de novo”) HF **[8]**.

To describe the severity of symptoms and exercise intolerance, the New York Heart Association (NYHA) functional classification is the most used in clinical practice **[Table 2].** It has been developed to help physicians measure the effects of cardiac symptoms on patients' daily activities **[11]**. Although the validity of the NYHA classification to measure functional status (a different concept from functional capacity and functional performance) has been confirmed, it has demonstrated suboptimal reproducibility and a lack of sensitivity for the detection of clinically important variations, in consequence of the subjective nature of the NYHA criteria and self-reported patient symptoms **[12,13]**.

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) has produced a classification based on structural heart disease and presence of symptoms **[14] [Table 2]**.

Advanced heart failure

End stage HF has reached epidemic proportions; albeit recent progresses in medical therapy in the last ten years and the introduction of Implantable Cardioverter Defibrillators (ICD) and Cardiac Resynchronization Therapy (CRT) devices, when it becomes advanced and refractory to medical therapy, prognosis remains severe with a lifespan risk at the age of 55 of 33% in men and 28% in women **[15]**.

The CONSENSUS trial represented the first example of lowering the number of HF-related deaths thanks to a pharmacological treatment **[16]**. Since then, various drugs have had a considerable impact on this outcome. Considering an annual

mortality rate of 20% and a mean survival time of 4.1 years at baseline, the use of an angiotensin-converting enzyme inhibitor (ACE-I), a beta-blocker, an aldosterone antagonist and an ICD decreases annual mortality by 70% and extends the mean survival time to 5.6 years **[17]**. Results from the recently published PARADIGM-HF [Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure] trial demonstrated that sacubitril-valsartan was superior in reducing the risks of death and hospitalization for HF compared to standard medical treatment **[18]**.

However, heart transplant (HTx) is actually considered the "gold standard" treatment for many patients with end-stage HF, with one year survival rate superior to 85% **[19]**. Moreover, during the last years it has demonstrated a poor epidemiological impact; the limitation of suitable death donors for withdrawal and transplantation of this organ represents the principal reason of yearly number of HTx performed in our and other European countries. Long permanence in waiting list exposes patients to high death risk (one year mortality around 8-10%, limited by allocation mechanisms that favour patients candidates in more severe conditions) and more progressive deterioration that causes the ineligibility for this treatment in 10-15% of the candidates for multiorgan failure, infections, cachexia **[20]**. HTx is also affected by several long term complications related to immunosuppressive therapy and finite graft survival.

The recent ISHLT 36th Adult Heart Transplant Report has described a change in the growing gap between the number of patients on waiting list and the number of HTx per year, showing significant higher HTx volumes, particularly in the most recent years in North America and other countries. This increase may reflect donor availability with the rising number of deaths owing to drug overdoses in the US and the extended use of "higher-risk" donor hearts. Also the addiction of nascent HTx programs in developing countries have contributed to these data **[21]**.

In Italy, according to the report of the Transplantation Information System, updated to August 31st 2019, the number of total donations and transplants performed has increased incredibly. In 1992 there were 329 organ donations for a

total of 1,083 transplants. In 2018, there were 1,371 donations and 3,407 transplants. The 2014-2018 trend has risen sharply, with a growth in donations of 24.4% and 2018 was the second best year ever, with 1,680 donors, well above the average of the last 5 years. In the first eight months of 2019, more HTx (239) were recorded than the entire 2018 **[Figure 3][22]**.

CHAPTER I

Mechanical circulatory support: classification and indications

In the last years, following the endemic shortage of donor hearts, MCS emerged as a readily available therapeutic option used to unload failing ventricles and maintain adequate peripheral organ perfusion.

Through the time of permanence of the device, they could be classified in short term and long term MCS. In the clinical scenario of acute HF with acute cardiogenic shock, short term MCS is used as a bridge to future clinical decision.

In the context of chronic end-stage HF, refractory despite optimal medical therapy, LVADs are used with different indications. According to European Society of Cardiology (ESC) Guidelines clinical indications to MCS are: Bridge to Decision (BTD), Bridge to Candidacy (BTC), Bridge to Transplant (BTT), Bridge to Recovery (BTR) and Destination Therapy (DT) **[Table 3[8]]**.

MCS used in patients with the indication BTD are short term MCS, like ExtraCorporeal Life Support (ECLS) or ExtraCorporeal Membrane Oxygenation (ECMO). Long term support could be divided in Right Ventricular Assist Devices (RVADs) and Left Ventricular Assist Devices (LVADs) which are commonly used with the indication to BTT or DT.

In accordance with the major guidelines and statements, the definition of patients eligible for MCS include those with clinically significant circulatory deterioration who require special care, including consideration for heart transplantation, continuous intravenous inotropic therapy, or admission to a hospice **[Table 4] [8,14].** Both European and American Guidelines, from ESC and ACC/AHA Guidelines recommend that the implantation of a LVAD should be considered in carefully selected patients with advanced HF (Class of Recommendation IIa). The ESC Guidelines makes a distinction between LVAD for BTT (Class of Recommendation IIa - Level of Evidence C) and for patients who are not eligible for heart transplantation (Class of Recommendation IIa, Level of Evidence B). A summary of different indications to MCS according to the American and European Guidelines is reported in **Table 5[8,14].**

INTERMACS (the Interagency Registry for Mechanically Assisted Circulatory

Support), in quality of responsible of the follow up of all long term MCS in USA, proposed a classification related to the risk's patient profile at the time of the implant **[Table 6]**. From this registry, seven different profiles have been defined plus three additional potential modifiers. INTERMACS 1 identifies the most dramatic clinical situation, a patient too compromised for long term LVAD support with higher post implantation mortality compared to other INTERMACS 2-7 profiles.

The Third Annual Report From IMACS Registry showed that from 2013 to 2017 a total of 16,286 LVAD implants were been performed **[Figure 4]** and INTERMACS profiles 1-3 constitute 85% of implants. In the last years, implantations in patients in critical cardiogenic shock has increased, despite evident worst prognosis**.** Two thirds of patients undergoing CF-LVAD support are in INTERMACS 1-2, as happened in the previous years. The proportion of ambulatory HF patients that identify INTERMACS profile between 4 and 7 that underwent LVAD implant, declined from 22% in 2013 to 13% in 2017 **[Figure 5] [23]**.

History of MCS

First clinical application of MCS in HF was performed after the second part of the 60's when a mechanical assist system was used in a patient with cardiogenic shock after cardiac surgery. In 1966 at Baylor College of Medicine the first ventricular assist device (VAD) was implanted as a "BTR" of LV contractile function. In 1969 Denton Cooley implanted the first total artificial heart (TAH) activated pneumatically in a patient with the aim of "BTT". The device was composed of two reciprocating pumps constructed entirely of synthetic materials and activated pneumatically in the orthotopic position by a control console connected by tubes passed through the patient's chest wall. The device supported the patient's circulation for 64 hours. Death of the recipient from Pseudomonas pneumonia occurred 32 hours after the allografting. The first successful prolonged use of a total mechanical substitute for the human heart had been recorded **[24]**.

Nine years later Norman et al **[25]** had an emergency implantation of an intracorporeal partial artificial heart (an abdominal left ventricular assist device - ALVAD) in a patient with acute bacterial endocarditis who developed a cardiac

failure during a procedure of aortic and mitral replacement. This device worked as a TAH for nearly 6 days, while a donor heart for transplantation was found. The ALVAD was removed and the patient received allografts of a heart and a kidney. The HTx was successful, but the patient died 15 days later from gram-negative sepsis.

In the following years the National Heart, Lung and Blood Institute started in 1975 a program of evaluation of VADs.

First principal intentions were to develop new systems totally implantable and with more biocompatible materials for long term therapy, to let patients move and have a good quality of life. In 1982 the first experience with a TAH was reported **[26]**. The device was developed at the University of Utah and was implanted in a 61-year-old man with chronic HF due to primitive cardiomyopathy. Death occurred on the 112$_{th}$ day, preceded by progressive renal failure and refractory hypotension, despite maintenance of adequate cardiac output.

Other positive experiences were reported by Levinson et al. **[27]**, but presence of high incidence of complications dampened the enthusiasm.

Due to the poor outcomes, there was a shift from the concept of total heart replacement, towards the development of a single chamber pump as cardiac support.

First generation of VADs

The first generation devices, attempting to recreate the pulsatility of a native heart, were either pneumatically or electrically driven membrane pumps, generating pulsatile flow with artificial heart valves as inlet and outlet. Connected to the heart via cannulas, these pumps could be used either as isolated left-, right- or biventricular assist device. In case of biventricular support, pump chambers had to be placed extracorporeal due to size; for exclusive LV support intracorporeal placement was possible. Initially these devices were designed only as BTT. Then, over the years, the reduction in size of the pumps allowed patients to be discharged with VAD at home. In 1984 there was the first successful HTx after LVAD implantation **[28]**.

Examples of first generation devices are Berlin Heart EXCOR (Berlin Heart, Berlin, Germany), Thoratec PVAD and Heartmate XVE (Thoratec, Pleasanton,

CA, USA) **[Figure 6 [29]]**. The Heartmate XVE was studied in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial which involved 129 HTx ineligible patients with NYHA functional class IV randomized to optimal medical therapy or to LVAD implantation. Median survival was increased by 8 months (of which 5 months were spent out of the hospital) in the HeartMate XVE arm, with a significant improvement also in quality of life. However, after 2 years, only 23% of patients were alive because of device failure or infection **[30]**. These data confirmed the limitations of this type of VADs: large size, noise emission, high risk of infection of cannulas and degradation of valves **[28]**.

Second generation of VADs

The next step in device development came with the transition from pulsatile to continuous flow. CF rotary pumps are composed by a blood inlet and outlet ports and a single rotating element that imparts energy to the blood to increase arterial blood flow and pressure.

Second generation VADs were much smaller and less noisy due to fewer moving parts. There was also limited surface area for blood contact, designed to reduce the incidence of adverse events, in particular thrombosis, infections and mechanical failures **[31].**

One of the first of these devices was the HeartMate II (HMII) (Thoratec, Pleasanton, California), an axial-flow device, that generated continuous flow using a rotor suspended in the blood through a mechanical bearing. It was initially studied in a randomized trial in HTx ineligible patients with advanced HF.

200 patients with NYHA functional class IV HF were randomized 2:1 to the HMII or Heartmate XVE device. The primary endpoint of survival, free of disabling stroke or the need for reoperation, to repair or replace the LVAD after a 2-year period was obtained in 46% of the HMII patients in comparison with the 11% of XVE patients. There were also significant reductions in most major adverse events except stroke rates. Two-year survival was significantly improved with the HMII (58% vs. 24%) as quality of life and functional capacity **[32]**. The device was approved by US Food and Drug Administration (FDA) with the indication BTT in 2008 as well as DT in 2010 **[Figure 7 [29]]**.

This kind of devices were designed exclusively for intrathoracic placement so the only possible implantation was as LVAD, because it was too big to be used as BiVentricular Assist Device (BIVAD).

From axial to centrifugal continuous–flow LVAD: the third generation of VADs

Transition from axial to centrifugal continuous-flow characterized the new third generation of LVAD. **[Figure 8[29]]**

Since the first generation of LVADs, modern implantable systems have clearly improved. The mortality in the early trials was 52% after one year compared to 25% with medical therapy **[30].** Since then mortality has further declined and with second generation continuous-flow pumps the survival has increased to 80% after 1 year and 70% after 2 years **[31]**.

Contemporary continuous flow (CF) LVADs consists of three basic components: an inflow cannula attached to the LV apex and draws blood from this chamber into the device, an impeller that moves the blood forward in parallel with native cardiac output (CO), and an outflow cannula that returns blood back into the proximal aorta or descending aorta.

The primary difference between centrifugal-flow and axial-flow pumps is in the design of their rotating elements **[Figure 9 [33]].** In Centrifugal CF pumps the rotating element acts as a spinning disk with blades that can be viewed as a "thrower" meaning that the fluid is captured and thrown tangentially off the blade tips. In contrast, axial CF pump rotating elements operate like a propeller in a pipe and can be viewed as a ''pusher''**[33]**.

The archetype LVAD in this group is the HeartWare ventricular assist device (HVAD) which was studied in "The HeartWare™ Ventricular Assist System as DT of Advanced Heart Failure (ENDURANCE)" study which made a comparison between HVAD (centrifugal flow VAD) and HeartMate II (axial flow device). The 446 patients were randomized in a 2:1 manner to the HVAD (n=297) vs. the HeartMate II (n=148). The primary end point was survival after 2 years free from disabling stroke or device removal for malfunction or failure.

HVAD had significantly higher incidence of ischemic or haemorrhagic stroke compared to HeartMate II but was non-inferior on primary outcomes **[34]**.

HeartMate 3TM is a third generation centrifugal continuous-flow LVAD with the rotor being suspended in the blood flow using a noncontact design through magnetic levitation. It received the European CE Mark approval in 2014. The main advantage of this type of system is the noncontact bearings. This design was thought with the aim of reducing heat formation, friction and shear stress and consequently decrease the possibility of thrombus formation.

According to the MOMENTUM 3 Trial, a randomized non-inferiority and superiority trial that compared the centrifugal-flow pump with the axial-flow pump in patients with advanced HF, irrespective of the intended goal of support (BTT and DT). Of 366 patients, 190 were assigned to the centrifugal-flow pump group and 176 to the axial-flow pump group. The results showed that a fully magnetically levitated centrifugal-flow pump was superior to a mechanical-bearing axial-flow pump with regard to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device **[35].**

Heartmate 3TM received the FDA approval for BTT in 2017 and for DT in 2018**.**

The 2019 Third Annual Report From the ISHLT Mechanically Assisted Circulatory Support Registry (IMACS Registry) demonstrated a transition from axial to centrifugal flow with a 4-year survival approximating to 60%. After 2.5 years of support, a trend in survival favouring centrifugal devices is described. Furthermore, gastrointestinal bleeding and pump thrombosis were more frequent in axial-flow recipients **[23]**.

CHAPTER II

LVADs in advanced heart failure: patient selection

The use of LVAD is a viable therapeutic option to improve survival and quality of life of patients with advanced and refractory HF. The evolution not only in technologies but also in the selection of patients and the development of competences in peri- and postoperative management have led to a constant improvement in the survival of LVAD carriers, currently estimated at around 87% after one year **[23]**.

However, the optimal timing of LVAD placement ("not too early and not too late") in the management of advanced HF remains a challenge.

The severity of end organ dysfunction at the time of implantation has a significant impact on hospital stay after surgery and one-year survival **[36]**. Prediction of survival with different risk scores is useful to recognize the right candidate. A single model is not sufficient to assess completely the risk in these patients because of a large number of variables. Consequently, different risk models have been validated to predict survival post LVAD implantation.

The Model for End-Stage Liver Disease (MELD) score considers laboratory data like bilirubin, creatinine, and international normalized ratio (INR). In patients on oral anticoagulation therapy, the MELD XI score is used, an adapted version based only on creatinine and bilirubin. Patients with a MELD score below 17 have a survival advantage over those with a score of 17 or above, and MELD XI has proven to be a similar predictor of survival. The coefficients used for MELD score calculation were derived from patients with multifactorial liver disease and no documented cardiac dysfunction **[37]**.

Another score studied in patients with advanced HF, is HeartMate II Risk Score (HMRS) that considers the following variables: age, INR, serum albumin, creatinine, and implant centre LVAD experience. The variables (except for age) constitute possible treatment targets, so pharmacological strategies or mechanical supports can be used to obtain better renal function (serum creatinine), better hepatic or right ventricular (RV) function (INR), and a better inflammatory/nutritional state (albumin). The HMRS score cut-offs distinguish

three risk groups: a low-risk group (HRMS < 1.58) with a 90-day mortality of 4%; a medium-risk group (1.58 - 2.48) with a mortality of 16%; and a high-risk group (HMRS > 2.48) with a mortality of 29% **[38]**.

Finally, there is the CRITT score that considers central venous pressure (CVP) greater than 15 mmHg, severe RV dysfunction, preoperative mechanical ventilation, severe tricuspid regurgitation (TR), and tachycardia. A score < 2 predicts successful isolated LVAD implantation **[39]**.

In the scores we have described, the RV function represents the common denominator; preoperative RV dysfunction represents a strong predictor of post implant mortality and a severe dysfunction constitutes an absolute contraindication to LVAD implantation.

Assessment of contraindications is critical, considering the cost, the burden, and the risk of the procedure. Not only cardiac factors have to be considered, but also extracardiac features: coexisting severe terminal comorbidity (renal, pulmonary, liver or neurological disease or evidence of advanced metastatic cancer); active bleeding, thrombocytopenia or the inability to be placed on anticoagulation; technical limitations like body surface area less than 1.5 m_2; social considerations like an inadequate patient compliance **[**other details in **Table 7] [40]**.

LVAD related complications

As stated by the last IMACS report, complications after LVAD implantation continue to limit long-term success of durable MCS therapies **[23]**.

In general, all major adverse events occur during the first 3 months after the implantation. The recognition that bleeding and thrombotic events constitute the Achilles heel of MCS technologies has led to the concept of hemocompatibility-related adverse events (HRAEs). These include stroke, peripheral thrombosis, de novo pump-thrombosis, and mucosal bleeding (especially in gastrointestinal site).

Hemocompatibility related complications

Bleeding

Due to the large surface area of artificial material in contact with blood, anticoagulant and antiplatelet therapies are necessary to prevent thrombus

formation. These drugs that predispose to bleeding complications, cannot entirely explain them.

Risk of bleeding in the setting of CF-LVAD is multifactorial; increased shear stress is associated to abnormalities like haemolysis and platelet activation, oxidative stress, increased circulating microparticles, loss of high molecular weight multimers of von Willebrand factor (vWF).

Acquired vWF syndrome represents one of the most important components of bleeding in LVAD patients. Physiologically vWF is made in the endothelial cells, released into the bloodstream as high molecular weight multimer that binds factor VIII and plays an important role in haemostasis. Predisposing systemic conditions like hepatic and renal dysfunction also have a relevant impact **[41]**.

Presence of old or development of new gastrointestinal lesion contributes to the introduction of gastrointestinal bleeding that has a troubling frequency and has been widely observed in axial CF- LVAD recipients **[23]**.

Thromboembolic events

Despite antithrombotic treatment, thromboembolic events are common. They include: cerebrovascular accident, arterial non-central nervous system embolism and pump thrombosis (PT).

Neurologic events are the primary cause of death **[23]**. Multivariate analysis showed that diabetes, complete aortic clamping with cardioplegic arrest, duration of support, and subtherapeutic INR values constitute independent predictors of stroke **[42]**.

PT is an uncommon but potentially catastrophic event, as a cause of device exchange or death. It is one of the major challenging problems and it has a multifactorial genesis: therefore, it is difficult to find a univocal solution.

The major factors include: pump design, patient risk factors (e.g. inherited coagulation disorders, compliance-related issues), management issues (e.g. implant technique, variations in physician treatments).

The MOMENTUM 3 trial showed that HeartMate 3TM had a significantly lower incidence of need for pump exchange in comparison with HMII (1 event [0.7%] vs 11 events [7.7%], respectively) as a result of complete absence of PT, whereas

the other device experienced a 10.1% incidence of confirmed or suspected thrombotic events **[43]**. The results of this study indicate that advances in VAD design and technology could have a great impact on this problem, but the weight of the other factors should not be underestimated.

Non hemocompatibility related complications

Right heart failure

Right heart failure (RHF) is defined as the presence of symptoms and signs of persistent RV dysfunction [CVP > 18 mmHg with a cardiac index < 2.3 L/min/m^2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (PCWP), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD implantation, inhaled nitric oxide, or inotropic therapy for a duration of more than 1 week at any time after LVAD implantation **[44]**.

It is one of the most troubling LVAD post-implantation complication that increases morbidity and mortality after surgery; for that reason it is important to predict its occurrence.

Multiple risk models have been proposed, none of which consistently predict the occurrence of RV failure accurately **[45].** Late RV failure is also being recognized as an issue. Predictors of RV dysfunction, both in early and late presentations, include a CVP/PCWP ratio > 0.63 and a blood urea nitrogen > 42 mmol/L **[46]**.

Need for RVAD implantation is associated with a drastic reduction in survival compared to isolated CF- LVAD implantation **[23]**.

Aortic regurgitation

Aortic regurgitation (AR) with different severity grades affects almost the 25%-30% of patients within the first year post LVAD implantation and it is a recognized increasing cause of recurrence of HF. The etiopathogenesis is multifactorial and including changes in the leaflets of the aortic valve (AV), altered root biomechanics, and excessive LV unloading, together promoting cusp remodelling and commissural fusion.

Multiple risk factors have been identified which include a persistently closed AV, prolonged duration of support, small body surface area (BSA), female gender,

older age, systemic hypertension, more than moderate mitral regurgitation (MR), larger aortic dimensions at implant and excessive LV unloading. Furthermore, variants in the anastomotic angle between the outflow graft and the ascending aorta have been recently recognized to induce structural changes in the aortic wall, contributing to the development and progression of AV disease. Nevertheless, it remains controversial if AR on LVAD has an independent impact on prognosis, and no clear recommendation exists regarding its optimal diagnosis criteria and treatment **[47].**

Infections

Infections are one of the leading causes of hospital readmission in LVAD patients. Its prevention or prompt diagnosis and recognition is fundamental to assess the correct and specific therapy. According to the last IMACS Report device-specific infections are less prominent, both early and late, in centrifugal-flow pump patients; an observation that may be related to the intra-pericardial location of the pump that avoids the large avascular pre-peritoneal pocket required by axial-flow technologies **[23]**.

In 2010, a core group of experts, including infectious diseases specialists, formed an ISHLT Infection Diseases Working Group to develop agreed criteria for definitions of infections in VAD patients. Infections were classified into three sections: VAD-specific infections, VAD-related infections, and non-VAD infections **[48]**.

Pneumonia and sepsis are the most common infectious complications (23% and 20%, respectively), followed by driveline site infections (DLIs), which occur in approximately 19% of LVAD recipients within one year after implant **[49]**.

Percutaneous DLIs is a late-onset infection, causing the majority of bloodstream infections in LVAD patients, with 85% of these infections reported to occur at more than 30 days after device implantation. The most common causative organisms are predominantly skin organisms, including staphylococcus species (staphylococcus epidermidis and staphylococcus aureus). Risk factors for DLIs development are multifactorial and involve patient factors, such as obesity, nutritional status, age, comorbidities (i.e. diabetes mellitus, chronic kidney

disease, depression); it may remain superficial or spread deeper along the driveline path and into the pocket or pump, or form an abscess onto the abdominal wall **[50]**.

Mild and moderate infections should be closely monitored; if the patient has signs of systemic infection, hospital recovery should be considered.

CHAPTER III

Functional capacity in LVAD patients: the determinants

Improvement in hemodynamic parameters is routinely demonstrated in patients implanted with CF-LVADs.

Nearly all patients undergoing CF-LVAD implantation have baseline NYHA functional class IV symptoms, and after 6 months more than 80% of patients improve to NYHA functional class I or II **[51]**.

However, functional capacity (FC) following LVAD implantation, assessed by cardiopulmonary exercise test (CPET), that is considered the gold standard to measure physical response to exercise **[52]**, remains considerably restricted.

In these patients in fact, FC assessed by maximum oxygen uptake (VO_2 peak), continues to be considerably limited with VO_2 peak values calculated at the CPET ranging from 11 to 20 ml/kg/min **[53]**.

Many factors contribute to FC impairment: device features, cardiac characteristics, comorbidities and patient's peculiarities.

The presence of a fixed pump speed and the absence of a ramp function determines the inability to increase cardiac output (CO) during exercise. In fact, the pump flow depends largely on the set speed. Both during light and maximum exercise, the progressive increase in pump speed seems to improve significantly VO_2 peak compared to fixed-speed pump **[54]**.

Apostolo et al. **[55]** analysed in 33 patients supported by Jarvik 2000 device, the impact of LVAD speed increase on CPET performance and on several physiologic parameters like muscle oxygenation, diffusion capacity of the lung for carbon monoxide (DLCO) and nitric oxide (DLNO), sleep disorder breathing and alveoli gas exchange. They reported that increasing progressive pump speed spreads VO_2 peak and muscle oxygenation. However, it deteriorates lung diffusion and increases obstructive apneas, most likely due to an increase in intrathoracic fluids.

Increasing pump speed may be associated to other possible complications like suction events (that could cause ventricular arrhythmias) or excessive overload of RV.

As for the contribution of LV residual function on FC, there is not agreement in literature. Some studies have reported a strict correlation between LVEF and VO_2, others have shown a weak relation between these two parameters **[56]**. This discrepancy could be explained by the heterogeneity of LVAD population studied; probably the effect of comorbidity is predominant in old people while hemodynamic is fundamental in younger patients.

In this last setting, contribution of RV function and AV abnormalities could be important. However, because of the evaluation of RV is challenging, no study has estimated the real effects of RV on FC in LVAD patients.

AR after LVAD implantation, as we said before, is very common, but its impact on exercise tolerance has not been clearly revealed.

Comorbidities, in particular the presence of abnormal skeletal muscle metabolism and low skeletal muscle mass, reduced oxygen extraction capacity and ventilation/perfusion mismatch affect FC. The increase in age is the first (and unmodifiable) factor to consider associated with the decrease in VO_2 peak; muscle wasting is related with exercise limitations and ergoreflex overactivity **[57,58]**.

Also, long duration of the cardiac disease, protracted hospitalization and physical deconditioning negatively influence exercise tolerance.

The role of aerobic training programmes in improving exercise capacity in HF patients has been established **[59]**. Exercise may improve oxidative capacity of skeletal muscles, peripheral vasodilatory and ventilatory responses, and reduce neurohormonal activation. It would seem useful to define exercise protocols in the treatment of these patients, with the aim of optimizing the peripheral factors so relevant in exercise tolerance **[60,61]**.

CHAPTER IV

The role of echocardiography in the management of LVAD patients.

Transthoracic echocardiography (TTE) is generally the first-line imaging modality used to screen LVAD candidates for structural and/or functional abnormalities that represent absolute or relative contraindications to device implantation.

After LVAD implantation TTE is routinely performed in the ambulatory follow up to check residual LV function or valve abnormalities.

Its role becomes fundamental in case of changes in clinical situation or emergency setting to assess acute complications like pump thrombosis or suction events.

According to the recommendation of the American Society of Cardiology **[62]**, we can consider 3 different protocols of execution for echocardiography, depending on the aim of the exam:

- LVAD surveillance echocardiography;
- LVAD problem-focused echocardiography;
- LVAD recovery echocardiography.

In all these protocols an echocardiographic procedure of LVAD parameters optimization could be performed.

LVAD surveillance echocardiography

Periodic LVAD surveillance echocardiographic exams are recommended, to establish patient-specific ‘‘baseline’’ parameters for both LVAD and native heart function. The first “LVAD surveillance echo exam” should be performed at approximately 2 weeks after device implantation or before hospitalization discharge, then surveillance TTE should be considered at 1, 3, 6, and 12 months post implantation and every 6 to 12 months thereafter **[62]**.

Basal echocardiography is routinely conducted by the clinicians to assess patient response to LVAD therapy and to detect subclinical pathological conditions like occult native heart alterations or unknown device related complications.

Just before performing basal echocardiography, blood pressure (BP) should be recorded, in fact it is an important parameter that reflects peripheral vascular

resistance and influences considerably ventricular unloading and the observed echocardiographic findings.

LV size, systolic and diastolic function are observed, in particular the LV End Diastolic Diameter (LVEDD) is the most reproducible measure of LV unloading; however, the most accurate evaluation of LV size is represented by the assessment of the LV End Diastolic Volume (LVEDV).

Nevertheless, measuring LV volumes and LVEF could be challenging, due to technical limitation like difficulty to detect endocardial border and poor quality of images. When possible, Simpson's biplane method of disks is recommended for the detection of LVEF.

The position of the interventricular septum and the presence of AR and/or MR are evaluated to quantify LV unloading and RV function. Also TR, if present, is measured to estimate pulmonary pressure.

The end diastolic interventricular septal position could be described as:

- Neutral (recommended condition);
- Leftward – shifted (in case of elevated RV end-diastolic pressure, excessive LV unloading; low LV preload);
- Rightward – shifted (in case of inadequate LV unloading; elevated LV afterload, pump dysfunction or severe AR).

Evaluation of AV opening is important because it depends on a great number of parameters: LVAD speed setting, native LV function, volume status and peripheral vascular resistance.

The best way to assess correctly the frequency and the duration of AV opening is to record multiple cardiac cycles with colour M-mode at a speed of 25-50 mm/s.

The optimal condition, according to the last guidelines indications, is to obtain at least intermittent AV opening **[62]**; in fact, the presence of persistent AV closure could cause aortic root thrombosis and de novo AR.

MR with a moderate-severe grade is frequently present before LVAD implantation; after, the LV unloading favours reduction of MV annular dilation and consequently a decrease of MR severity is observed. Persistence of significant MR may indicate inadequate LV unloading or inflow cannula malposition and interference with the submitral apparatus. Incidental finding of MR during

routinely echocardiography follow up has to be considered as possible LVAD device malfunction.

Also, the presence of moderate or severe TR may be due to inadequate LV unloading (functional TR) or excessive LV unloading with distortion of RV geometry and systolic dysfunction.

The role of RV function in LVAD patients is well established, especially before the implantation. Detection of RV size and function could be achievable, either for Tricuspid Annular Plane Systolic Excursion (TAPSE) or Fractional Area Change (FAC) and right-sided cardiac output. Peak systolic and nadir diastolic inflow-cannula and outflow-graft velocities that could be studied with Colour Doppler, are also measured to evaluate the presence of obstruction.

Sometimes when 2D imaging is not conclusive, 3D echocardiography could be useful to study precise relationships between inflow cannula, interventricular septum and other LV structures.

LVAD problem-focused echocardiography

This kind of procedure is performed when the patient presents changes in clinical conditions (i.e. appearance or worsening of HF symptoms, hypotension), device alarms, abnormal serologic findings (i.e. haemolysis) that can underline pump thrombosis, infections or abnormalities at the basal echocardiography.

Initially the exam is conducted at the baseline speed setting; if the patient is stable, speed changes could be carried out and subsequently images could be recorded.

For some type of device, in particular HeartMate II, it is possible to study the inflow cannula by pulse-wave (PW) and continuous wave (CW) Doppler to evaluate the eventual development of obstruction at higher pump speeds, starting from low pump speeds and increasing gradually the number of revolutions per minute (rpm).

At each new speed setting, Colour-flow and spectral Doppler have to be used to assess the degree of valve regurgitation and the RV outflow tract (RVOT) flow from parasternal view or other available windows.

Outflow-graft Doppler (possible for both the HMII and HVAD) should be tried at

the baseline speed and at other speeds if the patient is symptomatic or pump malfunction is suspected.

At the least, imaging of AV opening (M-mode), inflow-cannula placement, LV and RV size, and atrial and ventricular septal positions at each new speed may be useful, considering the indication of the analysis **[62]**.

A variety of complications could be detected: pericardial effusion, RV failure, LVAD suction, intracardiac thrombus, inflow or outflow cannula abnormalities.

LVAD recovery echocardiography

Recently, Uriel **[63]** discussed the possibility of myocardial recovery in LVAD patients. Sometimes, in very selected patients, a regression of HF syndrome with normalization of anatomic abnormalities chambers could happen, but this doesn't imply the normalization of cellular and transcriptional systems that remain pathologically modified.

For this reason, recovery protocol echocardiography is not habitually performed in MCS centres. This "weaning" protocol is actuated when a sufficient recovery of LV native function is evident at the basal echocardiography. Before starting the test, anticoagulation status has to be verified.

Gradual speed reductions are used to identify a pump speed at which there is no forward or reverse pump flow (net neutral flow). Frequent spectral Doppler evaluation of the LVAD inflow cannula and the outflow graft is used to determine the speed at which there is net neutral pump flow.

With the aim of testing the patient's native LV functional reserve, an exercise test (such as a 6-minute walking test or a CPET) should be considered at one or more time intervals at the net neutral low pump speed **[64,65]**. LV function parameters have to be assessed again; the protocol must be interrupted if the patient becomes symptomatic.

LVAD echo-optimization procedure

LVAD echo-optimization (EO) consists of routine comprehensive TTE at the baseline speed setting, followed by stepwise incremental adjustments to the LVAD speed (rpm), with collection of prespecified echocardiographic parameters

at each new speed (e.g. LVEDD, interventricular septal position, AV opening frequency/duration, TR and/or MR severity) **[66]**.

The minimum speed is defined as the speed below which the LVEDD is enlarged in relation to the baseline; the interventricular septum may be shifted rightward; MR may get worse; AV opening may occur or become more frequent, estimated AR and systolic pulmonary artery pressures may increase. Clinically, the patient develops reduced FC, congestion, and/or worsening end-organ damage.

The maximum speed is defined as the speed above which the interventricular septum shifts leftward and/or impedes flow into the inflow cannula; TR may worsen due to the left-ward interventricular septal shift with tricuspid valve annular distortion and/or RV enlargement; the AV may cease to open and AR (when present) may worsen. Some or all of these changes above the maximal speed may cause a ‘‘suction event’’ with low-flow alarms.

The optimal velocity is defined as the one that allows an intermittent AV opening and a neutral position of the interventricular septum without increasing AR or TR, associated or not to a dilatation of the RV [62].

The recommended speed range varies according to the indications given in the data sheet for each specific device: for the HeartMate II, the minimum and the maximum speed range is 6,000 and 15,000 rpm, the clinical recommended range is between 8,800 and 10,000 and the speed can be changed in increments or reduction of 200 rpm; for Heartware™ HVAD™ the maximum and the minimum speed ranges are respectively 1,800 and 4,000 rpm and the recommended speed range setting is 2,400-3,200 rpm; for the HeartMate 3™, the allowed speed is between 4,800 and 6,200 rpm with possible modifications of 100 rpm.

Beyond echocardiographic aspects, elements that should be monitored include:

• suction events;

• ventricular arrhythmias;

• symptoms that include palpitations, dizziness, dyspnoea, chest pain or headache;

• hypertension (defined as mean arterial pressure > 100 mmHg);

• hypotension (defined as mean arterial pressure < 60 mmHg).

The LVAD EO is generally performed in asymptomatic or minimally symptomatic patients with no device alarms or other clinical indicators of

abnormal LVAD or cardiac function.

Routinely EO procedure is performed only in the post-operative period and when clinically indicated; for this reason, it remains unknown whether routine EO is indicated in stable LVAD patients **[67]**.

Uriel recently presented a study analysing the use of 3D Echocardiography (3DE) analysis for patients undergoing echocardiography-guided ramp studies for LVAD speed optimization. This procedure resulted technically challenging and time consuming, but explored the value of the impact of HM3 speed settings on the volumes and shape of both ventricles. How morphologic and function changes in LV and RV during LVAD speed change, assessed with the use of 3DE, could help to optimize LVAD speed settings and improve their clinical outcomes, has to be assessed again **[68]**.

CHAPTER V

Materials and methods

Rational and study design

Subjects studied were HF patients supported with a continuous-flow LVAD: HeartMate II (Thoratec Inc., Pleasanton, CA) and HeartMate 3TM (HM3, Abbott, North Chicago, IL). All were ambulatory outpatients recruited by our Day Hospital of the Division of Cardiovascular Surgery at the University Hospital of Verona, from October 2017 to August 2019.

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

Inclusion criteria were:

- enrolment at least 3 months after LVAD implantation;
- compliance to the required follow-up schedule;
- age 18 or above or of legal age to give informed consent specific to state and national laws.

Exclusion criteria were:

- distance of less than 150 metres on the six-minute walk test (6MWT) or impossibility to perform CPET;
- poor acoustic window for echocardiographic imaging acquisition;
- recent findings of any major device-related complication (sepsis, thrombosis …).

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 that the subject was receiving was the operator dedicated to EO.

Patients were randomized in a 1:1 ratio to EO (EO group) versus standard settings (CONTROL group) after at least 3 months from the LVAD implant. Patients randomized to EO treatment performed echo-guided device programming 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 10**.

The trial was designed to test the hypothesis that functional capacity in CF-LVAD patients could be improved if pump speed is optimized using echocardiography. The primary end point of our study was peak oxygen uptake (VO_2 peak) change 3 months after the EO. The secondary end points were: RV function (assessed by echocardiography, evaluated by the fractional area change [FAC]); device-related hospital admissions; N-terminal brain natriuretic peptide (NT-proBNP) levels; CPET exercise time (ET) and changes in quality of life (QoL) perceived by the EuroQol scale and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Enrolment visit

Firstly, we collected data on health history, referring in particular to the aetiology of LV dysfunction, other diseases (i.e. atrial fibrillation, diabetes, pulmonary or kidney diseases), the date of the LVAD implantation and current medications.

Physical examination included assessments of pulse, blood pressure (BP), body temperature, weight and height, oxygen saturation (if possible, measured by pulse oximetry), exclusion of signs of heart failure (lung auscultation, jugular veins observation, extremity and abdomen examination) or LVAD dysfunction (inspection of the driveline and device connections, interrogation for device parameters and alarms).

In absence of pulsatility, heart rate (HR) was assessed using electrocardiography. A standard resting 12-lead electrocardiogram was usually done to analyse cardiac rhythm, QRS width and QTc interval.

Blood pressure measurements were obtained using a non-invasive automatic BP cuff. In absence of pulsatility, a Doppler probe was placed over the brachial artery with inflation and deflation of a manual BP cuff; the pressure at which the sound of blood flow returned to the brachial artery was recorded and described as mean arterial pressure (MAP).

The jugular veins were normally examined with the patient reclined at 45°; the lungs were investigated for signs of congestion (especially abnormal sounds like

bibasilar crackles); the abdomen and extremities were explored for signs of fluid overload (ascites, peripheral oedema).

Careful attention was given to the driveline, in order to exclude infections. LVAD controller parameters were recorded (alarms, rotary speed, power consumption, pump flow, pulsatility index).

Finally, patients were given 2 questionnaires to evaluate the perceived quality of life. It was measured using the EuroQol Five Dimensions 3L questionnaire (EQ-5D-3L™; EuroQol Group, Rotterdam, the Netherlands) and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

EuroQol is a standardized measure of health status, assessing the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain has three levels: no problems (score 1), some problems (2), extreme problems (3). We used an algorithm that allows the calculation of a synthetic score (EQ-5D Index) of perceived health status. The calculation of the EQ-5D Index score was obtained by subtracting from 1.000 the relevant coefficients and the constants for gravity level as reported in this table:

Dimensions	**Weight variables**		
	1	**2**	**3**
Mobility	- 0.0	- 0.069	-0.314
Self-care	- 0.0	- 0.104	-0.214
Usual activities	- 0.0	-0.036	-0.094
Pain/discomfort	- 0.0	-0.123	-0.386
Anxiety/depression	- 0.0	-0.071	-0.236
Constants	- 0.0	-0.081	-0.269

Self-rated health was measured on a visual analogue scale, the EQ-VAS, using a 20 cm vertical line with scores ranging from 0 (worst health he/she can imagine) to 100 (best health he/she can imagine).

The KCCQ is a validated instrument to assess health status in HF **[69]**. The self-administered questionnaire includes 23 items which quantify the importance of dyspnoea, fatigue, and oedema on physical, social, and emotional functions. The responses are categorized under 3 subscales (symptom burden, physical limitation and quality of life) with a range of possible subscale scores from 0 to 100, with

100 representing the least burden of symptoms. The total KCCQ score represents the mean of the three subscale score.

Measurement of blood chemistry and hematologic variables

Fasting blood samples were collected at baseline and at 3 months to assess parameters of haemolysis (lactate dehydrogenase - LDH and haptoglobin) or infection (complete blood count, high sensitivity C-reactive protein) and to investigate kidney (creatinine, blood urea) and liver function (bilirubin, alanine and aspartate aminotransferase). Also lipid profile (low-density lipoprotein - LDL, high-density lipoprotein – HDL and total cholesterol, triglycerides), blood glucose and serum electrolytes (sodium and potassium) were measured. Dosage of NT-proBNP, as secondary end-point of our study, was included in the evaluation. Lastly, measurement of Prothrombin Time - International Normalized Ratio (PT-INR) was fundamental to allow our procedure of EO in safe conditions (a value at least > 1.8 was requested).

Six minute walking test

A 6-minute walking test (6MWT) was done at baseline and at three months evaluation. It was conducted according to a standardized protocol (2002 American Thoracic Society guidelines), using a 30 metres flat, straight enclosed corridor with a hard surface.

Before each 6MWT, oxygen saturation and blood pressure were measured. Participants were asked to walk as far as possible without jogging or running for six minutes. They were also instructed to walk from end to end of the hallway, in order to cover as much ground as possible.

At 1 minute intervals they were encouraged and informed of the time remaining. The technician counted the number of laps completed and used a timer to stop the participant 6 minutes after the walk started. If they needed to slow down or stop to rest, they were permitted to do so and encouraged to resume walking as soon as they were able. The test was stopped in case of chest pain, intolerable dyspnoea, leg cramps or diaphoresis.

At the conclusion of the test, the patients were asked to rate his/her dyspnoea and fatigue levels. Oxygen saturation and blood pressure were measured and the distance covered in six minutes was recorded.

Echocardiographic assessment

Complete transthoracic echocardiographic (TTE) exams were performed at baseline and at three months in accordance with current American Society of Echocardiography guidelines, using a CX-50 xMatrix Philips cardiac ultrasound system (Philips S.p.A, Milan, Italy).

The first aim of TTE was the exclusion of clear thrombus; if the exam revealed it into the LV or in the aortic root, EO would not be performed, due to the possibility of thrombus dislodgment.

From the parasternal window, LV end-diastolic and end-systolic diameter, were measured in millimetres, then indexed to BSA. In addition, 2-dimensional echocardiography and M-mode were used from the parasternal window to record AV opening with classification as follows: AV opening after every cardiac cycle, intermittent AV opening, or complete AV closure. Valves regurgitation severity were quantified from all possible views, using a 4-point scale (none, mild, moderate, or severe).

From the apical window, LVEF was calculated using the Simpsons biplane method. Left atrial volume was measured by using the biplane method of disks from the apical 4-chamber and apical 2-chamber views at ventricular end-systole, then indexed to BSA to obtain the left atrial volume index (LAVI).

Mitral inflow was assessed with pulsed-wave Doppler placing a sample volume at the tips of the mitral leaflets. The early diastolic peak flow velocity (E velocity) and the late diastolic peak flow velocity (A velocity) were measured and the ratio of E/A was calculated.

The operator examined the RV using multiple echocardiographic windows. Basal RV linear dimension was calculated considering maximal transversal dimension in the basal one third of RV inflow at end-diastole in the RV-focused view; proximal RV outflow diameter (RVOT prox) was measured from the anterior RV wall to the interventricular septal-aortic junction (in parasternal long- axis view).

We selected tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (FAC) as measures of RV function.

TAPSE was acquired in the apical four-chamber view by aligning an M-mode cursor with the tricuspid annulus and measuring the longitudinal motion of the annulus.

FAC was measured from a dedicated RV apical four-chamber view, adjusting the transducer angle to focus on the RV chamber, with the aim of maximizing its chamber size. The endocardial border was traced from the lateral tricuspid annulus along the free wall to the apex and back to medial tricuspid annulus, along the interventricular septum at end-diastole and end-systole. Trabeculations, papillary muscles and moderator band were included in the cavity area.

We also considered estimated RV systolic pressure and TR as potential RVF predictors. Continuous-wave Doppler was used from multiple windows to record TR signals. Inferior vena cava diameter and its collapse were recorded in the subcostal view. Right atrial pressure (RAP) was estimated by using the inferior vena cava diameter and its change with respiration. Systolic pulmonary artery pressure (sPAP) was derived by using the modified Bernoulli equation as sPAP = $4(v)_2$ of peak TR velocity in meters per second + RAP expressed in mmHg.

Cardiopulmonary exercise test

For the exercise test, a bicycle ergometer was used (Quark CPET, COSMED, Rome, Italy). Before each test, the gas analysers and the flowmeter were calibrated at the atmospheric pressure, temperature and humidity of the effort test laboratory, in accordance with the manufacturers' instructions. Exercises were performed under standard environmental conditions with a comfort temperature (between 20 and 22 °C) and relative atmospheric humidity of 30–60%.

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 minutes. In almost all patients the initial workload was 10 Watts and it was increased at a 10 Watts/min ramp until patients reached exhaustion (just in one patient we used a 15 Watts/min ramp

protocol). Patients were motivated to make their maximal effort thus allowing a reliable measurement of VO_2 peak, calculated in millilitres per kilogram per minute (ml/kg/min). We considered the highest 30 seconds average VO_2 value over the last minute of the exercise phase.

The anaerobic threshold was measured with the V-slope analysis from the plot of VCO_2 vs. VO_2 on equal scales. This value was confirmed analysing ventilatory equivalents and end-tidal pressures of CO_2 and O_2. The ventilation (VE)/VCO_2 slope was calculated as the slope of the linear relationship between VE and VCO_2 form excluding the initial part of the test (potentially influenced by the presence of initial hyperventilation) and the final part (from the end of the isocapnic tamponade to the end of the exercise).

Other parameters included were: exercise time (measured in seconds), workload (Watt), rest and peak HR (bpm), VO_2 work slope [mL/kg/min/W], O_2 pulse (mL), VE peak [L/min].

A respiratory exchange ratio (RER) > 1.05 was used as an indicator of an adequate performed test. During exercise, patients were monitored with pulse oximetry and a continuous 12-lead electrocardiogram.

Echo-optimization procedure

LVAD EO consists of routine comprehensive TTE at the baseline speed setting, followed by stepwise incremental adjustments to the LVAD speed (revolutions per minute: rpm), with the collection of prespecified echocardiographic parameters at each new speed (e.g. LV end-diastolic diameter, interventricular septal position, AV opening frequency/duration, TR and/or MR severity).

Before starting the procedure, BP was recorded again. The patient's device speed was lowered to the minimum speed clinically recommended. After 2 minutes, the following parameters were recorded: LV end-diastolic dimension (LVEDD), LV end-systolic diameter (LVESD), frequency of AV opening, degree of AR, degree of MR, RV systolic pressure, blood pressure, and HR. The pump parameters were also recorded (power, PI, and flow).

LVEDD and LVESD 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 AR and MR was performed in the parasternal long-axis view using the Colour Doppler imaging technique. For assessment of AR and MR, the degree of regurgitation was graded from 0 to 4 (none; 1 mild; 2 moderate; 3 severe). RV systolic pressure was estimated from peak TR velocity using 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 8,800 and 10,000 and the speed can be changed in increments or reduction of 200 rpm; for the HeartMate 3TM, the allowed speed is between 4,800 and 6,200 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 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 AR and/or TR, associated or not to a dilatation of the RV.

The test was stopped in case of:

- decrease in LVEDD ≤ 3 cm
- suction events;
- ventricular arrhythmias;
- symptoms (palpitations, dizziness, dyspnoea, chest pain or headache);
- hypertension (MAP > 100 mmHg);
- hypotension (MAP < 60 mmHg).

At the end of the test, a new assessment of BP was done and images recorded were reviewed.

In patients randomized to EO treatment the echo-guided optimized setting was confirmed; in the CONTROL group, speed device was unchanged.

Statistical analysis and sample size

Kerrigan **[70]** proposed a design similar to our protocol, although with the intention of verifying the contribution of another tool (rehabilitation) to improve the functional capacity of patients with LVAD. It has been hypothesized that the

group subjected to EO undergoes a variation equal to the rehabilitated group reported by Kerrigan, while the non-optimized group behaves like the control group of that study. Since the study did not report the standard deviation of the differences, this 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 **[71]**. 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.

The Student's t-test and the chi-square test were used to compare groups at baseline for continuous and nominal data, respectively. Analysis of covariance (ANCOVA) was used to compare the differences in change from baseline to follow-up between the two groups. Statistical significance was defined as $p < 0.05$ (2-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).

CHAPTER VI

Results

Basal characteristics

A number of 27 patients consented to participate to the study. No statistically significant differences were observed among groups with respect to all baseline characteristics.

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); for other 8 patients the indication was "destination therapy" and "bridge to candidacy" only for one patient.

20 patients (74.1%) were implanted with HeartMate 3TM and the other 7 (25.9%) with a HeartMate II (without significant differences between the two groups). Average pump speed was 9,222 ± 273 rpm for HMII and 5,250 ± 228 rpm for HM3.

At rest, average HR and MAP were 76 ± 12 bpm and 84 ± 9 mmHg, respectively.

Considering associated pathologies, 10 patients (37%) suffered from diabetes, 4 (14.8%) were affected by chronic kidney disease (stage II in three cases, stage III in one case), 3 (11.1%) with chronic pulmonary pathologies, 4 (14.8%) patients with a history of surgically treated neoplasia.

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 postpartum cardiomyopathies. We did not find any statistically significant difference regarding the aetiology of cardiac disease between the two groups.

All patients were receiving pharmacological HF therapy according to the guidelines of European Society of Cardiology **[8]**.

Almost the entire population was treated with a renin-angiotensin-aldosterone system (RAAS) inhibitor (ACE inhibitor or Sartan) and a Beta-Blocker. Potassium-sparing diuretics were used in more than 60% of the patients.

Other details are described in **Table 8**.

Statistically significant differences in the baseline laboratory exams between the two groups were not detected **[Table 9]**. Elevated NT-proBNP levels have been found in our population; the mean concentration was 1,770 ± 1314 pg/ml with a median of 1,648 pg/ml.

Regarding the basal echocardiographic data **[Table 10]**, the average LVEF was 26.6 ± 2.3%, the LVEDDI 37.7 mm/m_2 ± 3.3, TAPSE 15.4 ± 2.9 mm and FAC 36.2 ± 4%.

At baseline pump speed, the AV was closed in 9 of 27 patients and constantly open in other 8 patients. AR was present in 15 patients: mild in 12 patients, moderate in the other 3.

EO was performed on four patients with HMII: in two cases a 200 rpm speed reduction was done, in two other cases the device speed was increased by 200 rpm. Nine patients with HM3 were echo-optimized: in five cases device speed was reduced (by 100 rpm in 4 patients, by 200 rpm in 1 patient); in the residual 4 cases, an increase of 100 rpm was performed.

Among the patients randomized to the CONTROL group, in six cases we found that the echo-optimized setting was better than the current speed setting.

Our population showed a basal reduced FC with VO_2 peak values between the two groups without significant differences, as well as for all the other parameters explored **[Table 11]**.

End-points

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 ANCOVA for VO_2 peak is reported in **Figure 11.**

Similarly, the increase in exercise time and 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**). Graphical representation of the ANCOVA for O_2 pulse is described in **Figure 12.**

A significant improvement was demonstrated also 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 end-point of our study; for other parameters the increase did not reach statistical significance **[Table 11]**.

Similarly, the increment in 6MW distance (6MWD) 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 of 7.7% similar to that recorded for VO_2 peak.

We did not document any device-related hospitalizations in either group during the three months follow up period.

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 **[Table 10]**.

Examining all the scores used to describe the trend in perceived quality of life, a significant enhancement was documented in the EO group **[Table 12]**: in particular, + 6.8% using EQ-5D-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**) and + 2.7% considering KCCQ (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**).

To conclude, no significant changes in laboratory parameters were observed, 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**).

Discussion

Various determinants have an influence on FC. Some previous reports analysed the effects of pump speed increase on exercise performance in LVAD patients with contradictory results: an upgrade was observed in some **[54,72]**, but not in all reports **[73]**. In another case the rise in VO_2 peak was correlated to worsening in lung diffusion and obstructive apneas **[55]**.

Moreover the role of RV kinetics is often underestimated: Murninkas et al. found a decrease in VO_2 peak of 0.97 ml/kg/min for each EF decrease of the RV of 10% **[74]**. A more favourable hemodynamic profile for the RV and a probable better response in terms of FC can therefore be expected from LVAD EO.

Uriel demonstrated that EO can help patient management **[75]**: in particular the hemodynamic improvement was evident with an increase in CO and a decrease in PCWP, confirmed by right heart catheterization (RHC). It remained to be tested whether this strategy could have a beneficial impact on relevant clinical outcomes such as FC or QoL.

To date, our study represents the first experience to show the positive effects of EO in LVAD patients on the FC expressed in terms of VO_2 peak and on the perceived QoL, considering two questionnaires.

For this reason, a comparison with other studies is very difficult; if we consider experiences investigating the role of some actions (rehabilitation, speed increase) on FC in LVAD carriers, our population is similar for age and aetiology of LV dysfunction. As to Jung's study **[72]**, our population presents relevant heterogeneity for duration in LVAD support.

Not all the considered studies reported medical therapy **[54,70]**; in comparison with studies reporting this datum **[72,73]**, in our population there were more patients in optimal medical treatment.

We studied a group of LVAD-supported patients in stable clinical conditions (17/27 patients declared NYHA I functional class, only two a NYHA III) and optimized pharmacological treatment; nonetheless, they presented a severe deconditioning, with only 11/27 patient with a VO_2 peak at baseline >14 ml/kg/min.

Giving credit to the laboratory exams, there are no significant anomalies in a population that has been carefully selected in order to exclude patients with clear organic problems (in particular relevant anaemia, infections or device dysfunctions).

Global echocardiographic data, in addition to confirming severe LV systolic dysfunction, reveal a substantially conserved RV function, as a result of an adequate patients' selection before LVAD implantation. The mean right atrioventricular gradient (25.8 ± 3.4 mmHg) confirms a satisfactory state of compensation, with filling pressures within the normal range.

The performance of a standardized EO was both safe and feasible in our patients. We followed all the indications suggested by the protocol proposed by Uriel and avoided applying the lowest and highest speeds outside the clinically suggested ranges.

No device-related hospitalizations were observed in the three-month 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.

Almost all patients were able to perform a maximal effort (RER 1.1 ± 0.06) without reporting any relevant adverse event related to the test.

The significant enhancement in VO_2 peak in the EO group probably constitutes the result of impaired hemodynamics, with consequent increased oxygen transport to skeletal muscles. Also O_2 pulse manifests a significant trend; this parameter represents the ratio of oxygen consumption to HR and expresses the volume of oxygen ejected from the ventricles with each cardiac contraction. This value is clearly correlated with stroke volume.

VO_2 peak increase obtained after EO is associated with a CO increase and an unchanged $\Delta(Ca\text{-}Cv)O_2$. The effect of physical training on FC is different, causing a change in peripheral blood flow distribution with a consequent reduction of $\Delta(Ca\text{-}Cv)O_2$ and no modification on CO; this is explained by the augmentation in skeletal muscle perfusion, upregulation of glycolytic enzymes, and decrease in catabolic catalysts (e.g., interleukin-1, interleukin-6, Tumor Necrosis Factor-alpha).

In our patients we have to consider also a greater exercise-induced HR increase, probably caused by a major contribution of residual LV myocardial function.

Native heart function may be an important determinant of FC, thinking that native CO can contribute an additional 3 litres during stress **[76]** even in patients with CF-LVADs. At any rate, on the role of residual myocardial function, there are no univocal results: in one study, VO_2 peak correlated with LVEF, especially at lower levels of LVAD support levels **[56]**; other studies have found no correlation between LVEF and VO_2 peak **[72]**.

We underline the significant increase of the exercise time in the EO group with the achievement of a significant higher peak HR compared to the CONTROL group. However, the average peak HR reached by our population remains low: on average, 71% of the maximum theoretical HR for the patient's age was reached, so far from the 85% threshold that represents the significance. It reflects a clear state of chronotropic incompetence, also if we consider that every patient was receiving beta-blockers and/or other antiarrhythmic drugs.

It was demonstrated that LVAD patients present a reduced chronotropic reserve and an uncommon HR recovery after implantation, confirming relevant cardiac autonomic abnormalities; these alterations seem to remain unchanged after LVAD implantation **[77]**. Also, the contribution of the HR to the pump is unclear. Salamonsen et al. **[78]** demonstrated that higher pump flows were associated with increased HR in CF-LVAD patients; on the other hand, Muthiah el al. **[79]** did not describe any impact of alteration of the HR by pacing on CF-LVAD flow in HVAD pumps.

Although it is not possible to predict accurately hemodynamic changes during physical exertion, EO certainly implies more appropriate pre- and afterload basal conditions with a consequent undoubted impact on VO_2 peak.

The improvement in terms of FC is also confirmed by the distance covered at the 6 minutes walking test. In relation to the prognostic significance of this result, a study **[80]** revealed that a distance of less than 300 meters in LVAD patients was independently associated with subsequent reduced survival.

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. Feasible and reproducible, they provides diagnostic and prognostic data. In patients with dilated cardiomyopathy, filling patterns described by E/A ratio correlate better than LVEF with filling pressures, functional class and prognosis **[81]**.

Multiple echocardiographic parameters were compared with simultaneous invasive RHC measurements in LVAD patients: an algorithm integrating E/A ratio, RAP, sPAP, and left atrial volume index showed a 90% accuracy in distinguishing normal from elevated LV filling pressures **[82]**.

Left atrial pressure is a strong predictor of symptoms, and a major prognostic factor for outcome, but very limited data are available on how LA pressures can be properly assessed in a non-invasive way: RHC remains the primary method to estimate RA and LA pressures in CF-LVAD patients presenting clear symptoms of suboptimal LV unloading.

Then, the results concerning the QoL present an important clinical and prognostic value. The KCCQ score is a composite measure of patient-reported symptoms and QoL, and is connected with mortality and morbidity **[83]**. Rodgers et al. **[84]** described significant improvements in the KCCQ score post-implantation, suggesting a time-dependent enhancement in clinical symptoms and QoL.

Indeed, in our experience, patients randomized into the EO group demonstrated a significant average KCCQ score increase of 3 points compared with a 0.6 point change in the CONTROL group.

This result has to be considered also for prognostic relevance, if we think that a change in the KCCQ score is considered clinically meaningful and more predictive of patient clinical status than BNP **[85]**.

The use of the EQ-5D-3L™ in LVAD studies has increased in recent years and evidence has been provided of its validity and reliability, especially in a recent study where both EQ-5D-3L™ and KCCQ were administered in all adult HTx centres in the UK, showing a substantial overlap between the two questionnaires **[86]**.

Health-related QoL evaluation through validated questionnaires is feasible and can be performed in routine practice. Clinicians should encourage the assessment

of health related- QoL to promote patient-centred care and make more specific use of QoL measurement tools.

Currently each medical centre performs an 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.

The utilization of echocardiography to optimize the LVAD speed is relatively new and its impact on short- and long-term clinical outcomes is still not clear.

Our experience suggests that EO has the potential of improving FC and QoL. These results are even more important if we consider that almost 70% of population came to our observation with an optimizable setting (in addition to the 13 patients of the EO group, even six patients of the control group could have been optimized, if we would have confirmed the modification of the device speed).

Compared to RHC (the gold standard of hemodynamic assessment), echocardiography is readily available, non-invasive and easily repeatable.

We analysed the effect of some variables on the primary end-point such as the type of device (HMII vs HM3), the aetiology of LV dysfunction (ischemic vs non ischemic) and the time of permanence of the LVAD and we have not found any kind of significant interaction. Therefore the influence of EO is independent of the specific characteristics of the LVAD patient.

Limitations

Limitations associated with this study should be mentioned, such as the small sample size and the consequent restriction in the findings' interpretation.

First, 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 CF-LVAD randomized clinical trials.

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

We chose a three-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.

Our aim was also to minimize interferences caused by physical training; in this three-month period we have invited patients not to change their daily physical activities.

Additionally, we believe that in the planning of an ideal long-term protocol of EO, it is right to execute this procedure every three months, considering how the patient's hemodynamics may vary also for climatic conditions and seasonality.

It was obviously not possible to mask in any way the modification of the patient's device speed; on the other hand, all investigators except the EO physician were not informed of the patient's randomization arm.

VO_2 peak is a relevant index of HF prognosis; its increase is a target of therapy and it is associated with survival improvement. In the studies we mentioned, VO_2 peak improvement was a temporary effect obtained after a pump speed increase of a few hours; this finding was considered only within the frame of exercise physiology evaluation with no applicability to HF treatment and prognosis.

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.

There are probably limits related to how much an abnormal hemodynamic profile could be "normalized" by EO; therefore the concomitant value of the optimization of medical therapy should not be underestimated.

Conclusions

The limitation in FC 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 LV and the presence of RV dysfunction and/or valves abnormalities have to be considered.

We believe that relevant clinical outcomes could be improved by periodic EO to achieve an optimal hemodynamic profile. VAFRACT is the first prospective randomized trial to evaluate the additional benefit of an EO approach on FC, measured by CPET, and on QoL in an LVAD optimization-free population.

In addition, follow-up is needed for a longer term outcome evaluation. Furthermore, it could be interesting to study the effects of a combined EO and long-term cardiovascular rehabilitation program.

TABLES AND GRAPHS

Figure 1[2]. Prevalence of heart failure for adults ≥20 years by sex and age (NHANES, 2013–2016).

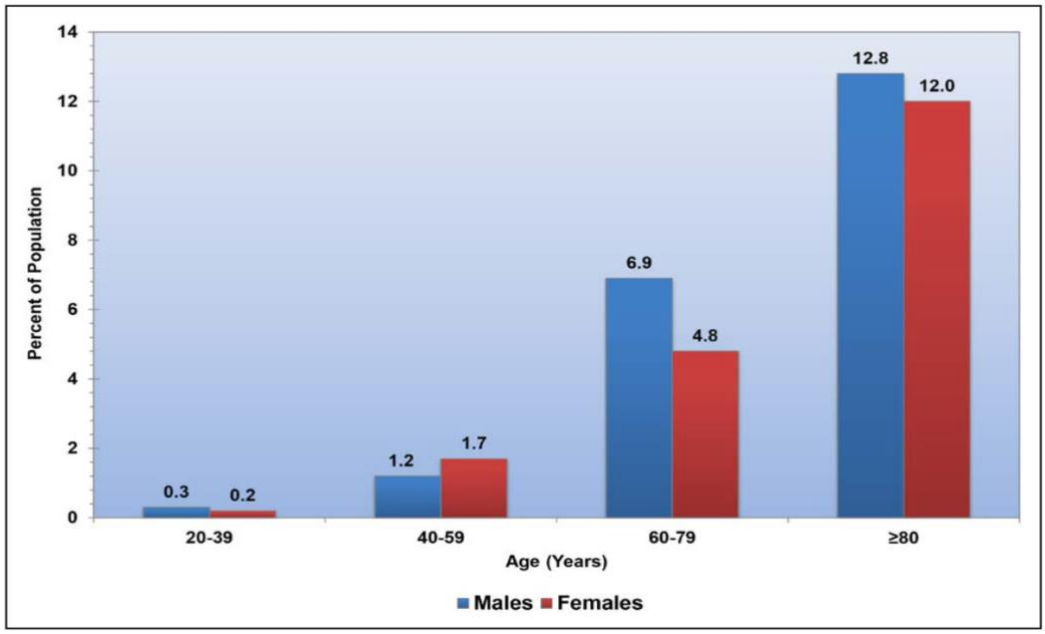


Figure 2. Hospital discharges for heart failure by sex *(United States, 1997–2014 National Hospital Discharge Survey/National Center for Health Statistics and National Heart, Lung, and Blood Institute.)*

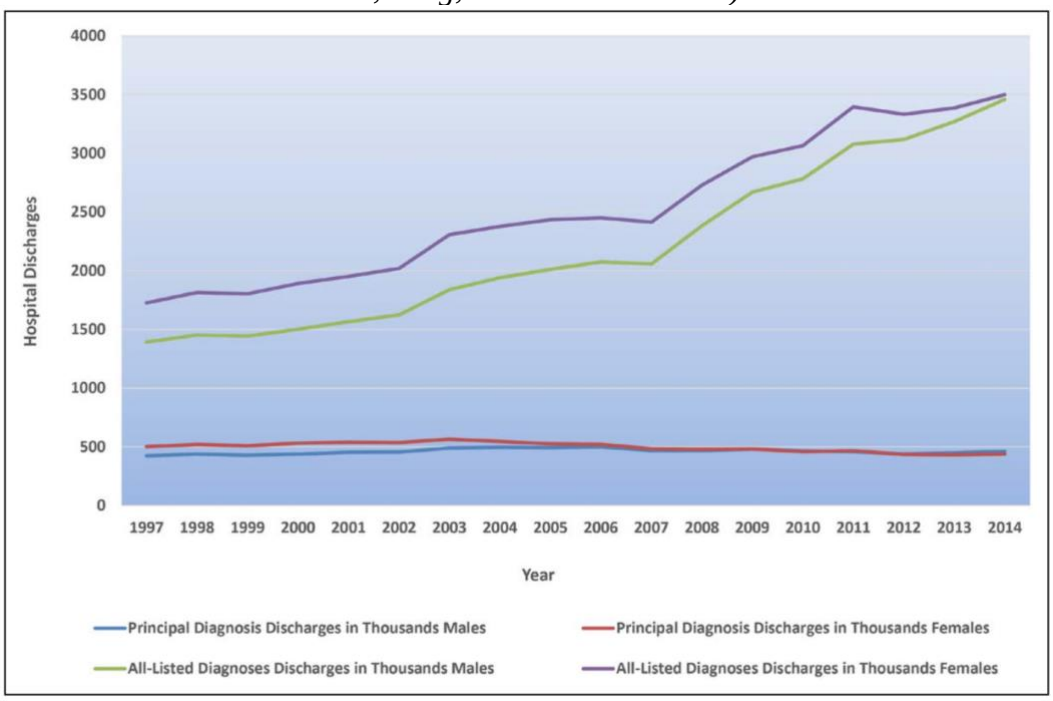


Table 1[8]. Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF).

		HFrEF	HFmrEF	HFpEF
CRITERIA	**1**	Symptoms ± Signs	Symptoms ± Signs	Symptoms ± Signs
	2	LVEF<40%	LVEF 40-49%	LVEF≥50%
	3	-	1. Elevated levels of natriuretic peptides 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE); b. diastolic dysfunction	1. Elevated levels of natriuretic peptides 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE); b. diastolic dysfunction

LVH = left ventricular hypertrophy; **LAE** = left atrial enlargement

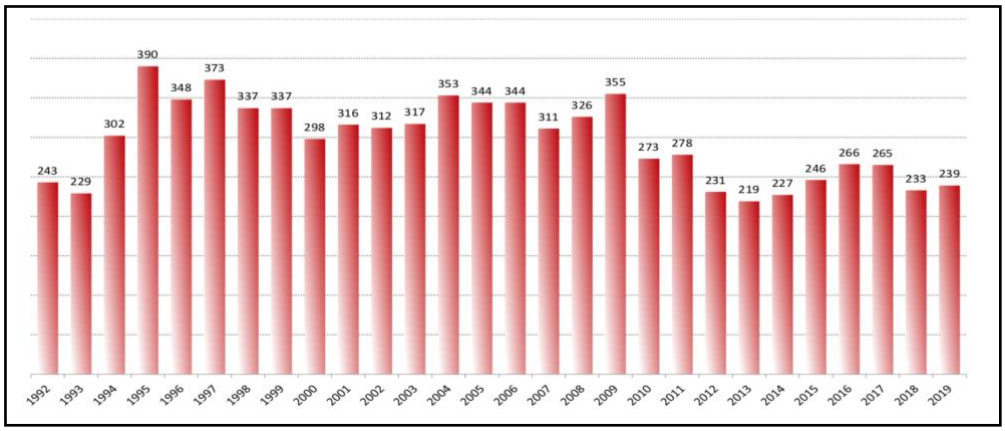
Table 2[14]. Comparison on the ACC/AHA stages of heart failure and NYHA Functional Classification

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but less than ordinary activity
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical
D	Refractory HF requiring specialized interventions	IV	

ACCF = American College of Cardiology Foundation; **AHA** = American Heart Association

HF= Heart Failure

Figure 3. Number of heart transplants by year in Italy (1992-2019*)



Data from "Sistema informativo trapianti", 31st August 2019.

Table 3[8]. Indications for mechanical circulatory support

BRIDGE TO DECISION (BTD)/ BRIDGE TO BRIDGE	Use of short term MCS (e.g. ECLS or ECMO) in patients with cardiogenic shock until hemodynamics and end-organ perfusion are stabilized, contra-indications for long term MCS are excluded (brain damage after resuscitation) and additional therapeutic options including long-term VAD therapy or heart transplant can be evaluated.
BRIDGE TO CANDIDACY (BTC)	Use of MCS (usually LVAD) to improve end-organ function in order to make an ineligible patient eligible for heart transplantation.
BRIDGE TO TRANSPLANTATION (BTT)	Use of MCS (LVAD or BIVAD) to keep patient alive who is otherwise at high risk of death before transplantation until a donor organ becomes available.
BRIDGE TO RECOVERY (BTR)	Use of MCS (typically LVAD) to keep patient alive until cardiac function recovers sufficiently to remove MCS.
DESTINATION THERAPY (DT)	Long-term use of MCS (LVAD) as an alternative to transplantation in patients with end-stage HF ineligible for transplantation or long-term waiting for heart transplantation.

ECLS = extracorporeal life support (ECLS); **ECMO** = extracorporeal membrane oxygenation (ECMO); **LVAD** = left ventricular assist device

Table 4[8]. Indication to ventricular assist device, according to European Society of Cardiology

Patients with >2 months of severe symptoms despite optimal medical and device therapy and more than one of the following:
LVEF<25% and, if measured, peakVO_2<12 mL/kg/min
≥ 3 HF hospitalizations in previous 12 months without an obvious precipitating cause.
Dependence on i.v. inotropic therapy.
Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥ 20 mmHg and SBP ≤80-90 mmHg or cardiac index ≤ 2L/min/m^2.
Absence of severe right ventricular dysfunction together with severe tricuspid regurgitation.

SBP = systolic blood pressure; **PCWP** = pulmonary capillary wedge pressure

Table 5[8,14]. Summary of different guidelines and indication criteria for long-term mechanical circulatory support

AHA/ACC Guidelines 2013	**ESC Guidelines 2016**
Class IIa	**Class IIa**
MCS is beneficial in carefully selected patients with stage D HFrEF in whom definitive management (e.g., cardiac transplantation) or cardiac recovery is anticipated or planned. **Level of Evidence: B**	An LVAD should be considered in patients with end-stage HFrEF despite optimal medical and device therapy and who are eligible for heart transplantation in order to improve symptoms, reduce the risk of HF hospitalization and the risk of premature death (BTT) **Level of Evidence: C**
Durable MCS is reasonable to prolong survival for carefully selected patients with stage D HFrEF. **Level of Evidence: B**	An LVAD should be considered in patients who have end-stage HFrEF optimal medical and device therapy and who are not eligible for heart transplantation to, reduce the risk of premature death. **Level of Evidence: B**

MCS = mechanical circulatory support; **HFrEF** = heart failure with reduced ejection fraction; **LVAD** = left ventricular assist device; **BTT** = bridge to transplant

Table 6: INTERMACS patient profile

Level	Description	Time to MCS
1	**"Crush and Burn"** – Critical Cardiogenic Shock	Within hours
2	**" Sliding fast on inotropes "** – Progressive decline	Within a few days
3	**"Stable but dependent on inotropes"** clinical stability on mild-moderate doses of intravenous inotropes (also patients stable on temporary circulatory support without inotropes)	Within a few weeks
4	Resting symptoms on oral therapy at home, "Frequent Flyer"	Variable
5	**Exertion intolerant ("housebound")** (Patients who are comfortable at rest but are intolerant of exercise)	Variable
6	**Exertion limited ("Walked Wounded")**	Variable
7	**"Advanced NYHA III"**	Not a candidate for MCS

MCS = Mechanical circulatory support

Figure 4[35]. Third annual report from IMACS Registry

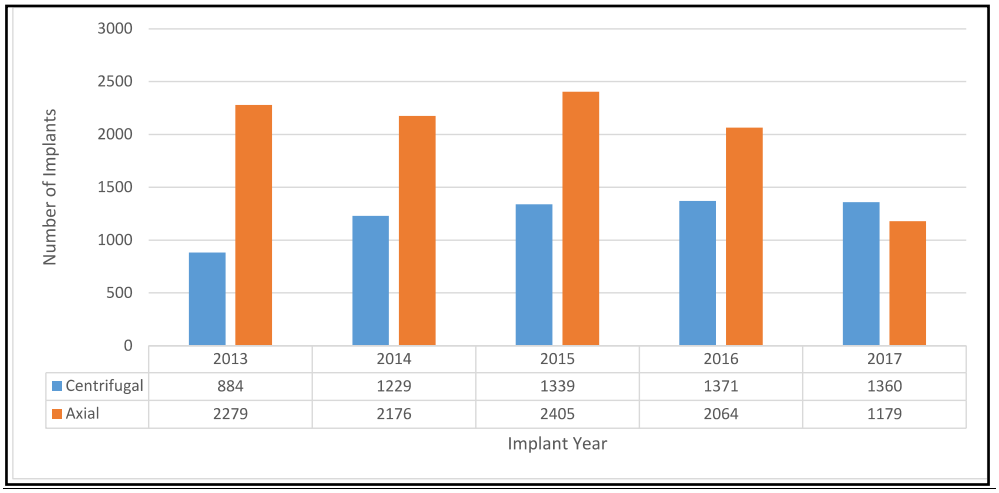


Figure 5[35]. Distribution of INTERMACS patient profiles by year of implant

	INTERMACS profile							
Implant year	1	2	3	4	5	6	7	Total
2013	467 (15%)	1,030 (33%)	979 (31%)	523 (17%)	92 (3%)	25 (1%)	24 (1%)	3,140 (100%)
2014	521 (15%)	1,193 (35%)	1,107 (33%)	440 (13%)	86 (3%)	22 (1%)	12 (0%)	3,381 (100%)
2015	605 (16%)	1,240 (33%)	1,334 (36%)	445 (12%)	65 (2%)	18 (0%)	19 (1%)	3,726 (100%)
2016	633 (19%)	1,096 (32%)	1,239 (36%)	371 (11%)	48 (1%)	19 (1%)	15 (0%)	3,421 (100%)
2017[a]	535 (21%)	831 (33%)	823 (33%)	265 (10%)	42 (2%)	18 (1%)	12 (0%)	2,526 (100%)
Total	2,761 (17%)	5,390 (33%)	5,482 (34%)	2,044 (13%)	333 (2%)	102 (1%)	82 (1%)	16,194 (100%)

[a]The marked drop in implants in 2017 compared with previous years likely reflects the enrollment of patients into the continued access protocol of the MOMENTUM 3 trial during this year. These patients received the study device and hence their data were not eligible for inclusion in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)/ISHLT Mechanically Assisted Circulatory Support (IMACS).

Figure 6 [29]. First generation of LVAD.

Pulsatile pumps generated to mimic function of native heart.

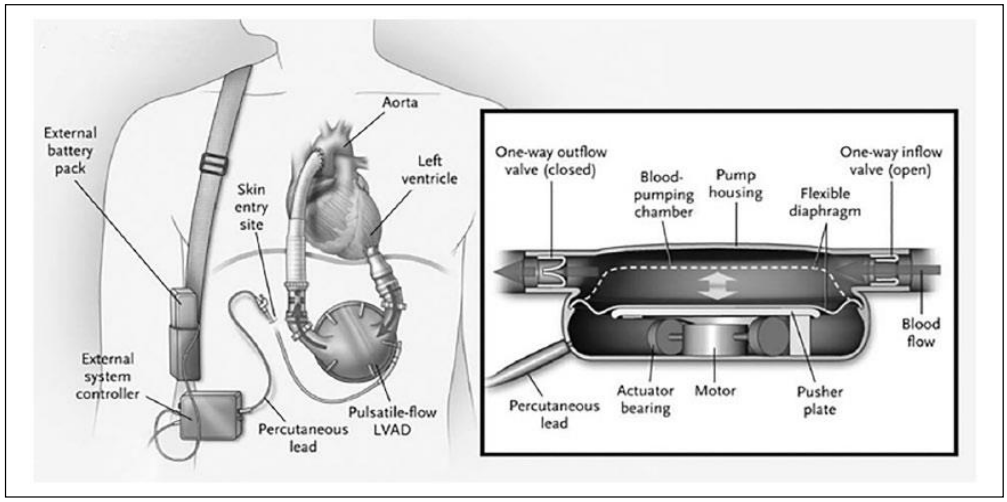


Figure 7 [29]. Second generation of LVAD

The pump rotor spins on two bearings located at the inlet and outlet stators. Valves and Chambers were eliminated.

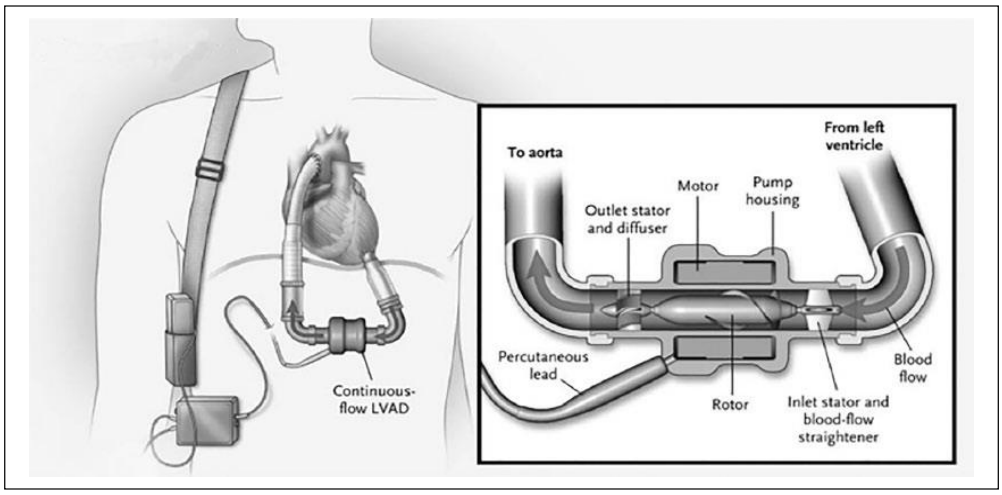


Figure 8 [29]. Third generation of LVAD

Hydrodynamic or magnetic levitation technology was introduced. These forces suspended the rotor, in this way there is no contact with the bearings, reducing the shear stress and stasis.

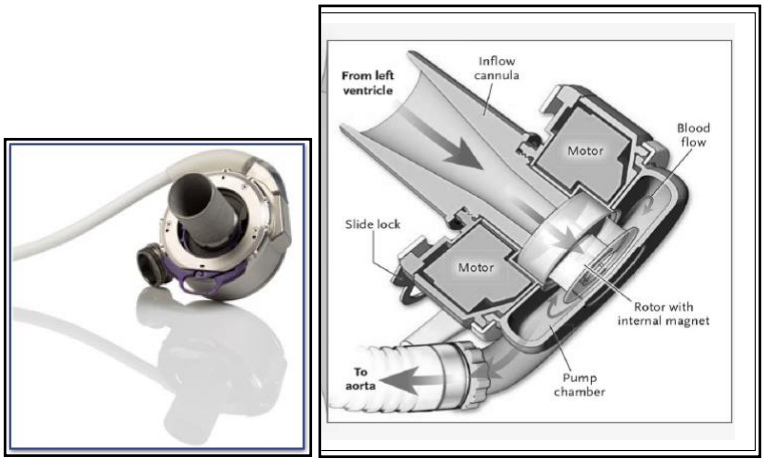
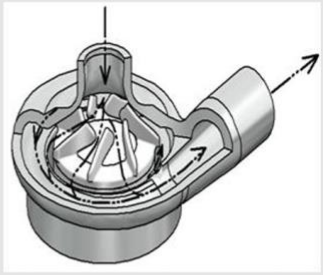


Figure 9[33]. Comparison of axial and centrifugal rotary pump response to physiologic conditions.

Conditions	Axial pump	Centrifugal pump
		
	Propeller in a pipe	Bladed disk spinning in a cavity
Decreased pre-load ↓ CBV, RHF Restricted Inlet Suction	Propeller screws itself into inlet fluid and pushes it at the outlet to increase suction at the inlet. Pump dP ↑↑ Power ↑ or ↓[a] Flow ↓	Fluid revolves centrifugally with the blades vs little resistance rather than to the outlet, limiting suction & power. Pump dP --- Power ↓↓ Flow ↓↓
Increased after-load ↑ SVR Restricted Outlet	Propeller pushes fluid harder into increased resistance causing high outlet pressures. Pump dP ↑↑ Power ↑ or ↓[a] Flow ↓	Fluid revolves centrifugally with the blades rather than to the outlet to limit power & outlet pressure increase. Pump dP --- Power ↓↓ Flow ↓↓
Decreased after-load ↓ SVR	Propeller pushes against less resistance producing highest flow. Pump dP ↓↓ Power ↑ or ↓[a] Flow ↑	Fluid is pumped through to the outlet against systemic resistance producing highest flow but highest power. Pump dP ↓ Power ↑↑ Flow ↑↑

↓, decreased; ↑, increased; CBC, circulating blood volume; Pump dP, pressure difference across pump inlet and outlet; RHF, right heart failure; SVR, systemic vascular resistance.

[a]Axial pumps in clinical use do not show a linear power vs flow relationships over the entire ventricular assist device operating flow range, making characterization of flow vs power relationships difficult.

Table 7 [40]. Contraindications to contemporary CF-LVADs.

Select contraindications to contemporary CF - LVADs
Life expectancy limited by non-cardiac condition to < 12 months
Presence of an active, uncontrolled infection
Intolerance to anticoagulant or antiplatelet therapies
Refractory severe end organ dysfunction or failure characterized by any of the following: • An international normalized ratio (INR)>2.0 not due to anticoagulant therapy • Total bilirubin >43 µmol/L (2.5 mg/dL), shock liver, or biopsy proven liver cirrhosis
History of severe chronic obstructive pulmonary disease (COPD) defined as the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) < 0.7 and FEV1 <50% predicted
History of stroke within 90 days of LVAD implant
Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration
Psychiatric disease/disorder, irreversible cognitive dysfunction, or psychosocial issues that are likely to impair compliance

Figure 10. Study flow chart

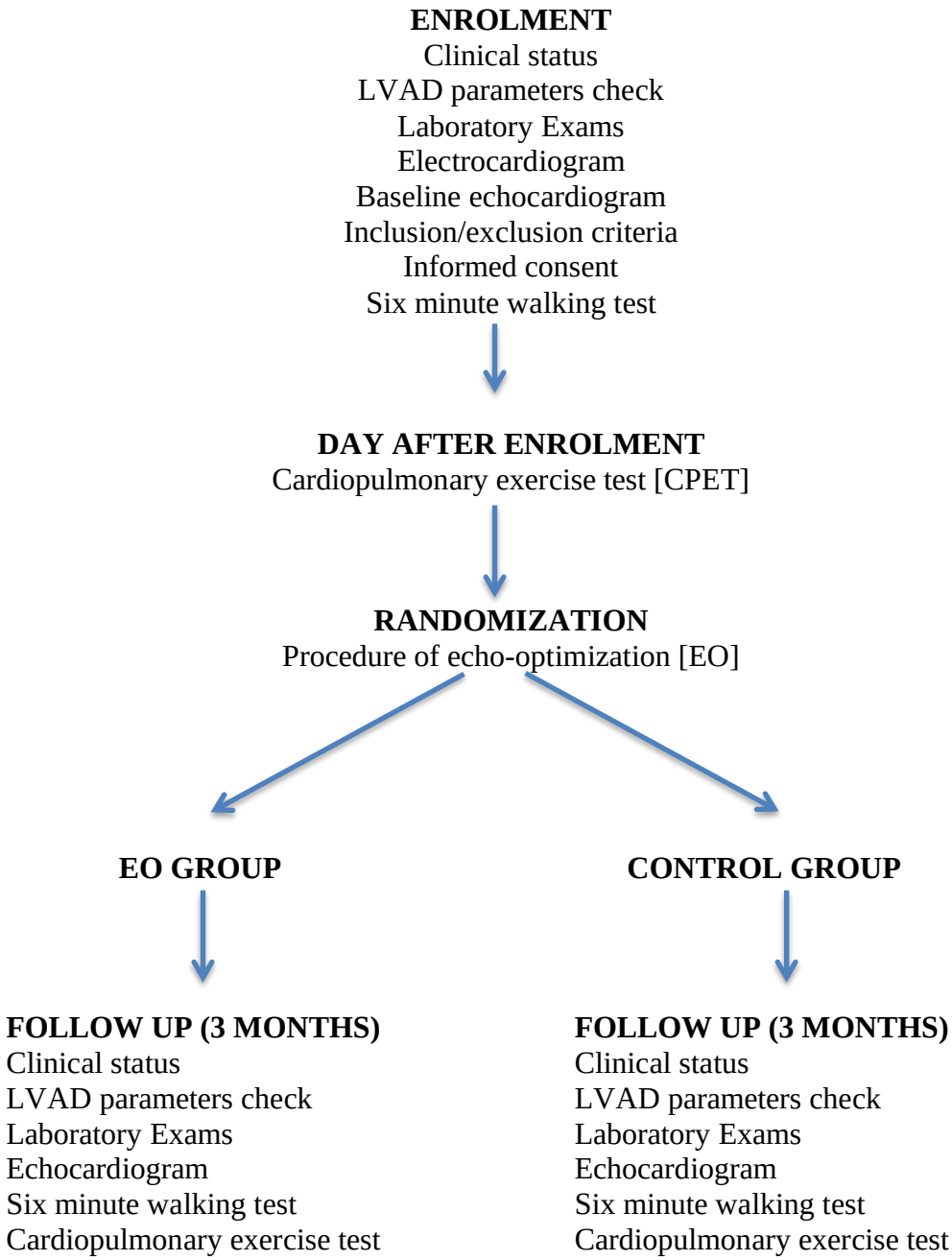


Table 8. Baseline characteristics [n = 27]

	CONTROL GROUP [N=14]	OPTIMIZED [N=13]	p
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 3TM	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	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
Sartans	28.6% (4)	30.8% (4)	0.93
Loop-diuretics	92.8% (13)	84.6% (11)	0.80
Potassium-sparing diuretics	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	7.1% (1)	7.7% (1)	0.91

BSA = body surface area; **BMI** = body mass index; **ACE** = angiotensin-converting enzyme

Table 9. Baseline laboratory exams

	CONTROL GROUP [N=14]	OPTIMIZED 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
Hemoglobin [g/L]	124.1 ± 12.9	134.4 ± 13.3	0.30
Hematocrit [L/L]	0.41 ± 0.03	0.41 ± 0.04	0.85
Platelets [10^9/L]	208 ± 53.4	209 ± 54.6	0.96
Prothrombine 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
Glycemia [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

HDL = high-density lipoprotein; **LDL** = low-density lipoprotein;
NT-proBNP = N-terminal pro-brain natriuretic peptide

Table 10. Echocardiographic parameters

	BASELINE		p*	FOLLOW UP		F	p**
	OPTIMIZED	CONTROL		OPTIMIZED	CONTROL		
LVEF [%]	26.5±2.4	25.7±2.7	0.45	26.7±2.2	25.9±2	0.4	0.53
LVEDDI [mm/m2]	37.8±3.9	37.6±2.8	0.88	37.8±4	37.9±2.5	1.9	0.18
LVEDVI [ml/m2]	106.9±16.7	108±16.8	0.87	107.2±16.9	108.6±16.8	0.6	0.43
E/A ratio	1.52±0.13	1.49±0.24	0.68	1.40±0.15	1.48±0.2	***4.3***	***0.04***
LAVI [ml/m2]	38.4±6.6	38.9±6.2	0.85	38.4±6.1	39.1±6.4	0.6	0.44
Basal RV diam. mm]	37.2±3.2	36.4±3.7	0.52	37.3±2.9	36.7±3.2	0.4	0.55
RVOT prox [mm]	29.2±3.1	28.8±3.3	0.80	29±2.9	29.2±3.1	0.7	0.40
EDRV area Index [cm2/m2]	9.8±0.5	10.1±0.6	0.74	9.8±0.6	10.2±0.5	1.3	0.26
RA area [cm2]	16.5±2.9	16.1±2.6	0.72	16.3±2.8	16.2±2.3	1.7	0.21
TAPSE [mm]	15.7±3.4	15.1±2.4	0.58	15.9±2.9	15.3±2.1	0.2	0.68
FAC [%]	36.5±3.8	35.8±4.1	0.72	36.8±3.2	35.7±4.2	0.5	0.47
RV-RA gradient [mmHg]	26.1±4.8	25.4±3.5	0.66	25.8±4.7	25.3±3.9	0.4	0.54

LVEF = left ventricular ejection fraction; **LVEDDI** = left ventricular end-diastolic diameter index; **LVEDVI** = left ventricular end-diastolic volume index; **LAVI** = left atrial volume index; **RV** = right ventricle; **RVOT** = right ventricular outflow tract; **EDRV** = end-diastolic right ventricular; **RA** = right atrium; **TAPSE** = tricuspid annular plane systolic excursion; **FAC** = fractional area change.

Table 11. Gas exchange and exercise performance measures

	BASELINE		p*	FOLLOW UP		F	p**
	OPTIMIZED	CONTROL		OPTIMIZED	CONTROL		
ET [seconds]	490±98	504±103	0.72	526±116	499±107	***6.7***	***0.02***
Workload [watt]	80.6±18.1	86.9±18.6	0.38	85.2±17.4	86.3±19.9	3.5	0.07
Rest Heart Rate [bpm]	76.8±14.5	76.5±10.1	0.96	75.5±11.6	74.9±11.2	0.1	0.74
Peak Heart Rate [bpm]	111.2±8.4	111.3±6.5	0.97	115.1±5.2	112±3.9	***5.1***	***0.03***
VO2 peak [mL/kg/min]	13.2±2.5	13.8±2.4	0.58	14.2±2.5	13.2±2.6	***19.5***	***<0.001***
VO2 work slope [mL/kg/min/W]	8.06±1.14	8.07±0.84	0.98	8.55±0.85	8.06±0.85	3.4	0.08
VE/VCO2 slope	42.5±6.1	42.2±7.7	0.90	43.5±8.8	44.4±11.2	0.58	0.45
O2 pulse [ml]	9.75±1.46	9.83±1.86	0.90	10.75±2.2	9.76±1.46	***10***	***0.004***
VO2 AT [%]	9.8±1.9	9.5±1.3	0.65	10.3±1.4	9.7±1.4	1.6	0.22
VE peak [L/min]	49.9±12.1	57.1±14.5	0.18	54±15.5	56.6±15.4	2.9	0.10
RER	1.07±0.07	1.12±0.06	0.06	1.09±0.05	1.12±0.04	0.35	0.56
6 minute walk test [m]	363±54	364±84	0.96	391±52	374±80	***3.6***	***0.04***

* significativity for difference at baseline between the two groups

** significativity for the difference in change from baseline to follow-up between optimized and control group (F value for one-way analysis of covariance, ANCOVA)

ET = exercise time; **VO2** = oxygen uptake; **VE/VCO2** = minute ventilation/carbon dioxide production; **AT** = anaerobic threshold; **RER** = respiratory exchange ratio

Figure 11. Graphical representation of the ANCOVA for VO_2 peak

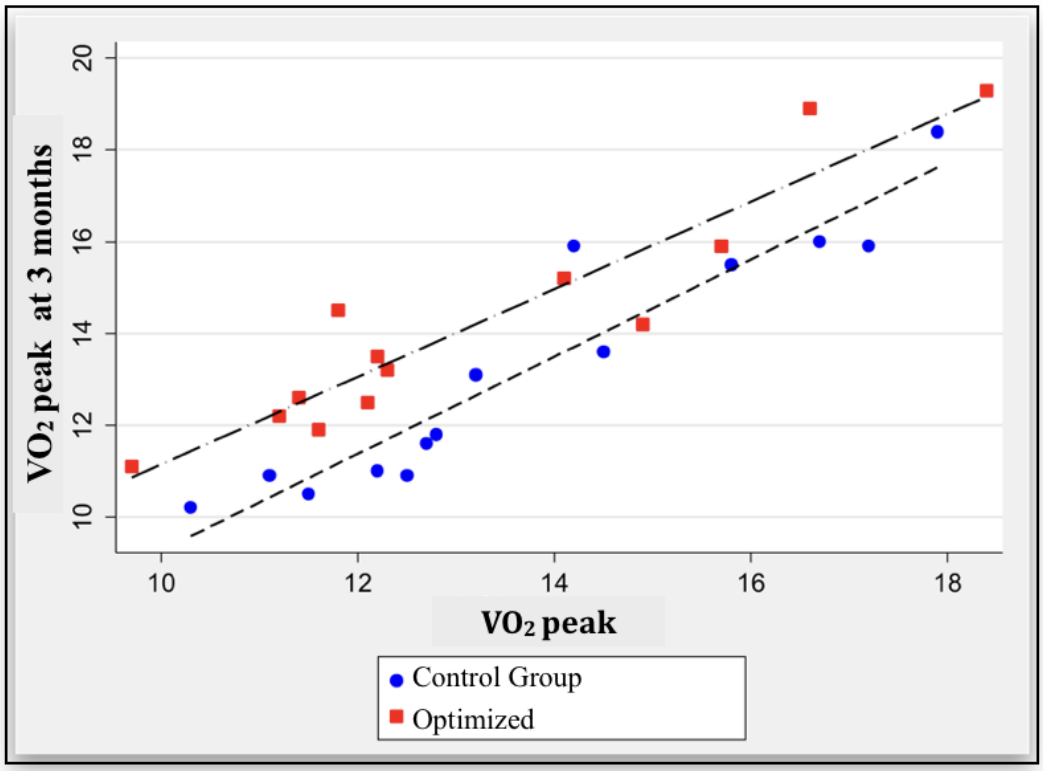


Figure 12. Graphical representation of the ANCOVA for O_2 pulse

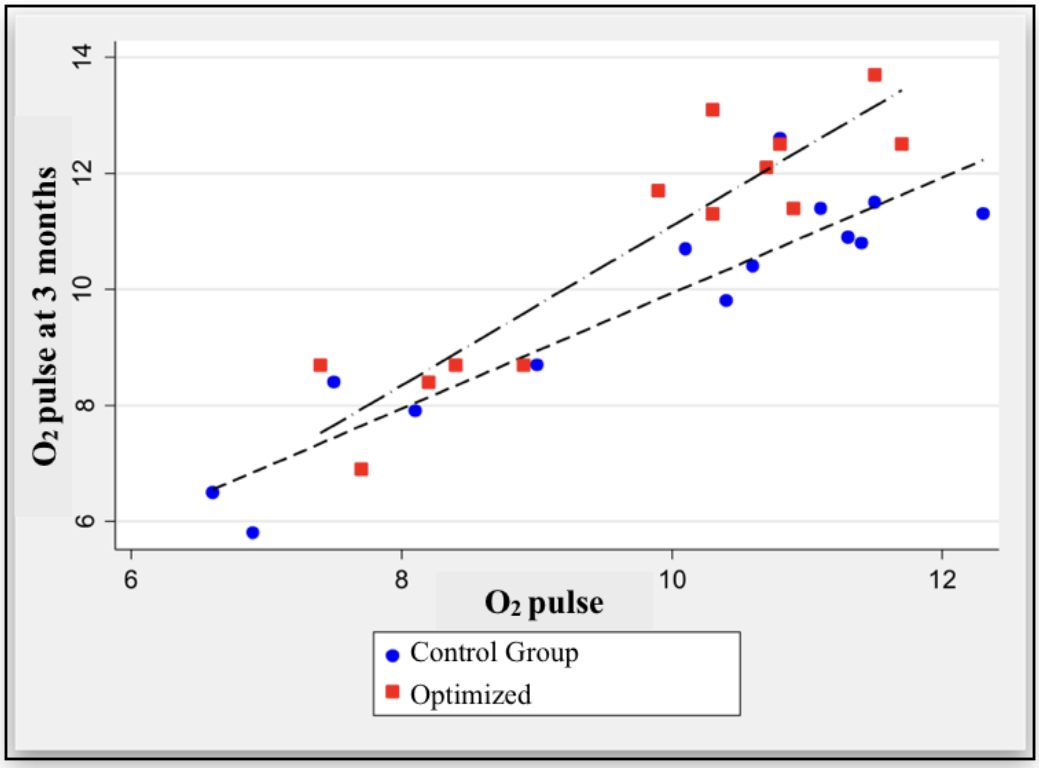


Table 12. Quality of life

	BASELINE		p*	FOLLOW UP		F	p**
	OPTIMIZED	CONTROL		OPTIMIZED	CONTROL		
EQ-5D-3L™	0.796±0.1	0.804±0.09	0.82	0.85±0.08	0.8±0.08	***19.6***	***<0.001***
VAS scale	71.1±9.8	74.4±13.5	0.48	77.8±11.1	74±12.1	***6.3***	***0.006***
KCCQ-23	81.6±6.9	83.3±7.9	0.56	84.6±5.6	83.9±7.2	***5.8***	***0.025***

EQ-5D-3L™ = EuroQol 5 dimensions, 3-levels questionnaire;
VAS = visual analog scale; **KCCQ** = Kansas City Cardiomyopathy Questionnaire.

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