ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

DOTTORATO DI RICERCA IN

SCIENZE CARDIO NEFRO TORACICHE

Ciclo 37

Settore Concorsuale: 06/D1 - MALATTIE DELL'APPARATO CARDIOVASCOLARE E MALATTIE DELL'APPARATO RESPIRATORIO

Settore Scientifico Disciplinare: MED/11 - MALATTIE DELL'APPARATO CARDIOVASCOLARE

THE ROLE OF INVASIVE HEMODYNAMIC EVALUATION AND PUMP OPTIMIZATION IN THE MANAGEMENT OF PATIENTS SUPPORTED WITH LEFT VENTRICULAR ASSIST DEVICES (LVAD)

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Esame finale anno 2025

Table of Contents

Abstract

Purpose. Despite improved outcomes, LVAD patients still present with frequent rehospitalizations, including those for heart failure (HF). The aim of this study was to investigate the changes in hemodynamic parameters after LVAD implant and the role of hemodynamic optimization obtained by the invasive ramp test (RT) in improving survival and reducing HF admissions.

Methods. This single-center study enrolled patients with centrifugal pumps implanted between 2013 and 2024. The devices utilized were hybrid levitation technology (HL) and fully magnetically levitated (FML). All patients who underwent right catheterization (RHC) after LVAD implant during the index hospitalization were included. RT was performed according to clinical practice and hemodynamic parameters were evaluated at different speed settings. Optimal hemodynamics were defined as a right atrial pressure < 10 mmHg, pulmonary capillary wedge pressure < 15 mmHg, and cardiac index > 2.2 l/min/m2. The endpoint was survival free from HF admission according to the hemodynamic profile at 24 months.

Results. This study enrolled 74 patients with a mean age of 54 ± 11 years. Ninety percent of the participants were male. The most common etiology of HF was dilated cardiomyopathy (57%). Forty-nine percent of the patients received HL devices, and 51% had FML. Fifty-two percent of the patients were in INTERMACS class 2 or 3, and 41% were on temporary mechanical support. RHC before discharge was available for 63 patients. After LVAD implant, there was a significant improvement in pulmonary pressure and a reduction in the indices of right ventricular function without changes in central venous pressure. At baseline, 41% of the patients already had an optimal hemodynamic profile, while an additional 14% achieved it after RT. At 24 months, survival free from HF admission was significantly reduced in patients with non-optimized profiles (81 vs. 58 %, OR 3.2 [1.2-8.2], p = 0.01). This difference was not significant when the effect of the ramp test was not considered (p=0.07). Univariate analysis revealed that the predictors of post-discharge mortality and HF hospitalizations were non-optimized profile (OR 3 [1.1-7.8], p 0.02), use of beta-blockers (B-b) (OR 2.5 [1.04-6], p 0.03), and HL device. In the multivariate analysis, only the non-optimized profile remained significant.

Conclusions. In patients with LVAD, survival free from HF admissions was significantly higher in those with optimized hemodynamics, and RT provided the opportunity to further improve hemodynamic profiles. The non-optimized profile was an independent predictor of mortality and hospitalization for HF.

Introduction

Heart failure (HF) is an increasingly prevalent condition that affects millions of individuals globally and is associated with reduced survival, impaired quality of life, and substantial costs for the healthcare system. Despite advancements in medical therapies, a significant proportion of HF cases progress to an advanced stage of the disease, characterized by persistent symptoms and poor tolerance to guideline-directed medical therapy (GDMT). Advanced HF is characterized by frequent readmissions and poor prognosis, with a 1-year mortality rate ranging between 25-75%[1,2].

In this context, heart replacement therapies (HRT), such as heart transplantation (HT) and left ventricular assist device (LVAD) implantation, represent the definitive treatment option in selected patients. These interventions substantially improve survival and quality of life. Due to the scarcity of donations that limits access to HT, durable mechanical circulatory support has emerged as a viable option to expand the population suitable for treatment, as a bridge to transplant strategy or destination therapy[3].

Over the last 25 years, mechanically assisted circulation and LVAD technology have evolved significantly, moving from pulsatile devices to fully magnetically-levitated centrifugal pumps[4]. Despite both pulsatile and axial-flow LVAD demonstrating improved survival as compared to medical therapy in patients ineligible for HT[5,6], the introduction of centrifugal pumps dramatically improved the outcomes of durable mechanical support. Both the hybrid levitation centrifugal device (HVAD, Heartware) and the fully magnetically levitated pump (Heartmate 3, Abbott) outperformed the previous axial-flow device[7,8]. Nevertheless, indirect comparisons showed that the fully magnetically levitated LVAD had an improved safety profile with reduced stroke and pump thrombosis rates[9,10], leaving the former the only commercially available LVAD.

Contemporary results from the MOMENTUM 3 randomized clinical trial showed a 1-year survival rate of 87%, similar to the 1-year survival rate after HT in Europe[8]. Long-term follow-up confirmed that survival with the device remained satisfactory throughout the years, being over 50% at five years[11]. Similarly, the STS registry 2022 report showed that the 1- and 5-year survival rates of patients undergoing centrifugal flow LVAD implants between 2017 and 2021 have improved (83.0% vs. 81.2% and 51.9% vs. 43.0%, respectively)[12]. Despite improved survival, patients supported with LVAD continue to experience a significant burden of adverse events, with only 30% remaining free of hospital readmission within 1 year of LVAD implantation[12]. Adverse events include pump thrombosis, stroke, gastrointestinal bleeding, infections, and persistent HF mainly caused by right ventricular failure (RVF)[13]. RVF is a significant driver of postoperative morbidity and mortality following LVAD implant and is estimated to occur in 9%-42% of patients, depending on the

diagnostic criteria used[14]. According to an analysis of the INTERMACS Registry, RVF incidence was 24% at 1-month and approximately 8–10% at all time points thereafter. RVF occurring relatively early post-LVAD implant (≤3 months) was a common and often transient condition, which was not associated with worse long-term prognosis once resolved. Conversely, RHF which presents late post-LVAD (>3–6 months) was more frequently a persistent disorder, with a significant risk of mortality[15].

The development of right ventricular failure is related to multiple factors, including pre-existing dysfunction, pulmonary hypertension, preoperative damage, and peculiar characteristics of the LVAD physiology. While pre-implant recipient characteristics and surgical insult strongly influence early dysfunction, the pathophysiology of long-term right ventricular dysfunction remains elusive and probably related to the long-term effect of single ventricle support and continuous-flow circulation, which is yet to be completely understood[16,17]. Therefore, the assessment of right ventricular function is of paramount importance in LVAD candidates and considers both echocardiographic and invasive hemodynamic parameters.

Standard echocardiographic parameters of right ventricular function, such as tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular systolic velocity by tissue Doppler (S'), failed to efficiently predict RV dysfunction. Evaluation of free-wall RV longitudinal strain (RVLS) derived by speckle-tracking echocardiography seems to be of more interest, as it reflects the right ventricular stroke work index. According to recent studies and meta-analyses, the most reliable parameters to evaluate are RVLS<12% and fractional area change (FAC) <35%[18–21]. Notably, none of these parameters alone is sufficient and a certain cut-off is not available, as many studies reflect the experiences of single centers. A full evaluation of RV function is complex, requires experienced operators, and should include multiple parameters.

Invasive hemodynamic assessment through right heart catheterization (RHC) provides a more detailed assessment of right ventricular function and its coupling with pulmonary circulation through different indices. The most relevant include the right ventricular stroke work index (RVSWI), right atrial pressure to pulmonary capillary wedge pressure ratio (RAP/PCWP) and pulmonary artery pulsatility index (PAPi). RVSWI has been investigated in multiple studies and meta-analyses, and is systematically lower in patients who experience RVF after implant[18]. The RAP-to-PCWP ratio offers insights into the mechanism of right ventricular dysfunction. Indeed, high CVP and low RVSWi can depend on worsening right heart function as a result of increased left-sided filling pressures and thus pulmonary hypertension or on intrinsic right ventricular dysfunction. In the first case the RV benefits from LVAD implantation, whereas patients in the second group are at risk of RV failure. RAP/PCWP will be low in those with right-sided dysfunction as a result of persistently high left filling pressure,

whereas in the case of intrinsic RV dysfunction, this ratio will be high. The PAP index rapports the pulmonary pulse produced by the right ventricle to its preload expressed as right atrial pressure and describes right ventricular failure in different situations, including acute heart failure in right ventricular myocardial infarction and LVAD implant. Because of the complex nature of right ventricular function in HF, multiple parameters must be evaluated alongside echo-derived measures rather than relying on a single cutoff value[16–18]. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for mechanical circulatory support endorse the use of the aforementioned hemodynamic indices in the evaluation of LVAD candidates, with RVSWI < 300, PAPi < 1.85, and RAP/PCWP < 0.63, which are associated with an increased risk of right ventricular failure[22].

Apart from pre-implant evaluation, invasive hemodynamic assessment provides the opportunity to gain a deeper understanding of the changes that characterize LVAD support and response of the right ventricle. Furthermore, it offers the possibility to actively improve the hemodynamic profile after the implant and improve the patient's condition through the performance of the invasive ramp test. To this end, RHC is performed at different pump speed settings to improve circulatory parameters, aiming at the optimal pump configuration in which the right and left filling pressures are acceptably low, and the cardiac index is the highest obtainable. Notably, different studies have shown that such an approach in stable LVAD patients could lead to better outcomes with a lower rate of subsequent HF hospitalization[23–26].

We designed this study to assess changes in invasive indices of right ventricular function after LVAD implant and the role of the RHC-guided ramp test in reducing the risk of poor cardiovascular outcomes.

Methods

Study population

We created a single-center registry enrolling all consecutive patients who underwent a centrifugal-flow LVAD implant at IRCCS Sant'Orsola – Malpighi Hospital from 2012 to August 2024. From 2012 to 2022, patients were retrospectively included, whereas starting from 2023, all consecutive implants were prospectively recorded. The indication for LVAD was given by the Advance Heart Failure Multidisciplinary Team (composed of cardiologists dedicated to heart failure, cardiac surgeons, anesthesiologists, LVAD coordinator technicians, and psychologists) according to clinical practice. The choice of device was made by the surgeons according to the available technologies and anatomical and functional aspects. Echocardiography and right heart catheterization were performed

according to clinical practice, before and after implant. Clinical follow-up was performed every 3-6 months as usual practice at our center. For the present analysis patients with repeated RHC after implant during the index implant hospitalization were analyzed.

Clinical characteristics included demography, laboratory values, RHC and echocardiography performed at the closest time point to LVAD implant and medical therapy at discharge.

This study was approved by the local IRB.

Hemodynamic evaluation

As per center protocol all patients underwent RHC before LVAD implant and before discharge, except for those who died during the index hospitalization. Right heart catheterization was performed through a right jugular or femoral venous access with a 7F Swan Ganz Catheter with zero level recorded at mid thoracic level. The right atrial, pulmonary artery, and pulmonary capillary wedge pressures were recorded. Cardiac output was calculated using the thermodilution method and the indirect Fick method. The derived measures were calculated as follows:

- RVSWI: (cardiac output/heart rate) × (mean pulmonary artery pressure – right atrial pressure) × 1000
- RAP: PCWP: ratio of RAP to PCWP pressure;
- pulmonary pulsatility index (PAPi): (systolic pulmonary artery pressure – diastolic pulmonary artery pressure)/right atrial pressure

The ramp test (RT) was performed before discharge according to the center practice by a heart failure cardiologist and the LVAD coordinator, which manages the pump speed. During RT, a first RHC at basal speed is performed and pump parameters are registered. After the basal measures, RHC is repeated at decremental and incremental speeds. At each speed change, echocardiography is performed and left ventricular end diastolic diameter (LVEDD), degree of mitral, tricuspid and aortic regurgitation, RV function and aortic valve opening are reported. Speed changes are not scheduled in a protocol but are guided by HF professionals according to hemodynamics to obtain normal filling pressures and the highest cardiac output.

For this study, patients with available hemodynamic data were divided into two groups according to whether they had optimized hemodynamics. “Optimal profile” was defined when all following variables were respected:

- Right atrial pressure < 10 mmHg
- Pulmonary capillary wedged pressure < 15 mmHg
- Cardiac Index $\geq$ 2.2 l/min/m^2

Optimal hemodynamics were assessed at the basal RHC and after the ramp test, recording the number of patients that obtained this profile after the ramp test. The final hemodynamic profile was used to evaluate the impact on prognosis.

Outcomes

The principal aims of this study were to assess the changes in hemodynamic parameters of right ventricular function after LVAD implant and the difference in survival free from all-cause death and HF readmission according to the optimized hemodynamic profile. The principal outcome measure was survival from first HF readmission at 24 months. Patients who underwent HT during follow-up were censored alive at the time of transplantation. As an exploratory outcome, we investigated the role of HF medications in subsequent cardiovascular outcomes.

In addition to the primary outcome measures, in-hospital outcomes, including severe RVF, assessed according to the latest INTERMACS definition and death, were recorded.

Statistical analysis

Continuous variables are presented as mean and standard deviation if normally distributed, or as median and interquartile range (IQ) in case of skewed distribution. Categorical variables were presented as numbers and percentages. Continuous variables were compared using the Kruskal–Wallis test and paired sample t-test as appropriate. Categorical variables were compared using the $\chi 2$ test. Univariate Cox regression analysis was conducted to evaluate predictors of optimized hemodynamic profiles.

Survival was estimated with the Kaplan-Meier analysis and comparison between groups was analyzed with the Log-rank method. Univariate Cox proportional hazard regression analysis was used to identify the risk factors for the primary outcome measure, including medical therapy at discharge. All factors with $p< 0.05$ at univariate analysis were then tested in a Cox proportional hazard regression multivariable model. Statistical significance was set at $p < 0.05$. All analyses were conducted using the JMP Pro 17 statistical software.

Results

Study population

Seventy-four continuous-flow left ventricular assist devices (LVAD) were implanted at our institution during the study period. The general characteristics of the study participants are presented in *Table 1*. The majority of patients were male (90.5%), with a mean age of 54 ± 12 years and a mean BMI of 25.1 ± 3.7 kg/m2. The predominant etiology of LV dysfunction was dilated cardiomyopathy (56.8%), followed by ischemic etiology (41.9%). Eleven percent of the patients had undergone

previous cardiac surgery, and 8% had previously undergone transcatheter edge-to-edge (TEER) mitral valve repair. The laboratory profile of patients indicated a slightly reduced mean hemoglobin value (12.1 ± 1.9 g/dl) and preserved renal function, with a mean eGFR of 70.4 ± 34.5 ml/min/m2. The mean serum sodium and albumin levels were within normal ranges. HVAD devices were implanted in 48.6% of patients, while HeartMate3 devices were used in the remaining 51.4%. As anticipated, the implant volume increased over time. Moreover, pump-type distribution varied across years, as HVAD was only available until 2021, and HM3 was implanted at our institution since 2017 (*Figure 1*).

Table 2 shows the baseline echocardiographic and hemodynamic characteristics of the study population. The subjects exhibited severe left ventricular (LV) dysfunction with a mean left ventricular ejection fraction (LVEF) of 21.3% ± 5.4% and severely dilated left ventricles, with a mean end-diastolic volume of 269±110.9 ml. Significant mitral regurgitation (MR) was present in 61% of the patients, while severe or moderate-to-severe tricuspid regurgitation (TR) was observed in 21.6 %. Regarding right ventricular function, the mean fractional area change (FAC) value was 27.1±12.3%, and the mean tricuspid annular plane systolic excursion (TAPSE) was 15.9±4.4 mm. Right ventricular strain evaluation was not available as it was not routinely performed at our institution.

Pre-implant right heart catheterization (RHC) was performed in all patients. The mean preimplant right atrial pressure was 7±3.8 mmHg. Post-capillary pulmonary hypertension was common, with a mean pulmonary artery pressure (mPAP) of 34.5 ± 10.3 mmHg, and a mean pulmonary capillary wedge pressure of 23.4 ± 8 mmHg. As anticipated, cardiac output and cardiac index (both obtained via the Fick method) were markedly reduced pre-implant. Right ventricular function, as assessed by hemodynamic parameters, was generally preserved before implantation, with a mean pulmonary artery pulsatility index (PAPi) value of 4.8 ± 2.9, right ventricular stroke work index (RVSWi) of 565 ± 265, and atrial-capillary ratio of 0.3 ± 0.1.

As demonstrated in Table 3, the majority of the population (71.6%) underwent urgent LVAD implantation, defined as implantation performed during hospitalization for HF rather than during a dedicated elective admission. Consequently, at the time of LVAD implantation, the prevalent INTERMACS classes at implant were 4 (39.2%), 3 (23%) and 2 (31.1%). Implants in class 5 were relatively uncommon. Half of the patients received LVAD with a bridge to transplant (BTT) approach, 17.6% of patients were implanted as destination therapy (DT), and the remaining implantations were performed either as bridge to candidacy (BTC) or bridge to decision (BTD). At the time of LVAD implantation, 40.6% of patients were on mechanical support, largely an intra-aortic

balloon pump (IABP), while only 2 were supported with Impella 5.5. and one with Impella CP, respectively.

In-hospital outcomes

The median duration of stay in the Intensive Care Unit (ICU) was 11 days [IQR, 7–22]. Severe right ventricular (RV) failure necessitating temporary right ventricular assist device (RVAD) implantation was observed in 5% of the study population. Surgical revision was required in 24.3% of the patients, with cardiac tamponade being the most prevalent cause. Gastrointestinal bleeding was observed in 6.7 of the patients, stroke (ischemic and hemorrhagic) occurred in 6.7% of the patients, with only one case of disabling stroke and pump thrombosis in two patients. It is noteworthy that both patients who experienced pump thrombosis during hospitalization received HVAD. Due to severe RV failure and inability to further optimize the device, one patient underwent urgent transplantation and subsequently died. In-hospital mortality occurred in 9 patients, representing a rate of 12.1%.

Medical therapy was available for all patients at discharge. As shown in *Table 3*, the largest part of the population was prescribed diuretic therapy (76%), with a median daily dose of furosemide of 50 mg/day [IQR 25;100]. Guideline-directed medical therapy was well-titrated in most patients: 74% were on renin-angiotensin system inhibitors (RAASi), 71% on mineralocorticoid receptor antagonists (MRA), and 22% on SGLT2i. Beta-blocker use was less common (45.8%).

Invasive hemodynamic evaluation and ramp test

Post-implant RHC data were available for 63 patients, which constituted the study population to assess outcomes. As anticipated, hemodynamics improved with a significant decrease in pulmonary pressure and pulmonary vascular resistance, and a significant increase in cardiac output and index (*Table 4 and Figure 2a,b,c*). Right atrial pressure remained unchanged after implant. The parameters reflecting RV function (PAPi and RAP/PCWP) significantly decreased after LVAD, thereby revealing occult RV dysfunction. Specifically, there was a 70% mean decrease in PAPi values and a 37% mean increase in the RAP/PCWP ratio.

The optimal profile, as previously defined, was observed in 26 (41%) patients, with an additional 8 patients (14%) achieving the optimal profile after the ramp test. Consequently, 55% of patients exhibited an optimal hemodynamic profile at discharge (*Figure 3*). During ramp test, pump speed was increased in the vast majority of cases (86%), with a mean increase of 326±140 rpm for Heartmate 3 and 128±75 rpm for HVAD.

When comparing the pre-implant clinical, echocardiographic and hemodynamic characteristics alongside device type and post-surgery main complications, the two groups exhibited differences.

Patients who achieved an optimal profile after the ramp test less frequently underwent previous TEER (0.047), had more frequent significant tricuspid regurgitation (p=0.01), and were more likely to have received the Heartmate 3 device (p=0.02). As shown in *Table 5,* other characteristics were comparable, except for a trend towards lower hemoglobin levels and slightly lower LVEF (p=0.1).

Follow-up events and outcomes

The median follow-up was 20 months (IQR 9-35) with a maximum of 74 months. During this period, 22 patients (33%) underwent HT, which was urgent in 16 cases, 16 patients died (24%), and eight were readmitted for HF (12%). None of the 3 patients that died after RHC but before discharge achieved an optimized profile. The survival free from HF readmission in the overall population was 87% at 12 months and 69% at 24 months.

Patients discharged with an optimized profile showed improved survival compared to those who did not achieve the hemodynamic goal (OR 3.2 [1.2-8.2], p = 0.01), with survival free from HF admission at 24 months of 81% compared to 58% (*Figure 4*). At one year, the survival rates were 100% and 80%, respectively. When the same analysis was performed considering patients with only an optimized basal RHC profile (i.e., without active pump optimization), this difference only approached statistical significance (p=0.07).

Hemodynamic optimization, absence of beta-blocker therapy at discharge, and support with Heartmate 3 were associated with improved survival free from HF readmissions. However, hemodynamic optimization remained the only independent predictor (OR 2.7 (1.02-7.09), p = 0.04) (*Table 6*).

Discussion

This study investigated the alterations in hemodynamics and the significance of pre-discharge invasive pump optimization in patients receiving LVAD implant. The principal findings can be summarized as follows: 1) after LVAD implant, there is a nominal reduction in hemodynamic indices of right ventricular function, even in the presence of improved pulmonary hemodynamics; 2) more than half of the patients exhibited a suboptimal hemodynamic profile in terms of biventricular filling pressures and cardiac index; 3) proactive pump management with invasive ramp testing before discharge yielded an optimized profile in an additional 14% of patients and was independently associated with improved survival free from HF hospitalization.

LVAD implant implies a unique physiology in which the failing left ventricle is mechanically assisted with active unloading and adequate cardiac output (CO), whereas the right ventricle needs to accommodate the increased CO and venous return. Several mechanisms are involved in the

physiology of LVAD-assisted patients, including changes in pulmonary circulation, preexisting right ventricular dysfunction, and changes in the geometry and function of the interventricular septum[16,17]. The reduction in pulmonary artery pressure as a consequence of active unloading reduces the right ventricular afterload, whereas the septal shift caused by the LVAD could hinder the systolic interaction between the two ventricles and reduce septal-dependent right ventricular contraction. The functional reserve of the right ventricle is a key factor in defining the results of this balance. The physiology of the right ventricle in this context is complex, and it is characterized by interactions with the unloaded left ventricle both in series (the two ventricles that are sequentially associated with pulmonary and systemic circulation) and in parallel (as they share the interventricular septum in systolic and diastolic function)[27]. Ultimately, the interplay of these factors determines the hemodynamic situation of these patients, which strongly influences clinical outcomes and functional capacity.

Although studies addressing the longitudinal effects of LVAD implant on right ventricular function are lacking, several models have attempted to elucidate the response of the right ventricle at different LVAD speeds. Such studies applied to the LVAD population, often limited to very small sample sizes, and yielded different results. In particular, Tran et al[29] reported minimal effects of pump speed increase on PV curves, aligned with observations with standard RHC, showing that higher pump speed was associated with a decrease in PCWP and an increase in CO without effects on central venous pressure[30]. Conversely, Brener and colleagues[27] reported variable adaptations of right ventricular function during a ramp test. In particular, they described systolic interventricular dependence, combined systolic and diastolic relationships, and the absence of interactions. Despite being limited to four patients, this finding underscores the concept that physiological response during LVAD support can vary greatly, and this complex interaction is yet to be fully understood.

More recently, larger studies have provided novel insights into the physiology of the right ventricle during LVAD support. Scheel and colleagues[31] found that indices of right ventricular function, such as end-systolic elastance (a measure of systolic performance) and ventricular-vascular coupling, were significantly reduced in LVAD patients as compared to healthy subjects. Interestingly, LVAD patients had scattered changes in systolic elastance in response to speed change, and those with a baseline reduced ventricular-vascular coupling exhibited a reduced systolic reserve in response to speed increase with the inability to increase systolic function, even with a progressive reduction in afterload. They demonstrated that PAPi is the best surrogate for impaired ventricular-vascular coupling, a relevant finding in clinical practice considering the limited applicability of conductance catheter studies.

In our cohort, we found a significant decrease in hemodynamic parameters of right ventricular function after LVAD implant in a selected population with overall good pre-implant parameters, well above the thresholds provided by the current guidelines. We observed a significant decrease in PCWP and pulmonary pressure and an increase in CI with no differences in RAP, consistent with the findings described during a structured ramp test. The fact that a decline in PAPi and increase in RAP/PCWP were found in patients with an effective unload of the pulmonary circulation may imply the presence of a right ventricular dysfunction intrinsic to the LVAD physiology, irrespective of pre-implant hemodynamic parameters. These findings were observed in stable patients before discharge, underlining the fact that this phenomenon is also present in case of uneventful clinical course and is not limited to those experiencing early right ventricular failure. This observation confirms the importance of selecting candidates with good pre-implant hemodynamic parameters, as those with borderline right ventricular function and poor functional reserve could present with a complicated course and suboptimal hemodynamics after the implant.

However, it is not obvious whether these reductions in functional indices truly reflect impaired systolic performance, as the mechanistic explanation of these aspects of right ventricular function remains elusive. Scheel and colleagues[31] described that systolic properties of the right ventricles were associated with septal but not free wall contraction, as assessed by strain analysis, reinforcing the concept that modification in ventricular geometry plays a pivotal role in this context. On the other hand, Brener and colleagues[32] reported that speed increase has no impact on systolic elastance and influences diastolic function (i.e., inducing larger end-diastolic volume of the right ventricle), thereby questioning the principle of the involvement of systolic septal motion in right ventricular dysfunction. They described two different patterns of response to left ventricle unloading based on increased or stable RVSWI; however, this behavior could not be associated with pre-implant characteristics or other widely used instrumental parameters. In our cohort we observed a decrease in PAPi after the implant which might imply worse ventricular-vascular coupling even in comparison with advanced HF, but could be an oversimplification of systolic function as it reflects pressure but it does not provide information on the inotropic response. Indeed, in the work by Brener et al[32], increased LVAD speed reduced systolic RV pressure without affecting effective contractility (i.e., systolic elastance). In our study, we observed an increase in the RAP:PCWP ratio, which could be a marker of impaired RV function. However, this change was driven by a reduction in PCWP rather than an increase in RAP, and it is not discernible whether this is an adaptive diastolic response of the RV rather than a systolic impairment. Taken together, these observations underscore the complex role of ventricular interactions in LVAD physiology and the lack of reliable parameters that can be used in clinical practice.

All patients in our study presented with a stable clinical condition before discharge, independent of the hemodynamic parameters. However, half of the population presented with a suboptimal hemodynamic profile in terms of filling pressures and cardiac index, a finding consistent with previous reports[24–26]. However, our analysis adds certain aspects to this topic. Indeed, the optimal profile has been generally defined based on filling pressures alone and using more liberal values (i.s. RAP< 12 mmHg and PCWP < 18 mmHg), which represents, to some extent, a persistent degree of HF in this population. Moreover, despite being frequently described, not all previous studies had the value of CI as a requisite for defining hemodynamic optimization. We applied a strict definition almost resembling normal physiology at rest, while with published criteria, a larger proportion of our population would have been considered as "optimized." Previous reports consistently showed that LVAD patients had impaired exercise capacity, modest increase of cardiac output up to submaximal effort and increased filling pressures during exercise[29,33,34]. To this extent, it can be argued that starting from a near-normal resting condition could improve exercise capacity and consequently quality of life, but this hypothesis has not been tested in our study and needs further evaluation in a dedicated analysis.

We identified several differences between patients achieving optimal hemodynamic profile and those without, including the type of device (with HVAD performing worse), previous TEER, and a more frequent presence of significant tricuspid regurgitation in patients discharged with an optimal profile. HVAD is no longer commercially available for new implants and worse outcomes as compared to Heartmate 3 have already been described[10]. Moreover, it cannot be excluded that since HVAD were more commonly implanted in the earlier phase of our LVAD program, this finding could be influenced by a time bias. TEER has been shown to be safe in patients with LVAD; nevertheless, some concerns have been raised regarding the physiological interplay of these two interventions[35,36]. The prevalence of significant tricuspid regurgitation in optimized patients is counterintuitive, as it has been variably associated with an increased risk of RVF after LVAD implant[37,38]. However, the mechanisms for TR could be different, including severe dilation of the right ventricle and afterload mismatch caused by severe pulmonary hypertension, but with a functional RV reserve. In our study, we were not able to fully characterize this finding, and we studied patients who survived to hospital discharge; thus, we cannot exclude a selection bias. Therefore, these observations should be cautiously interpreted.

Despite steady improvements in outcomes, the hospitalization rate in patients with LVAD, including those for heart failure, remains high. With improved survival and reduced hemocompatility-related events (i.e., pump thrombosis, bleeding, and stroke) with current devices, right ventricular dysfunction is becoming a major determinant of quality of life and long-term survival. Consequently,

understanding the mechanisms and reducing readmissions are of paramount importance for further improvement of LVAD therapy results. It has already been proven that ramp tests help improve a suboptimal hemodynamic profile in apparently stable patients. In the randomized trial Ramp-IT UP study, Uriel et al.[24] proved the safety and feasibility of structured hemodynamic invasive monitoring and showed a trend to reduction of adverse events including HF rehospitalizations, but this was not statistically significant. In Ramp-IT UP trial 67% of patients presented optimal hemodynamic profile at first invasive evaluation. In 2019, Imamura et al.[25] showed in a non-randomized prospective study that optimized hemodynamic profile reduces hospitalizations for heart failure, reinforcing the role of ramp test in reducing follow-up events in LVAD patients. In this study, an improved hemodynamic profile led to a significantly reduced admission rate at one year with 44% of patients being free from all-cause hospitalizations, which was driven by a decrease in HF hospitalizations. More recently, Rubistein et al.[26] reported the outcomes of hemodynamic optimization in a contemporary cohort of stable ambulatory patients supported by the Heartmate 3 device. They showed optimized filling pressures in 58% of the patients, which increased to 65% after the ramp test. They confirmed that optimization was associated with an absolute reduction in cardiac readmission-free survival of 34% and 25% at six months and 1-year. Our results are consistent with these previous findings with some relevant differences. The proportion of optimized patients in our cohort was lower than that previously reported, and the cause of this difference could be two-fold. First, we applied a more stringent definition of hemodynamic optimization. Second, we reported a systematic assessment prior to discharge, whereas the other studies included stable ambulatory patients evaluated 6 months or more after the implant. It is possible that the early hemodynamic profile is still influenced by the operative course and that patients included at other time points could have already been managed noninvasively. The absolute reduction in readmission-free survival at 24 months was > 20%, which is comparable to other reports. However, it should be noted that this prognostic gain is reached earlier in the clinical course as it was assessed after discharge, whereas the benefit seen in previous studies is observed later in the clinical course, as these patients were observed several months after the implant. To this extent, the incremental value of a systematic pre-discharge assessment with respect to delayed evaluation in apparently stable patients needs to be further investigated in a dedicated analysis. However, in our population, the benefit of an optimized profile was evident when the effect of the ramp test was considered. Therefore, early ramp test appears to be associated with prognostic benefit.

In addition to hemodynamic optimization, we found an increased risk of HF readmission associated with beta-blocker use and HVAD support, although this was not confirmed in a multivariate analysis, and the optimized hemodynamic profile was the only independent predictor. Beta-blockers are a

cornerstone of medical therapy of HF, but they may exert a detrimental effect on right ventricular inotropism particularly in the early post-surgery vulnerable phase. However, this observation must be considered hypothesis-generating and needs to be tested in a broader population. No other treatments were associated with improved survival rates.

Study limitations

This study had several limitations. The retrospective nature of the study may have introduced uncontrolled bias. The sample size was limited, and the number events was low, therefore limiting the ability to investigate all potential risk factors for study outcomes.

The ramp test was performed according to clinical practice with the lack of a structured protocol for speed management and at the discretion of the physician in charge, leading to a degree of heterogeneity in the hemodynamic data. Suboptimal acoustic windows during the ramp test limited the analysis of echocardiographic data. The definition of hemodynamic optimization was based on physiological grounds and differs from other reports, therefore limiting the potential reproducibility.

Another limitation is the long period of time covered by the study, in which both medical therapy and available devices changed. However, this study describes current clinical practice and adds to the existing conceptual framework of the beneficial role of hemodynamic optimization with invasive ramp test in patients with LVAD.

Conclusions

This study investigated the changes in hemodynamic parameters following left ventricular assist device (LVAD) implant and examined the role of invasive ramp testing in optimizing the hemodynamic profile and improving survival free from heart failure readmission. LVAD implant was associated with a significant improvement in pulmonary circulation pressures and a reduction in common indices of right ventricular function without changes in right atrial pressure, without a significant impact on hemodynamic optimization. The ramp test facilitated the achievement of an optimized hemodynamic profile that was independently associated with improved survival.

Tables

Table 1. Baseline characteristics of the population

	N (74)
Age, y (m ± sd)	54 ± 12
Male gender, n (%)	67 (90.5)
BMI, kg/m^2 (m ± sd)	25.1 ± 3.7
DM2, n (%)	18 (24.3)
Current smoker, n (%)	8 (10.8)
LV disfunction etiology, n (%) – Ischemic – DCM – HCM	 31 (41.9) 42 (56.8) 1 (0.01)
COPD, n (%)	8 (0.1)
ICD, n (%)	59 (81.9)
Previous cardiac surgery, n (%)	8 (10.8)
Previous TEER, n (%)	6 (8.1)
Hb, g/dl (m ± sd)	12.1 ± 1.9
Creatinine, mg/dl (m ± sd)	1.5 ± 0,8
eGFR, ml/min (m ± sd)	70.4 ± 34.5
Sodium, mg/dl (m ± sd)	135.9 ± 4.2
Pump type, n (%) – Heartware (HVAD) – HeartMate 3	 36 (48.6) 38 (51.4)
Indications for implant	
Urgency, n (%)	53 (71.6)
INTERMACS class, n (%) – 2 – 3 – 4 – 5	 23 (31.1) 17 (23.0) 29 (39.2) 5 (6.7)
Implant strategy, n (%) – Bridge to transplant – Bridge to candidacy – Bridge to decision – Destination therapy	 37 (50.0) 16 (21.6) 8 (10.8) 13 (17.6)
Mechanical circulatory support	30 (40.6)

Table 2. Baseline echocardiographic and hemodynamic characteristics

	N (74)
Echocardiography	
LVEDD, mm (m ± sd)	69.8 ± 10.0
LVEDV, ml (m ± sd)	269.0 ± 110.9
LVEF, % (m ± sd)	21.3 ± 5.4
Mitral regurgitation 3+/4+, n (%)	45 (60.8)
Tricuspidal regurgitation 3+/4+, n (%)	16 (21.6)

sPAP, mmHg (m ± sd)	49.8 ± 15.9
RVEDA, cm^2 (m ± sd)	25.3 ± 6.5
FAC, % (m ± sd)	27.1 ± 12.3
TAPSE, mm (m ± sd)	15.9 ± 4.4
Right heart catheterization	
RAP, mmHg (m ± sd)	7.0 ± 3.8
mPAP, mmHg (m ± sd)	34.5 ± 10.3
PCWP, mmHg (m ± sd)	23.4 ± 8.0
Cardiac output (Fick), m ± sd	3.3 ± 0.8
Cardiac index (Fick), m ± sd	1.7 ± 0.4
PVR (Fick), uW m ± sd	3.8 ± 2.2
PAP index (m ± sd)	4.8 ± 2.9
RVSW index (m ± sd)	565 ± 245
RAP/PCWP (m ± sd)	0.3 ± 0.1

Table 3. Therapy at discharge

	N (66)
Diuretics, n (%)	50 (75.7)
Furosemide dose, mg/die M [IQR]	50 [25;100]
RAAS, n (%) – ACEi/ARBS – ARNi	49 (74.2) 44 (66.7) 5 (7.5)
Beta-blockers, n (%)	28 (42.4)
SGLT2i, n (%)	15 (22.7)
MRA, n (%)	47 (71.2)
Sildenafil, n (%)	8 (12.1)

Table 4. Right Heart Catheterization changes after LVAD

	Pre (N 63)	Post (N 63)	*p*
RAP, mmHg (m ± sd)	7.0 ± 3.8	7.8 ± 4.1	0,84
mPAP, mmHg (m ± sd)	34.5 ± 10.3	22.1 ± 6.7	<0.001
PCWP, mmHg (m ± sd)	23.4 ± 8.0	11.2 ± 5.9	<0.001
Cardiac output (Fick), m ± sd	3.3 ± 0.8	4.6 ± 0.8	<0.001
Cardiac index (Fick), m ± sd	1.7 ± 0.4	2.4 ± 0.4	<0.001
PVR (Fick), uW m ± sd	3.8 ± 2.2	2.4 ± 1.0	<0.001
PAP index (m ± sd)	4.8 ± 2.9	3.4 ± 2.5	0.006
RAP/PCWP (m ± sd)	0.3 ± 0.1	0.8 ± 0.5	<0.001

Table 5. Characteristics associated with optimized hemodynamic profile

	Optimized profile n=34	Non optimized profile n=29	p
Age	55.2 ± 10.9	53.6 ± 12.1	0,6
Male gender	32 (94%)	26 (89%)	0,5
BMI	24.9 ± 3,7	25.9 ± 3,4	0.2
Previous TEER	1 (3%)	5 (17%)	0.047
eGFR ml/min/m2	67.8 ± 29.9	64.5 ± 32.5	0.67
Hemoglobin, g/dl	12.6 ± 1.6	11.8 ± 1.6	0.1
Left ventricle end-diastolic volume	262.8 ± 89	264.6 ±1 08	0.9
LVEF %	20.5 ± 5.2	22.7 ± 5.3	0.1
Moderate to severe mitral regurgitation	23 (69%)	15 (51%)	0.3
Moderate to severe tricuspid regurgitation	10 (30%)	3 (10%)	0.01
RAP	6 (5-10)	5 (4-10)	0.7
PCWP	25 ± 8	22.3 ± 8	0.2
PAPi	4.8±2.7	4.8±2.6	0.9
RVSWI	541.5 ± 240.9	590.7 ± 272.5	0.5
RAP:PCWP	0.29 ± 0.13	0.31 ± 0.14	0.4
Device type			0.02
HVAD	16 (55%)	9 (26%)	
Heartmate 3	25 (73%)	13 (49%)	
Need for RVAD	1 (3%)	2 (7%)	0.4
Surgical revision	6 (18%)	9 (31%)	0.3

Table 6. Predictors of mortality and hospitalizations for heart failure

	Univariate analysis		Multivariable analysis	
	Odds ratio	p	Odds ratio	p
Age		0.5		
eGFR		0.6		
Etiology		0.14		
INTERMACS		0.32		
HVAD device	2.8 (1.1-7.2)	0.02		0.26
Hemodynamic profile: not optimized	3.2 (1.2-8.2)	0.01	2.7 (1.02-7.1)	0.04
Beta blockers at discharge	2.68 (1.1-6.3)	0.02		0.28
RASI at discharge		0.28		
MRA at discharge		0.17		

Figures

Figure 1. LVAD implant increased through the years

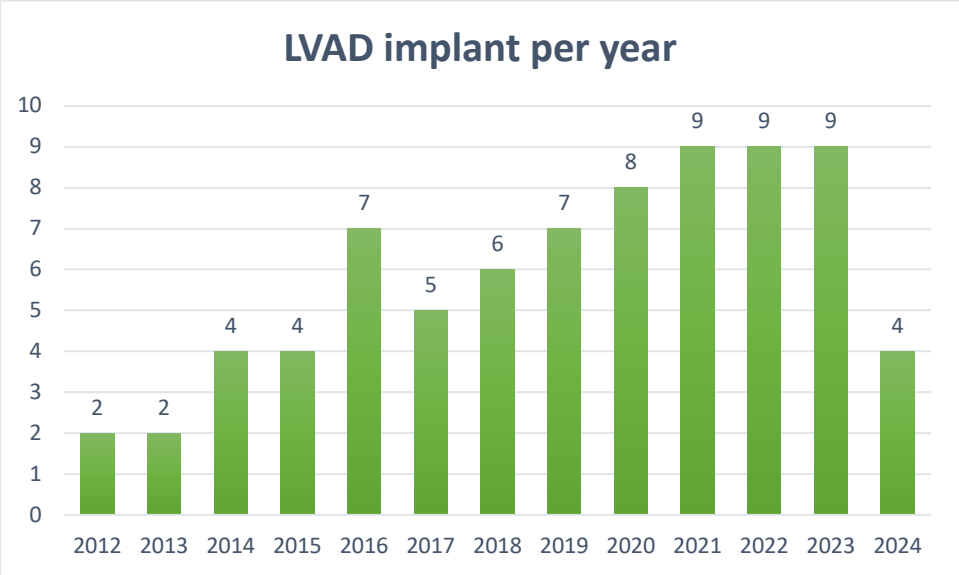


Figure 2a. Right ventricular function index changes at RHC after LVAD implant

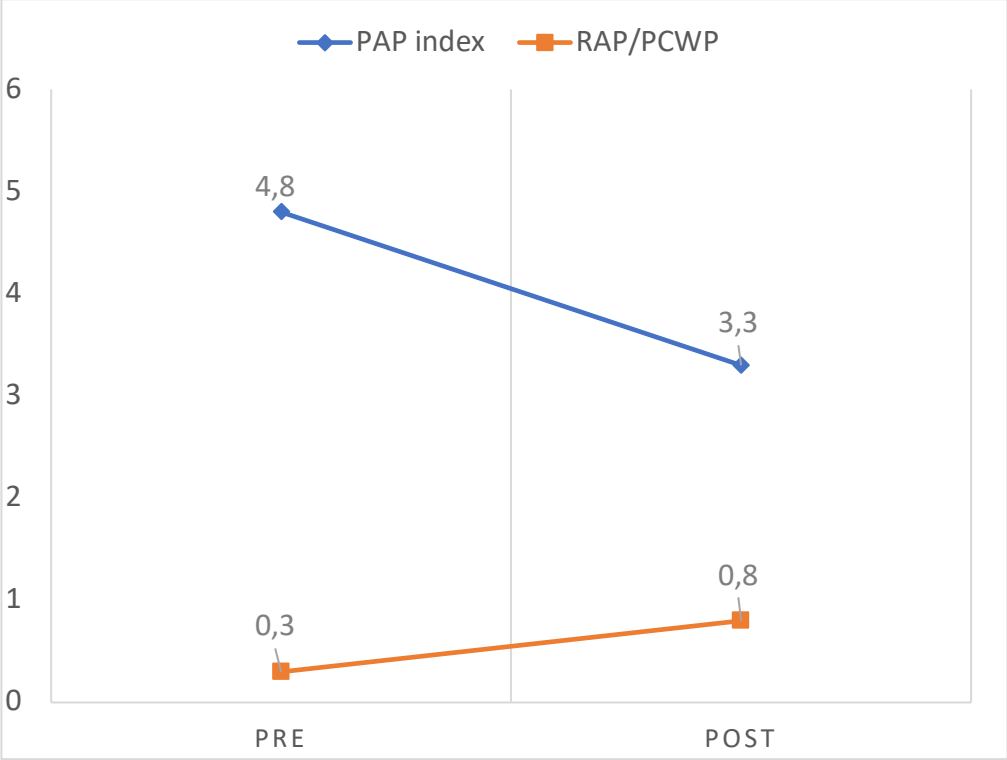


Figure 2b. Hemodynamic changes at RHC after LVAD implant

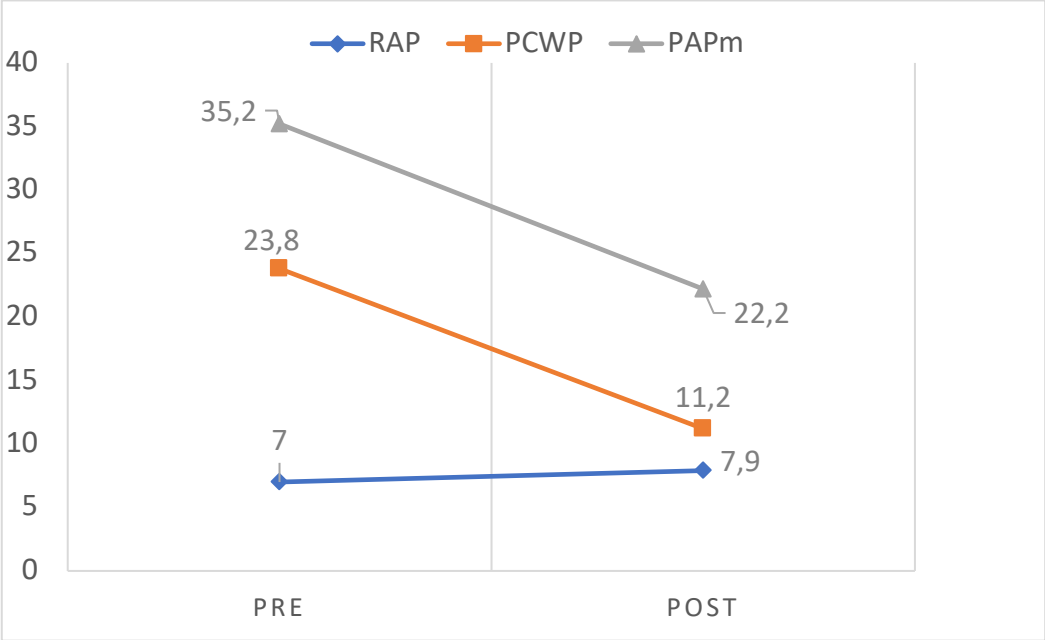


Figure 2c. Cardiac Index changes at RHC after LVAD implant

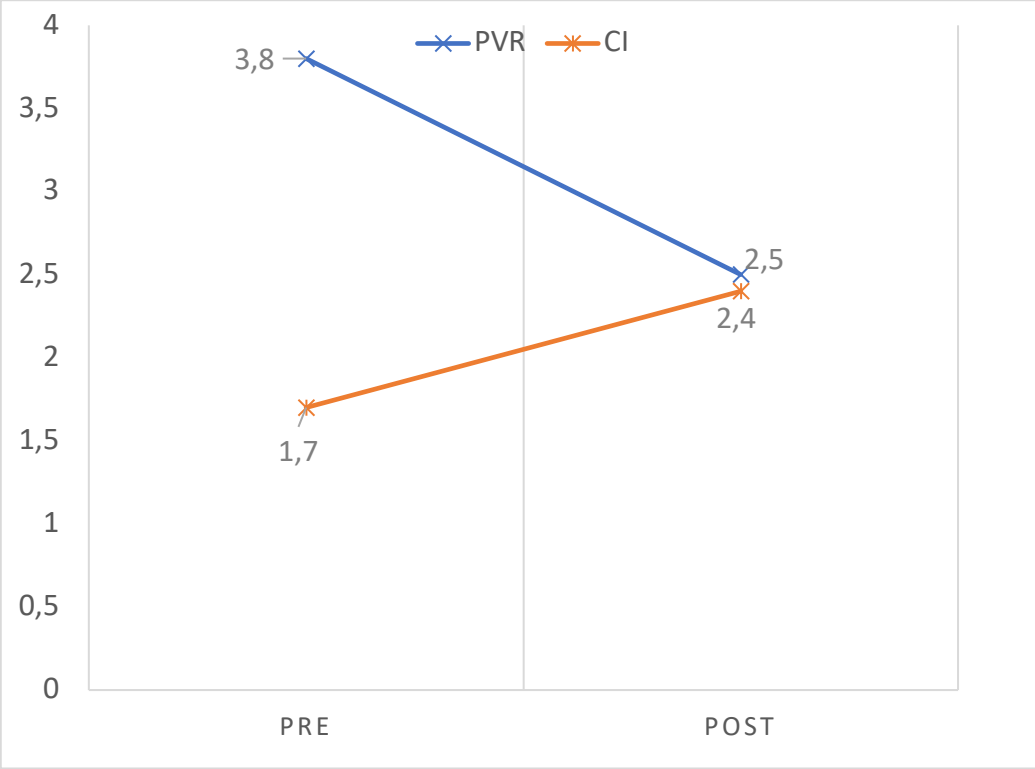


Figure 3. Hemodynamic optimization after ramp test

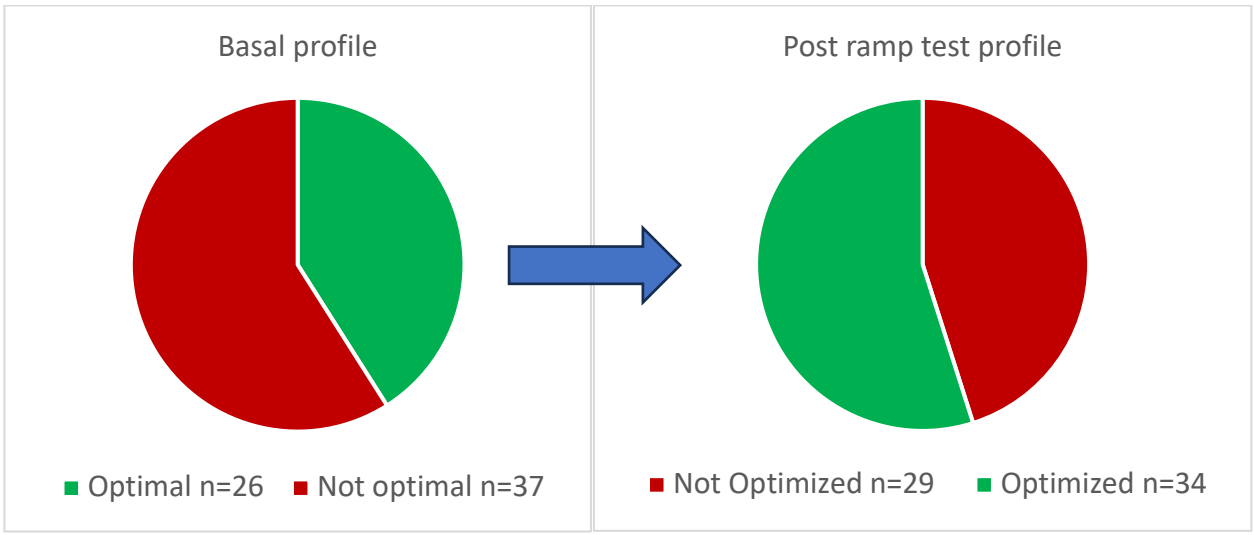
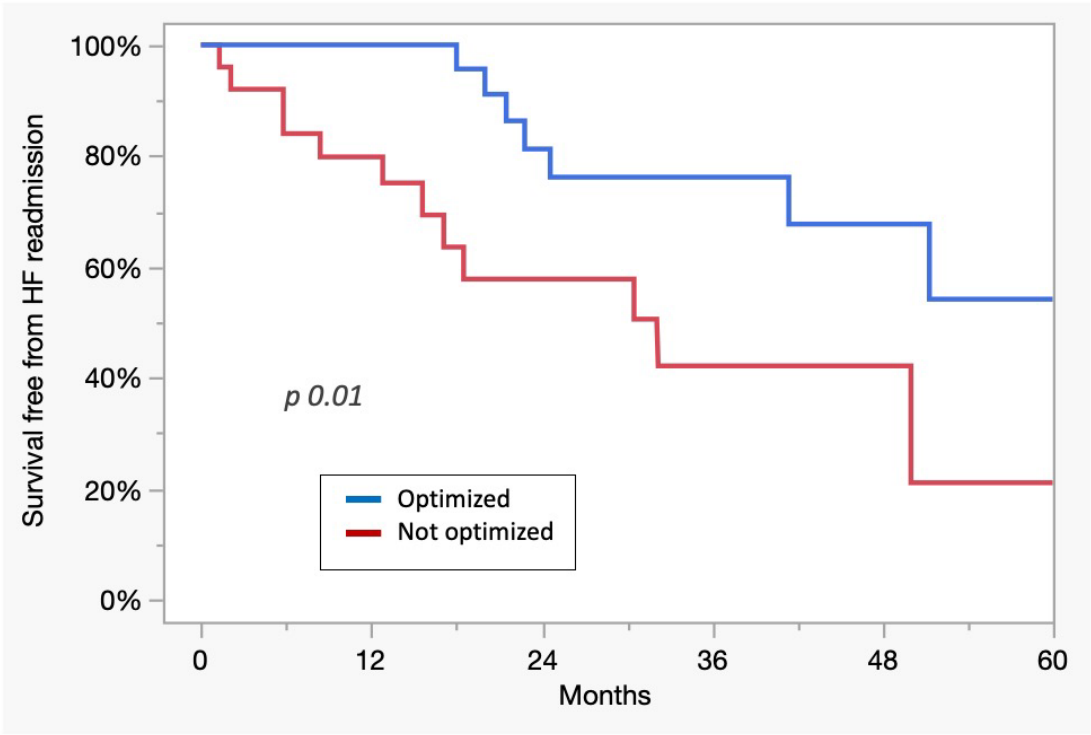


Figure 4. Survival free from all-cause death and HF hospitalizations at long-term follow-up according to the hemodynamic profile



N. at risk

Optimized	34	27	17	11	6	3
Not optimized	26	18	10	6	4	2

References

1. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and Prognostic Significance of Heart Failure Stages: Application of the American College of Cardiology/American Heart Association Heart Failure Staging Criteria in the Community. *Circulation*. 2007;115(12):1563-1570. doi:10.1161/CIRCULATIONAHA.106.666818

2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368

3. Truby LK, Rogers JG. Advanced Heart Failure. *JACC Heart Fail*. 2020;8(7):523-536. doi:10.1016/j.jchf.2020.01.014

4. Berardi C, Bravo CA, Li S, et al. The History of Durable Left Ventricular Assist Devices and Comparison of Outcomes: HeartWare, HeartMate II, HeartMate 3, and the Future of Mechanical Circulatory Support. *J Clin Med*. 2022;11(7):2022. doi:10.3390/jcm11072022

5. Rogers JG, Butler J, Lansman SL, et al. Chronic Mechanical Circulatory Support for Inotrope-Dependent Heart Failure Patients Who Are Not Transplant Candidates. *J Am Coll Cardiol*. 2007;50(8):741-747. doi:10.1016/j.jacc.2007.03.063

6. Slaughter MS, Rogers JG, Milano CA, et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device. *N Engl J Med*. 2009;361(23):2241-2251. doi:10.1056/NEJMoa0909938

7. Rogers JG, Pagani FD, Tatooles AJ, et al. Intrapericardial Left Ventricular Assist Device for Advanced Heart Failure. *N Engl J Med*. 2017;376(5):451-460. doi:10.1056/NEJMoa1602954

8. Mehra MR, Uriel N, Naka Y, et al. A Fully Magnetically Levitated Left Ventricular Assist Device — Final Report. *N Engl J Med*. 2019;380(17):1618-1627. doi:10.1056/NEJMoa1900486

9. Numan L, Ramjankhan FZ, Oberski DL, et al. Propensity score-based analysis of long-term outcome of patients on HeartWare and HeartMate 3 left ventricular assist device support. *ESC Heart Fail*. 2021;8(2):1596-1603. doi:10.1002/ehf2.13267

10. Potapov EV, Nersesian G, Lewin D, et al. Propensity score-based analysis of long-term follow-up in patients supported with durable centrifugal left ventricular assist devices: the EUROMACS analysis. *Eur J Cardiothorac Surg*. 2021;60(3):579-587. doi:10.1093/ejcts/ezab144

11. Mehra MR, Goldstein DJ, Cleveland JC, et al. Five-Year Outcomes in Patients With Fully Magnetically Levitated vs Axial-Flow Left Ventricular Assist Devices in the MOMENTUM 3 Randomized Trial. *JAMA*. 2022;328(12):1233. doi:10.1001/jama.2022.16197

12. Shah P, Yuzefpolskaya M, Hickey GW, et al. Twelfth Interagency Registry for Mechanically Assisted Circulatory Support Report: Readmissions After Left Ventricular Assist Device. *Ann Thorac Surg*. 2022;113(3):722-737. doi:10.1016/j.athoracsur.2021.12.011

13. Gustafsson F, Ben Avraham B, Chioncel O, et al. HFA of the ESC position paper on the management of LVAD-supported patients for the non-LVAD specialist healthcare provider Part 3: at the hospital and discharge. *ESC Heart Fail*. 2021;8(6):4425-4443. doi:10.1002/ehf2.13590

14. Frankfurter C, Molinero M, Vishram-Nielsen JKK, et al. Predicting the Risk of Right Ventricular Failure in Patients Undergoing Left Ventricular Assist Device Implantation: A Systematic Review. *Circ Heart Fail*. 2020;13(10). doi:10.1161/CIRCHEARTFAILURE.120.006994

15. Kapelios CJ, Lund LH, Wever-Pinzon O, et al. Right Heart Failure Following Left Ventricular Device Implantation: Natural History, Risk Factors, and Outcomes: An Analysis of the STS INTERMACS Database. *Circ Heart Fail*. 2022;15(6). doi:10.1161/CIRCHEARTFAILURE.121.008706

16. Rajapreyar I, Soliman O, Brailovsky Y, et al. Late Right Heart Failure After Left Ventricular Assist Device Implantation. *JACC Heart Fail*. 2023;11(8):865-878. doi:10.1016/j.jchf.2023.04.014

17. Varshney AS, DeFilippis EM, Cowger JA, Netuka I, Pinney SP, Givertz MM. Trends and Outcomes of Left Ventricular Assist Device Therapy. *J Am Coll Cardiol*. 2022;79(11):1092-1107. doi:10.1016/j.jacc.2022.01.017

18. Bellavia D, Iacovoni A, Scardulla C, et al. Prediction of right ventricular failure after ventricular assist device implant: systematic review and meta-analysis of observational studies: Meta-analysis of right ventricular failure determinants after LVAD implant. *Eur J Heart Fail*. 2017;19(7):926-946. doi:10.1002/ejhf.733

19. Sciaccaluga C, Soliman-Aboumarie H, Sisti N, et al. Echocardiography for left ventricular assist device implantation and evaluation: an indispensable tool. *Heart Fail Rev*. 2022;27(3):891-902. doi:10.1007/s10741-021-10073-1

20. Kato TS, Jiang J, Schulze PC, et al. Serial Echocardiography Using Tissue Doppler and Speckle Tracking Imaging to Monitor Right Ventricular Failure Before and After Left Ventricular Assist Device Surgery. *JACC Heart Fail*. 2013;1(3):216-222. doi:10.1016/j.jchf.2013.02.005

21. Todaro MC, Khandheria BK, Paterick TE, Umland MM, Thohan V. The Practical Role of Echocardiography in Selection, Implantation, and Management of Patients Requiring LVAD Therapy. *Curr Cardiol Rep*. 2014;16(4):468. doi:10.1007/s11886-014-0468-5

22. Saeed D, Feldman D, Banayosy AE, et al. The 2023 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support: A 10- Year Update. *J Heart Lung Transplant*. 2023;42(7):e1-e222. doi:10.1016/j.healun.2022.12.004

23. Uriel N, Sayer G, Addetia K, et al. Hemodynamic Ramp Tests in Patients With Left Ventricular Assist Devices. *JACC Heart Fail*. 2016;4(3):208-217. doi:10.1016/j.jchf.2015.10.001

24. Uriel N, Burkhoff D, Rich JD, et al. Impact of Hemodynamic Ramp Test-Guided HVAD Speed and Medication Adjustments on Clinical Outcomes: The RAMP-IT-UP Multicenter Study. *Circ Heart Fail*. 2019;12(4):e006067. doi:10.1161/CIRCHEARTFAILURE.119.006067

25. Imamura T, Jeevanandam V, Kim G, et al. Optimal Hemodynamics During Left Ventricular Assist Device Support Are Associated With Reduced Readmission Rates. *Circ Heart Fail*. 2019;12(2):e005094. doi:10.1161/CIRCHEARTFAILURE.118.005094

26. Rubinstein G, Moeller CM, Lotan D, et al. Hemodynamic Optimization by Invasive Ramp Test in Patients Supported With HeartMate 3 Left Ventricular Assist Device. *ASAIO J*. 2024;70(8):641-650. doi:10.1097/MAT.0000000000002167

27. Brener MI, Hamid NB, Fried JA, et al. Right Ventricular Pressure–Volume Analysis During Left Ventricular Assist Device Speed Optimization Studies: Insights Into Interventricular Interactions and Right Ventricular Failure. *J Card Fail*. 2021;27(9):991-1001. doi:10.1016/j.cardfail.2021.04.019

28. Bouchez S, Erb J, Foubert L, Mauermann E. Pressure–Volume Loops for Reviewing Right Ventricular Physiology and Failure in the Context of Left Ventricular Assist Device Implantation. *Semin Cardiothorac Vasc Anesth*. 2023;27(4):283-291. doi:10.1177/10892532231198797

29. Tran T, Muralidhar A, Hunter K, et al. Right ventricular function and cardiopulmonary performance among patients with heart failure supported by durable mechanical circulatory support devices. *J Heart Lung Transplant*. 2021;40(2):128-137. doi:10.1016/j.healun.2020.11.009

30. Uriel N, Adatya S, Malý J, et al. Clinical hemodynamic evaluation of patients implanted with a fully magnetically levitated left ventricular assist device (HeartMate 3). *J Heart Lung Transplant*. 2017;36(1):28-35. doi:10.1016/j.healun.2016.07.008

31. Scheel PJ, Cubero Salazar IM, Friedman S, et al. Occult right ventricular dysfunction and right ventricular-vascular uncoupling in left ventricular assist device recipients. *J Heart Lung Transplant*. 2024;43(4):594-603. doi:10.1016/j.healun.2023.11.015

32. Brener MI, Kanwar MK, Lander MM, et al. Impact of Interventricular Interaction on Ventricular Function. *JACC Heart Fail*. 2024;12(7):1179-1192. doi:10.1016/j.jchf.2023.12.001

33. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. *J Heart Lung Transplant*. 2015;34(4):489-496. doi:10.1016/j.healun.2014.11.001

34. Jung MH, Hansen PB, Sander K, et al. Effect of increasing pump speed during exercise on peak oxygen uptake in heart failure patients supported with a continuous-flow left ventricular assist device. A double-blind randomized study. *Eur J Heart Fail*. 2014;16(4):403-408. doi:10.1002/ejhf.52

35. Ammirati E, Van De Heyning CM, Musca F, et al. Safety of centrifugal left ventricular assist device in patients previously treated with MitraClip system. *Int J Cardiol*. 2019;283:131-133. doi:10.1016/j.ijcard.2019.02.039

36. Kreusser MM, Hamed S, Weber A, et al. MitraClip implantation followed by insertion of a left ventricular assist device in patients with advanced heart failure. *ESC Heart Fail*. 2020;7(6):3891-3900. doi:10.1002/ehf2.12982

37. Gonzalez-Fernandez O, Bouzas-Cruz N, Ferrera C, et al. Effect of Preoperative Tricuspid and/or Mitral Regurgitation on Development of Late Right-Sided Heart Failure After Insertion of the HeartWare Left Ventricular Assist Device. *Am J Cardiol*. 2020;125(2):236-243. doi:10.1016/j.amjcard.2019.10.005

38. Veen KM, Mokhles MM, Soliman O, et al. Clinical impact and 'natural' course of uncorrected tricuspid regurgitation after implantation of a left ventricular assist device: an analysis of the European Registry for Patients with Mechanical Circulatory Support (EUROMACS). *Eur J Cardiothorac Surg*. 2021;59(1):207-216. doi:10.1093/ejcts/ezaa294