Research Article

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# Left Ventricular Assist Device To Treat Post-Capillary Pulmonary Hypertension.

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## ABSTRACT

**Background :** Pulmonary hypertension (PH) is a common complication of heart failure (HF) with a significant impact on disease progression, and mortality. Left ventricular assist device (LVAD) implantation can improve haemodynamic status and survival as a "bridge to transplantation". Aim of this study is to characterise haemodynamic after LVAD implantation based on the latest definitions of the PH Guidelines 2022, and to identify predictors of haemodynamic changes.

**Methods :** Patients with advanced HF with reduced ejection fraction (HFrEF) implanted with LVAD between 2011 and 2021 were retrospectively reviewed. Variables obtained by right heart catheterisation (RHC) were compared between baseline (T1) and after LVAD implantation (T2). Difference between pulmonary vascular resistance (ΔPVR) at T1 and T2 was analysed by linear regression.

**Results :** Of the 100 patients with LVAD implantation, 37 patients were selected for the analysis. Mean age was 49 ± 13 years and 76 % were male. Thirty-three out of 37 patients (91.7%) had PH at baseline, whose 27 patients (75%) with combined post-capillary and pre-capillary (Cpc) PH. At T2, PH was observed in 20 out of 37 patients (54.1%) whose 6 patients (16.7%) with Cpc-PH. Significant reductions in mean pulmonary arterial pressure (22 ± 8 mmHg, Δ = - 14 mmHg, p <0.001) and pulmonary vascular resistance (2.3 ± 1.1 WU, Δ = - 1.0 WU, p <0.001) were observed. Linear regression showed that cardiac index was inversely correlated with ΔPVR.

**Conclusions :** LVAD implantation resulted in a significant improvement in PH, suggests that PH in end-stage HFrEF is mostly due to a passive mechanism.

## INTRODUCTION

Heart failure (HF) is a common disease that affects 1 to 2% of the adult population in developed countries with an increasing prevalence with age (1). Prognosis of HF depends on many factors such as structural or functional cardiac abnormalities as pulmonary hypertension (PH) (1). Up to 10% of HF patients will progress to an advanced HF (2) despite optimal medical treatment (3,4) requiring heart transplantation (HT) and/or mechanical circulatory support (MCS).

Even tough HT remains the gold standard therapy for advanced HF, shortage of donor hearts, restrictive criteria and recipient contraindications (5) limit this strategy increasing time and mortality on the HT waiting list. In 2021, 12% of patients listed for a heart transplantation died on the Eurotransplant heart waiting list (6).

PH commonly observed in HF is a marker of severity, bad prognosis (7) representing sometimes a contra indication to HT. Especially, PVR >3 WU is a challenging condition, associated with poor HT outcomes. It is recommended to reduce PVR and assess its reversibility up to HT (5). Therefore, the implantation of MCS such as a left ventricular assist device (LVAD) appears to be an alternative making a patient eligible for HT called "bridge to candidacy". LVAD can also be used as a "bridge to transplantation" (BTT), improving haemodynamic status, organ function and survival allowing patients to wait for a transplantation (5).

A recent revision of PH Guidelines, published in 2022, defined PH as a mean pulmonary arterial pressure (mPAP) >20 mmHg at rest, as assessed by RHC (8). Based on the pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR) haemodynamic classification distinguishes two groups of PH: pre-capillary PH (PAWP ≤15 mmHg, PVR >2WU) and

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post-capillary PH (PAWP >15mmHg) (8). Overall, post-capillary PH can be classified in two haemodynamics status based on PVR: isolated post-capillary (Ipc) PH (PVR ≤2 WU) or combined post-capillary and pre-capillary (Cpc) PH (PVR >2 WU). Unclassified patients have high mPAP (>20 mmHg) but low PAWP (≤15 mmHg) and low PVR (≤2 WU), usually associated with pulmonary overflow disease (7,8)

Five clinical groups of PH are described (9). PH due to left heart disease (PH-LHD) is the most common PH group affecting up to 80% of PH patients (10). Contrary to other clinical groups, the phenotype of HF is characterised by a post-capillary PH. PH-LHD is due to a passive backward transmission of filling pressures (10,11): thus, PH is a symptom of HF. However, about 10% of patients with PH-LHD have a Cpc-PH (12), a more severe condition with a worse prognosis (10,13) even if their underlying mechanisms are not completely understood. LVAD unloading the left ventricle into the aorta, can improve Ipc-PH by reducing passive backward transmission of high filling pressures from left heart (10). In the case of Cpc-PH, their degree of reversibility is not completely known.

The aims of our study were 1) to characterise pulmonary haemodynamics before and after LVAD implantation in patients with HF with reduced ejection fraction (HFrEF); 2) to identify predictors of haemodynamic changes following LVAD implantation.

## MATERIALS & METHODS

### Patients

We performed a retrospective analysis of patients with a LVAD implanted as BTT, at our centre in Brussels (Belgium) between 1st January 2011 and 31st December 2021. All adults (≥ 18 years of age) who had a RHC before LVAD implantation were selected. For final analysis, only patients with a RHC after LVAD implantation were enrolled.

### Variables Collected

Clinical, biological, echocardiographic and haemodynamic variables of interest were gathered during pre (T1) and post-LVAD implantation (T2). Statistical analysis was drawn before and after LVAD implantation.

RHC was performed by a same team according to standardized guidelines using Swan-Ganz catheter. Heart rate (HR), systolic and diastolic blood pressure (sBP, dBP) were obtained by non-invasive method. Right atrial pressure (RAP), pulmonary artery pressures (PAP), PAWP were measured at the end of expiration and after quality check of pressure curves. Cardiac output (CO) was obtained by thermodilution method. Transpulmonary pressure gradient (TPG) were calculated from "mean PAP – PAWP". Others variables were calculated according to Guyton et al (14).

Transthoracic echocardiographies (TTE) were performed during assessment period for LVAD implantation and post LVAD implantation. We gathered variables of interest estimating right ventricular function such as tricuspid annular plane systolic excursion (TAPSE) and S-wave and estimated systolic pulmonary artery pressure (sPAP) based on tricuspid velocity. Interaction between the right ventricle and pulmonary circulation (couplage) was studied using TAPSE/sPAP ratio.

All complications observed during the first 30 days following LVAD implantation were collected. Early severe RVF was defined according to EUROMACS (15) as use of unplanned right sided circulatory support, use of inotropic support for ≥14 days, or nitric oxid (NO) ventilation for ≥ 48 hours.

### Predictor of haemodynamics Outcome

Haemodynamics outcome was defined as the difference in PVR before and after LVAD implantation: ΔPVR = PVRT1 – PVRT2. We examined different baseline characteristics such as demographic, treatment, biological, echocardiographic and haemodynamics variables, to identify potential predictors of outcome.

### Analysis

Data was analysed with the Statistical Package for the Social Sciences (SPSS) 25.0. Qualitatives variables are presented as frequency distributions and percentages. Continuous variables are expressed as mean ± standard deviation (SD). Variables with more than 50% missing data were not analysed. Statistical comparison was drawn by paired t-test with a p value ≤ 0.05 considered statistically significant. Univariate and multivariable linear regression models were performed to study the association between ΔRVP and potential predictors. Variables included in our multivariable model were selected depending on their statistical association with the outcome in the univariate analysis (p <0.10), collinearity and the number of final cases. The coefficient and their 95% confidence intervals were derived from the model. Collinearity between the variables was checked by the variance inflation factor (VIF).

## RESULTS

One hundred patients had an LVAD implantation between 2011 and 2021 in our centre. Seventy one out of the 100 LVAD patients had a RHC before LVAD implantation whose 37 patients had a RHC after LVAD implantation and were selected for the final analysis (Figure 1).

Thirty-four patients (92%) included in the final analysis were implanted with a centrifugal LVAD HeartWare® (Medtronic, USA). Three patients (8%) were implanted with a centrifugal LVAD HeartMate III® (Abbott, USA)

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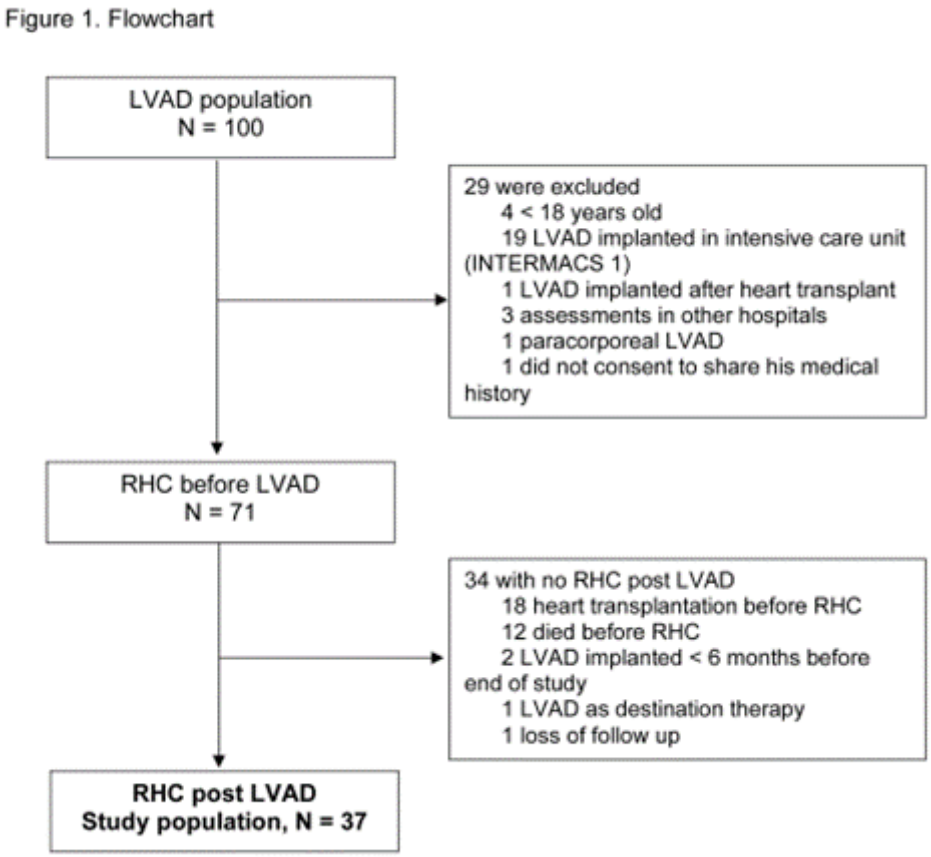
**Figure 1.** Flowchart




LVAD : left ventricular assist device ; INTERMACS : Interagency Registry for Mechanically Assisted Circulatory Support, RHC : right heart catheterisation;

**Demographic**

Patients having RHC before and after LVAD implantation were included as the study population. Baseline characteristics of these 37 patients are shown in table 1. Mean age was 49 years and 76 % were male. All patients were in New York Heart Association (NYHA) class III or IV. The majority were in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) class 3 (48.6%), followed by INTERMACS class 2 (27%) and 4 (18.9%). Aetiology of HF was mostly represented by dilated (43.2%) and ischemic (40.5%) cardiomyopathy. HF patients received optimal medical treatment for HFrEF according to 2016 Guidelines from European Society of cardiology (16). Sodium–glucose cotransporter-2 inhibitors (SGLT-2i), recently recommended in HFrEF regardless of the presence or absence of diabetes (1), were not used in the practice during the study period. Fifty-nine percent of patients were on inotropes during baseline RHC.

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**Table 1.** Baseline characteristics

| n = 37 | T1 |
|---|---|
| **Demographics** | |
| Age (years) | 49.3 ± 13.1 |
| Male, n (%) | 28 (75.7) |
| BMI (kg/m²) | 25.9 ± 3.8 |
| **NYHA class (%)** | |
| III | 57.1% |
| IV | 42.9% |
| **INTERMACS class, n (%)** | |
| 1 | 2 (5.4) |
| 2 | 10 (27.0) |
| 3 | 18 (48.6) |
| 4 | 7 (18.9) |
| **Aetiology, n (%)** | |
| Dilated cardiomyopathy | 16 (43.2) |
| Ischemic cardiopathy | 15 (40.5) |
| Valvular cardiopathy | 2 (5.4) |
| Others cardiopathy | 4 (10.8) |
| **Treatment (%)** | |
| Inotropes# | 59.5 |
| Beta blocker | 78.4 |
| RAA inhibitor/ARNI | 86.5 |
| Diuretic | 78.4 |
| Spironolactone | 56.8 |
| Antiarythmics° | 24.3 |
| Resynchronization therapy* | 10.8 |

Data are presented as n (%) or as mean ± standard deviation.

T1 : pre implant examination; BMI: body mass index; NYHA: New York Heart Association; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; Inotropes during RHC#: dobutamine, dopamine, noradrenaline, milrinone or levosimendan; RAA: renine angiotensine aldosterone; ARNI: angiotensin receptor-neprilysin inhibitor; Antiarythmics°: amiodarone ou sotalol; Resynchronization*: cardiac resynchronization therapy as CRT-P or CRT-D

**Biological and Echocardiographic Markers**

All biological and echocardiographic variables were collected at the same time with RHC variables (table 2). There was no statistical difference in biological markers between T1 and T2. However, echocardiography analysis showed a significant reduction in LV end-diastolic diameter (6.91 ± 1.09 cm to 6.32 ± 1.26 cm; p=0.013), a significant decrease in right function using TAPSE (14.14 ± 3.97 mm to 11.18 ± 2.84 mm; p=0.001) and S-wave (9.6 ± 2.4 cm/s to 7.0 ± 1.6 cm/s; p<0.001) after LVAD implantation. Echocardiography analysis also showed an improvement in the TAPSE/sPAP ratio (0.306 ± 0.113 mm/mmHg to 0.420 ± 0.211 mm/mmHg; p=0.045).

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**Table 2.** Comparison of variables of interest with paired Student test

| | T1 | T2 | p value |
|---|---|---|---|
| **Laboratory values** | | | |
| NT-proBNP (pg/ml) | 5659 ± 4977 | 3541 ± 6244 | 0.299 |
| Creatinine (mg/dl) | 1.3 ± 0.6 | 1.2 ± 0.4 | 0.313 |
| BUN (mg/dl) | 54.2 ± 45.2 | 47.3 ± 24.8 | 0.401 |
| Sodium (mEq/L) | 138 ± 5 | 139 ± 3 | 0.113 |
| Total bilirubin (mg/dl) | 1.1 ± 0.7 | 0.9 ± 1.0 | 0.264 |
| AST (U/L) | 47 ± 76 | 27 ± 23 | 0.178 |
| ALT (U/L) | 68 ± 122 | 23 ± 14 | 0.053 |
| **Echocardiographic** | | | |
| LV internal EDD (cm) | 6.91 ± 1.09 | 6.32 ± 1.26 | 0.013 |
| TAPSE (mm) | 14.14 ± 3.97 | 11.18 ± 2.84 | 0.001 |
| S-wave (cm/s) | 9.6 ± 2.4 | 7.0 ± 1.6 | <0.001 |
| sPAP (mmHg) | 49.1 ± 15.7 | 30.3 ± 9.7 | <0.001 |
| TAPSE/sPAP (mm/mmHg) | 0.306 ± 0.113 | 0.420 ± 0.211 | 0.045 |
| **Haemodynamic** | | | |
| HR (bpm) | 84 ± 19 | 75 ± 15 | 0.030 |
| MAP (mmHg) | 78 ± 12 | 80 ± 20 | 0.669 |
| sPAP (mmHg) | 53 ± 18 | 34 ± 12 | <0.001 |
| dPAP (mmHg) | 28 ± 10 | 16 ± 7 | <0.001 |
| mPAP (mmHg) | 36 ± 11 | 22 ± 8 | <0.001 |
| PAWP (mmHg) | 23 ± 9 | 11 ± 5 | <0.001 |
| RAP (mmHg) | 9 ± 5 | 7 ± 6 | 0.084 |
| TPG (mmHg) | 12 ± 5 | 9 ± 4 | <0.001 |
| DPG (mmHg) | 4 ± 4 | 4 ± 3 | 0.464 |
| CO (L/min) | 3.9 ± 1.2 | 4.4 ± 0.8 | 0.027 |
| CI (L/min/m²) | 2.0 ± 0.6 | 2.3 ± 0.5 | 0.018 |
| PVR (Wood Unit) | 3.3 ± 1.3 | 2.3 ± 1.1 | <0.001 |
| CPA (ml/mmHg) | 2.3 ± 1.2 | 3.9 ± 2.0 | <0.001 |

Values are expressed as mean ± standard deviation.

T1: pre-implant examination; T2: post-implant examination. p value ≤ 0.05 was considered statistically significant.

N-terminal pro-B-type natriuretic peptide; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase

LV internal EDD: left ventricular internal end-diastolic dimension; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure.

HR : heart rate ; MAP : mean arterial pressure ; sPAP : systolic pulmonary artery pressure ; dPAP : diastolic pulmonary artery pressure ; mPAP : mean pulmonary artery pressure ; PAWP : pulmonary artery wedge pressure ; RAP : right atrial pressure ; TPG : transpulmonary pressure gradient ; DPG : diastolic pulmonary pressure gradient ; CO : cardiac output ; CI : cardiac index ; PVR : pulmonary vascular resistance ; CPA : pulmonary arterial compliance

**Right Heart Catheterisation**

At T1 examination, 33 patients (91.7%) had PH whose 27 patients (75%) with Cpc-PH and 3 patients (8.3%) with Ipc-PH. Two patients (5.6%) had pre-capillary PH and 1 patient had unclassified PH. One patient had missing values.

Detailed data of the study population are shown in table 2 and figure 2. Post-implant RHC was performed on 14 ± 9 months after LVAD implantation. A significant reduction in both mPAP (22 ± 8 mmHg, Δ = - 14 mmHg, p<0.001) and PVR (2.3 ± 1.1 WU, Δ = - 1.0 WU, p<0.001) was observed after LVAD implantation. LVAD implantation also improved pulmonary arterial compliance (3.9 ± 2.0 ml/mmHg vs 2.3 ± 1.2 ml/mmHg, p<0.001). After LVAD implantation, PAWP decreased significantly from 23 ± 9 mmHg to 11 ± 5 mmHg (p<0.001). In consequence, TPG improved.

After LVAD implantation, at T2 examination, 20 patients (54.1%) had PH whose 9 patients (25%) with pre-capillary PH, 6 patients (16.7%) with Cpc-PH, and 3 patients (8.3%) with Ipc-PH. One patient had unclassified PH (figure 3).

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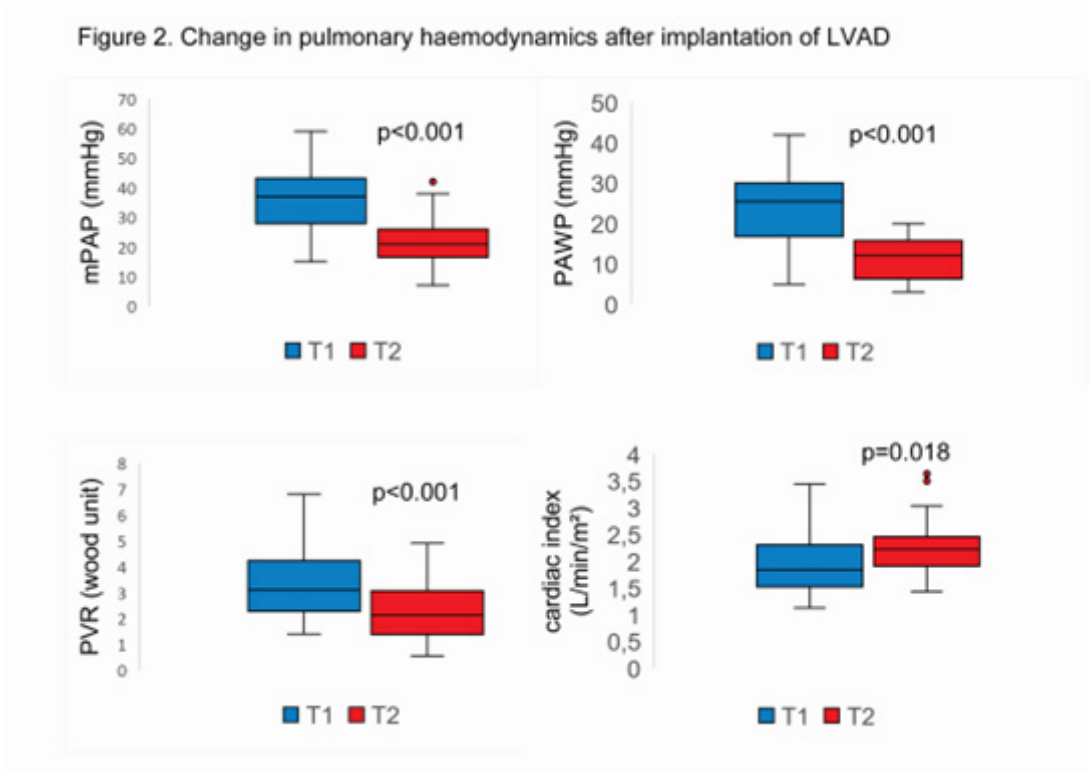
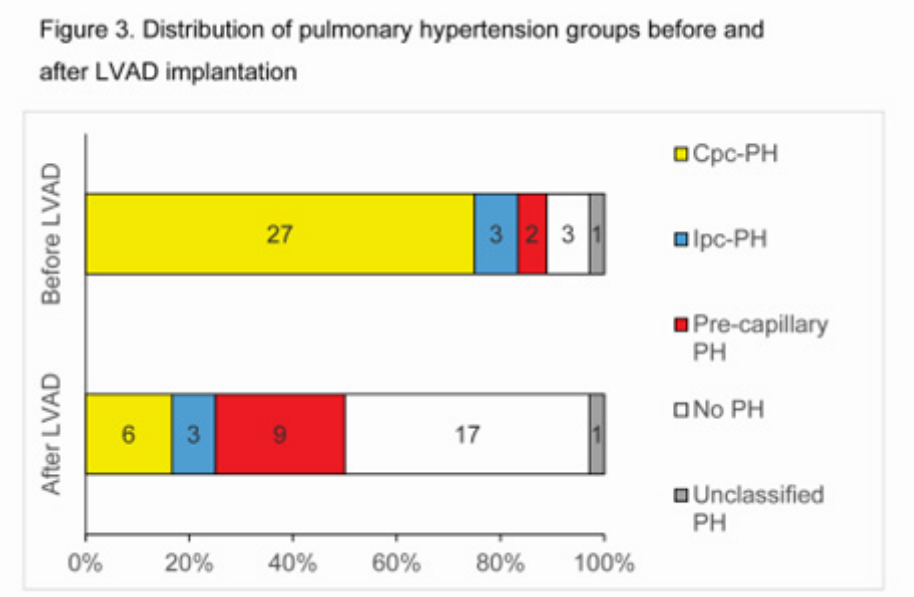
**Figure 2.** Change in pulmonary haemodynamics after implantation of LVAD




T1: pre-implant examination; T2: post-implant examination. p value ≤ 0.05 was considered statistically significant.

mPAP : mean pulmonary artery pressure ; PAWP : pulmonary artery wedge pressure ; PVR : pulmonary vascular resistance ; CI : cardiac index

**Figure 3.** Distribution of pulmonary hypertension groups before and after LVAD implantation




PH: pulmonary hypertension; Cpc-PH: combined post-capillary and pre-capillary PH; Ipc-PH: isolated post-capillary PH; LVAD: left ventricular assist device

**Post LVAD period**

A total of 20 patients (54%) out of 37 had at least one serious complication in the early 30-day post LVAD period (table 3). Severe RVF was observed in 7 patients (18.9%), including 1 patient on temporary right ventricular assist device (RVAD) support and 1 patient on extracorporeal membrane oxygenation (ECMO).

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Twenty patients (54%) were successfully bridged to transplantation with a mean time on LVAD of 790 ± 362 days. Two patients (5.4%) died before HT (mean time on LVAD 523 ± 30 days). At the end of the study period, 15 patients remained on Eurotransplant HT waiting list.

**Table 3. Complication in the early 30-day post LVAD period**

| Complication, n (%) | n = 37 |
|---|---|
| Circulatory shock | 10 (27%) |
| Reoperation for bleeding | 8 (21.6%) |
| Severe RVF | 7 (18.9%) |
| Sepsis | 7 (18.9%) |
| Pericardial tamponade | 5 (13.5%) |
| APO | 2 (5.6%) |
| Stroke | 1 (2.7%) |
| Death | 0 |

Data are presented as n (%). RVF: right ventricular failure; APO: acute pulmonary oedema

**Predictor model in the study population**

The univariate linear regression showed that age, cardiac index and mPAP are significantly associated to the dependent variable ΔPVR (Table 4). Other baseline characteristics as biological, echocardiographic variables are not associated with our predictable variable. The multivariable linear regression showed in table 5 revealed that only cardiac index is significantly associated to ΔPVR (p value 0.014). After adjustment, we did not observe a significant association of age and mPAP with ΔPVR.

**Table 4.** Unadjusted univariable analysis for outcome of ΔPVR

| (n=35) | beta | CI | p value |
|---|---|---|---|
| **Covariate at T1** | | | |
| Male vs Female | -0.220 | -1.386 ; 0.945 | 0.703 |
| Age (per 1 year increase) | -0.037 | -0.075 ; 8.8.10-5 | 0.051 |
| BMI (per 1-kg/m² increase) | -0.071 | -0.204; 0.061 | 0.282 |
| Ischemic cardiopathy or no | -0.167 | -0.680 ; 0.345 | 0.511 |
| Dilated cardiomyopathy or no | -0.084 | -1.126 ; 0.958 | 0.871 |
| Use of vasopressors or no# | -0.579 | -1.601 ; 0.443 | 0.258 |
| Resynchronization therapy | 0.641 | -1.168 ; 2.451 | 0.476 |
| NT-proBNP (per 1-unit increase) | -4.470.10-5 | -1.10-4; 1.10-5 | 0.158 |
| Creatinine (per 1-unit increase) | 0.507 | -0.327 ; 1.341 | 0.225 |
| BUN (per 1-unit increase) | 0.009 | -0.002 ; 0.020 | 0.109 |
| Sodium (per 1-unit increase) | -0.056 | -0.152 ; 0.039 | 0.239 |
| Total bilirubin (per 1-unit increase) | 0.125 | -0.734 ; 0.985 | 0.767 |
| AST (per 1-unit increase) | 0.006 | -0.002 ; 0.013 | 0.135 |
| ALT (per 1-unit increase) | 0.003 | -0.002 ; 0.008 | 0.187 |
| HR (per 1-bpm increase) | 0.007 | -0.020 ; 0.035 | 0.588 |
| MAP (per 1-mmHg increase) | 0.011 | -0.036 ; 0.058 | 0.649 |
| mPAP (per 1-mmHg increase) | 0.045 | 0.001 ; 0.090 | 0.046 |
| PAWP (per 1-mmHg increase) | 0.039 | -0.020 ; 0.097 | 0.191 |
| RAP (per 1-mmHg increase) | 7.537.10-5 | -0.094 ; 0.094 | 0.999 |
| IC (per 1-L/min/m² increase) | -1.049 | -1.829 ; -0.268 | 0.010 |
| LVEF (per 1-% increase) | -0.030 | -0.119 ; 0.059 | 0.495 |

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| | | | |
|---|---|---|---|
| LV internal EDD (per 1-cm increase) | -0.203 | -0.730 ; 0.325 | 0.438 |
| TAPSE (per 1-mm increase) | -0.043 | -0.178 ; 0.092 | 0.521 |
| S-wave (per 1-cm/s increase) | 0.015 | -0.205 ; 0.236 | 0.888 |
| TAPSE/sPAP (per 1-mm/mmHg increase) | -2.203 | -6.429 ; 2.023 | 0.293 |

p value ≤ 0.10 was considered statistically significant. CI : confidence interval; T1: pre-implant examination. BMI: body mass index; vasopressor#: inotropes during right heart catheterisation; N-terminal pro-B-type natriuretic peptide; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase. HR: heart rate ; MAP: mean arterial pressure; mPAP : mean pulmonary artery pressure ; PAWP : pulmonary artery wedge pressure ; RAP : right atrial pressure; CI : cardiac index ; LVEF: left ventricular ejection fraction; LV internal EDD: left ventricular internal end-diastolic dimension; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure.

**Table 5.** Multivariable linear regression for ΔPVR

| (n=34) | beta | CI 95% | P value |
|---|---|---|---|
| Cardiac index | -0.979 | -1.745 ; -0.214 | 0.014 |
| Age (per 1-y increase) | -0.023 | -0.059 ; 0.013 | 0.201 |
| mPAP | 0.035 | -0.008 ; 0.078 | 0.107 |

p value ≤ 0.05 was considered statistically significant.

## DISCUSSION

In this study focused on patients with HFrEF who received an LVAD, our results indicate the following: 1) before LVAD implantation 92% of patients had PH, reduced to 54% post-implantation. 2) there was a significant improvement in PVR and pulmonary arterial compliance after LVAD implantation. 3) Cpc-PH patients are the most common before LVAD implantation. The number of pre-capillary PH patients increases after LVAD implantation. 4) additionally, we identified the cardiac index as a predictor of haemodynamic outcomes.

Pre transplant pulmonary hypertension is associated with early complications and a worse short-term survival after HT. Cpc-PH refractory to medical therapy may be considered a contraindication (17) for HT due to the high risk of acute right HF and the high mortality rate (18,19). PH is often a consequence of end-stage HF, affecting about 72% of patients with LHD (20). In these patients, increase in left ventricular pressure has a passive effect on pulmonary circulation leading to a post-capillary PH. Some patients will evolve with a pre-capillary component combined with post- capillary PH. Mechanisms involved are not completely understood. It can be explained by endothelial dysfunction, increased production of thromboxane A2 and endothelin 1, and decreased availability of nitric oxide and prostacyclin. All these mechanisms induce pulmonary vasoconstriction followed by the remodeling of the arterial wall, which is characterised by medial hypertrophy and intimal fibrosis (10,21).

The aim of treatment of PH-LHD is to normalize the wedge pressure, and, consequently, LVAD support can play a critical role. Since the 1990s, many authors have shown a decrease of PH during LVAD support (22–26). The prospective study by Zimpfer et Al (22) followed 35 patients with not reversible Cpc-PH, defined by PVR greater than 3.5 WU despite reversibility testing. Data was obtained before and after pulsatile or continuous LVAD implantation. They demonstrated normalisation of loading pressure, cardiac output and PVR after LVAD implantation. Al Kindi et al (26) retrospectively compared LVAD to Inotrope in Cpc-PH patients with high PVR (> 5WU) or high TPG (>16mmHg). Despite the non-homogeneous group and lack of information on inotropic medications, this study emphasises equivalent decreasing of pulmonary pressures and PVR between the two groups. Only about a third of the patients in the two groups normalised these haemodynamic variables. In a Cpc-PH population, Selim et al (25) retrospectively showed a significant reduction in pulmonary pressures and PVR after fifty-one LVAD implantations, even in the group with high PVR (≥ 5 WU). In our study, we have shown that LVAD reduces both mPAP (22 ± 8mmHg, Δ = - 14 mmHg, p <0.001) and PVR (2.3 ± 1.1 WU, Δ = - 1.0 WU, p <0.001) as measured by RHC 14 ± 9 months following LVAD implantation. Our subgroup analysis has shown that Cpc-PH is mostly treatable, emphasising the impact of LVAD on the reversibility of PVR. At T1 examination, 27 patients (75%) had Cpc-PH compared with 6 patients (16.7%) after LVAD implantation. Reversibility is mainly driven by normalisation of left-sided filling pressures and improvement of cardiac output. This observation supports the hypothesis that PH in LHD is mostly due to a passive mechanism (7,10). The improvement in PA compliance is also likely to be a result of the same process, i.e reduction in PAWP and increase in left ventricular systolic ejection volume. However, after LVAD

implantation we observed 9 patients (25%) with pre-capillary PH, who were in the Cpc-PH group before LVAD implantation. This observation suggests that there is a small proportion of patients with not reversible pre-capillary component in the CpC-PH group. This is unlikely due to masked post capillary PH based on our clinical and haemodynamic assessment. Is there a fixed pre-capillary component of Cpc-PH? Due to the design of our study and the small number of patients, we need to be careful in our interpretation. On the one hand, the reversibility of PVR is particularly time-dependent and related to patients' characteristics (22,24,27), this may explain some of the patient with persistent high PVR in our study. On the other hand, some authors have pointed out similarities between idiopathic pulmonary arterial hypertension and Cpc-PH (12,28,29). Further studies are needed to clarify the physiopathology and consequences of a persistent pre-capillary component in the HF population.

Additionally, we observed that RV systolic dysfunction worsens after LVAD implantation in our study at T2 examination. This observation is emerging in the literature as showed by Fujino et al, and its mechanism remains unclear (30). These authors demonstrated a decrease in RV function, estimated by pulmonary arterial pulsatility index, in 22 patients in the follow-up period after LVAD implantation. Right heart adaptation to pulmonary circulation after LVAD implantation can be estimated by echocardiographic measures such as TAPSE and S wave which represent the longitudinal contractility of the RV. Using a conductance catheter, it is possible to obtain pressure-volume loops changing RV afterload. Analysis of these loops estimates the RV-arterial coupling, reflecting the adaptation of RV systolic function to its afterload (31,32). However, in practice this invasive method is not usually performed, therefore the TAPSE/sPAP ratio has been proposed by Guazzi et al to estimate RV-arterial coupling (33). Our results have shown that the TAPSE/sPAP ratio was improved at T2. This observation proves the adaptation of the RV to its afterload conditions in the long-term.

In the present study, prevalence of PH and Cpc-PH is higher than in other series (22–24), mainly due to the evolving definitions of PH over the past decades. At the beginning of our study, we classified patients based on the PH Guidelines 2015 (11), identifying PH in 81% before LVAD implantation whose 50% with Cpc-PH. As a recently revised threshold (mPAP and PVR thresholds from 25mmHg to 20mmHg and from 3WU to 2WU respectively) (8), PH prevalence increased to 92% whose 75% with Cpc-PH. It is important to note that the definition of PH due to LHD is regularly revised (8,11,34) in order to identify patients at risk of developing complications of PH.

In our study population, most patients (20/37 patients, 54%) had a successful heart transplantation. Unfortunately, 2 patients (5.4%) died before HT. At T2 RHC, all patients were successfully bridged to heart transplant candidacy with PVR <5 WU, and the mean PVR was 2.3 ± 1.1 WU. As a result, for a large proportion of patients waiting for HT, LVAD support plays a critical role. LVAD implantation reduces morbidity and mortality in patients on the waiting list for a heart transplant. However, the procedure is not totally free of complication. In our series, we found that 54% of patients developed at least one major complication in the first 30 days after LVAD implantation. Among these, severe RVF observed in 18.9% of patients is provoked by a failure of right heart adaptation as explained by Holman et Al (35). Soliman et al (15) observed about 21% of RVF in 2988 patients in the first 30 days after LVAD implantation and they found five predictors of outcome, especially the use of multiple intravenous inotropes, INTERMACS class and high "right atrial pressure/PAWP" ratio were correlated with RVF. In our study population, more than 90% and 80% of patients had abnormal mPAP and PVR respectively, so acute RVF is not only caused by PH.

We have shown that the cardiac index is inversely associated with PVR changes after LVAD implantation, independently of age and mPAP. This association is largely explained by the significant increase in cardiac output after LVAD implantation. Nevertheless, our results are limited by the number of variables included in our regression models. To our knowledge, there is no validated model to predict haemodynamic changes following LVAD implantation. Only one study by Gulati et Al (36) tested predictors variables of PVR change. They focused on the trend in PVR in 1581 Cpc-PH patients after LVAD implantation. Investigators observed a significant decrease in PVR, especially in the first three months. Preoperative haemodynamic variables such as pulmonary artery pressures and CO were significantly associated with PVR change after LVAD. Further studies with a tailored design are needed to establish a predictive model.

This study has several limitations. First, our study is limited by its retrospective design and small number of patients. Systematic RHC after LVAD implantation has been performed in our hospital since 2016, which explains the number of LVAD patients excluded from the final analysis. Second, our paired study excluded patients who did not undergo RHC before LVAD implantation, so this LVAD population is inherently selected. However, the external validity of the haemodynamic changes applies to the PH population due to LHD. Third, our regression model includes multivariable analysis with a small number of events, caution should be done.

## CONCLUSION

To the best of our knowledge, our study is the first to characterise haemodynamic changes after LVAD implantation based on the latest definitions of the PH Guidelines 2022. We have shown that LVAD implantation in heart transplant

candidates significantly reduced mPAP (Δ = - 14 mmHg) and PVR ( Δ = - 1 WU), mainly driven by a normalisation of left-sided filling pressures and improvement in cardiac output. The small proportion of patients with persistent high PVR after LVAD implantation should be investigated in further studies. Our results suggest that PH in end-stage HFrEF is mostly due to a passive mechanism associated with a natural ageing process. Cardiac index may be used as a predictor of haemodynamic outcomes after LVAD implantation.

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