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ORIGINAL ARTICLE

Left Ventricular Assist Devices in Pulmonary Hypertension Group 2 With Significantly Elevated Pulmonary Vascular Resistance: A Bridge to Cure

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Background Pulmonary hypertension secondary to left heart disease (WHO Group 2) is a known risk factor in patients with heart failure. The favourable effect of left ventricular assist devices (LVAD) on pulmonary hypertension has been demonstrated before, although this effect has not been well-studied in advanced pulmonary arterial bed disease with a significant elevation in pulmonary vascular resistance.

Methods We reviewed the records of 258 LVAD patients in our institution. Patients with elevated mean pulmonary artery pressure (mPAP > 25 mmHg) and elevated pulmonary vascular resistance (PVR ≥3 Wood units) were included in the study. Patients were divided into two groups based on their baseline PVR (PVR = 3–5 Wood units (WU) vs. PVR > 5 WU). The groups were studied for the changes in their pulmonary haemodynamics after the placement of LVAD.

Results Fifty-one (51) patients were included in the study. All patients showed a significant improvement in their pulmonary haemodynamic parameters post LVAD placement. In the group with the higher PVR, mPAP dropped from a baseline of 43 ± 7 mmHg to 22 ± 6 mmHg post LVAD placement ($p < 0.001$), while PVR dropped from 6.3 ± 1.2 Wood units to 2.2 ± 1.1 Wood units ($p < 0.001$). In a subgroup of patients who underwent cardiac transplantation post LVAD (n = 14), all patients maintained a normalised PVR (<3WU) one year post cardiac transplantation.

Conclusions Left ventricular assist devices can reverse pulmonary hypertension WHO Group 2 with significantly elevated PVR; this effect is not dependent on the baseline PVR, and is maintained up to one year post cardiac transplantation.

Keywords LVAD • Pulmonary hypertension • WHO group 2 • High PVR

Introduction

End-stage heart failure (HF) is a complex disease with limited treatment options, with orthotropic heart transplantation (OHT) being the gold standard. HF is often complicated by pulmonary hypertension (PH), which is a known contributing factor to worse outcomes in patients with HF with reduced ejection fraction (HFrEF), both the recipients of cardiac transplantation and those who are conservatively managed [1–5]. In patients with HF and elevated mean pulmonary artery pressure (mPAP), a high (and fixed) pulmonary vascular resistance (PVR) is a widely accepted indicator

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for an ''out of proportion'' pulmonary hypertension. In other words, the elevation in PVR indicates an active disease process involving the pulmonary vascular wall and causing a further elevation in mPAP instead of passively transmitting the left-sided pressures.

In addition to signalling an existing pulmonary vascular disease, the degree of PVR elevation reflects the severity of underlying pathology. For example, the intimal thickness and fibrosis of the pulmonary vasculature, which are believed to be the underlying histopathological changes in the ''fixed'' phase of PH, were shown to be proportionate to the elevation in PVR [6,7]. The degree of elevation in PVR is also a predictor of outcomes; according to the data obtained from the International Society for Heart and Lung Transplantation (ISHLT) registry, there is a linear relationship between baseline PVR and mortality in patients post cardiac transplant [8]. In fact, the 2006 ISHLT guidelines listed PVR >5 Wood units (WU) as a contraindication for cardiac transplantation [9].

Studies in the past have shown that left ventricular assist device (LVAD) implantation leads to a significant reduction in mPAP [10,11], with many PH patients eventually listed for OHT after achieving a significant improvement in their pulmonary haemodynamics [12], although one recent study suggested that only one-third of the patients with fixed PH achieve normalisation of PVR with LVAD [13].

In this cohort, we studied the effect of LVAD on patients with pulmonary hypertension secondary to HFrEF (WHO Group 2) who have a significantly elevated PVR (≥5 WU), and compared them to patients with moderately elevated PVR (3–5 WU). Our study aims at answering a number of important clinical questions about the likelihood of a patient with significantly elevated PVR to be bridged to normalisation; will these patients achieve the same drop in PVR after LVAD placement compared to patients with lower PVR? Will this normalisation follow a comparable course between the two groups? And will the pulmonary haemodynamics continue to be normal long after cardiac transplantation is performed?

Methods

Study Population

The heart failure and transplant registry at the University of Nebraska Medical Center, Omaha, NE includes 258 patients who received LVAD therapy between January 2009 and June 2016. We searched the registry for patients with pulmonary hypertension and elevated PVR (mPAP >25 mmHg and PVR ≥ 3.0 WU) on a right heart catheterisation (RHC) performed within 60 days prior to LVAD placement. We divided the study patients into two subgroups; patients with significantly elevated PVR, defined as PVR > 5 WU; and those with moderately elevated PVR (PVR between 3–5 WU). All patients included in this study had a repeat RHC done after LVAD placement, with mPAP, PVR, transpulmonary gradient (TPG), pulmonary capillary wedge pressure, and cardiac output reported. The study was approved by the institutional review board at the University of Nebraska Medical Center (IRB # 343-17-EP). Patients did not sign a consent form given the retrospective nature of the study. The study did not receive any funding.

Statistical Analysis

Baseline characteristics of the patients were reported as mean (SD) for continuous variables, and frequency (%) for discrete variables. Student t-test was used to compare the variables between the group with the higher PVR (>5 WU) and the group with the moderately elevated PVR (3–5 WU). Paired Student t-test was use to compare post LVAD haemodynamic measurements to the baseline measurements for the same group of patients. Further evaluation of the impact of LVAD on PVR was performed by dividing the study subjects into three tertiles based on their pre-LVAD PVR. The groups were then compared for the changes in PVR over time using log-rank test. Lastly, a linear regression model was built to investigate the relationship between the baseline PVR of the subjects and the changes in PVR after LVAD placement. Results were considered statistically significant if a p-value of ≤ 0.05 is achieved.

Results

Baseline Characteristics

Baseline characteristics and the comparison between the two groups are shown in Table 1. The 51 patients included in this study were predominantly white (n = 42, 82%), middle aged (mean age 56 ± 13 years) males (n = 38, 75%). There were no significant differences between the high PVR and low PVR groups at baseline except for the haemodynamic measurements.

Vasodilator Reversibility Testing for Baseline PVR

Nitroprusside testing was done as a part of the baseline RHC in nine (41%) of the significantly elevated PVR group. Out of those, seven patients (78%) had a non-reversible PVR (defined as persistent PVR ≥ 3 WU despite the highest dose of nitroprusside given during RHC).

Impact of LVAD on the Pulmonary Circulation

We studied the pulmonary circulation pressures of the two groups before and after placement of LVAD. mPAP, PVR, TPG, and pulmonary wedge pressure in both groups showed a significant drop towards normalisation post LVAD placement (Figure 1). The group with PVR≥ 5 WU had a higher PVR and TPG at baseline compared to the lower PVR group, although after LVAD placement the two groups had comparable pressure measurement of all the four variables (Table 2). The linear regression model showed a strong correlation ($r = 0.87$, $p < 0.001$) between baseline PVR and the drop in PVR post LVAD placement (Figure 2), estimated PVR drop = −2.4 + 1.04*baseline PVR.

Table 1 **Baseline characteristic.**

	All patients (n = 51)	Moderately elevated PVR (n = 29)	Significantly elevated PVR (n = 22)	P
Age	56 (13)	57 (15)	56 (10)	0.73
Men	38 (75)	22 (76)	16 (73)	0.81
Caucasian	42 (82)	23 (79)	19 (86)	0.6
BMI	30 (7.8)	30 (9)	29 (5)	0.12
BNP	995 (772)	940 (817)	1,072 (718)	0.2
Ischaemic CMP	21 (41)	12 (41)	9 (41)	0.9
COPD	17(33)	8 (28)	9 (41)	0.5
DM	21 (41)	11 (38)	10 (45)	0.9
HTN	31 (61)	18 (62)	13 (59)	0.9
HLP	21 (41)	13 (45)	8 (36)	0.5
Smoker	31 (61)	16 (55)	15 (68)	0.7
LVEF	17 (9)	16 (7)	18 (10)	0.99
LVAD-Heartmate	44 (86)	27 (93)	17 (77)	0.19
Indication-Bridge to cardiac transplantation	36 (71)	20 (69)	16 (73)	0.9
Time between LVAD placement to RHC in days	134 (80)	134 (91)	134 (65)	0.77
COP (Fick's) L/min	2.9 (0.6)	3.1 (0.6)	2.6 (0.5)	<0.001
CI	1.8 (0.3)	1.9 (0.3)	1.6 (0.32)	0.004
Mean BP	81 (19)	78 (21)	86 (13)	0.13
Baseline haemodynamics				
mPAP (mmHg)	42 (7)	40 (6)	43 (7)	0.12
PVR (Wood units)	5.5 (2)	3.8 (0.5)	6.3 (1.2)	<0.001
TPG (mmHg)	15 (4)	14 (3)	18 (5)	0.001
PW (mmHg)	26 (7)	26 (5)	25 (7)	0.53
RV dysfunction	27 (53)	14(48)	13 (59)	0.2
Intermacs score 0.9				
I	11 (22)	7 (24)	4 (18)	
II	18 (35)	11 (38)	7 (32)	
III	13 (25)	6 (21)	7 (32)	
IV	9 (18)	5 (17)	4 (18)	
Beta blockers	44 (86)	25 (86)	19 (86)	0.9
ACEi/ARBs	30 (59)	16 (55)	14 (64)	0.6
Inotropes	40 (78)	24 (83)	16 (73)	0.8
ICD/CRT	48 (94)	26 (90)	22 (100)	0.07
AI	8 (16)	4 (14)	4 (18)	0.5
Mild	7 (14)	4 (14)	3 (14)	
Moderate	1 (2)	0	1 (5)	
Severe	0	0	0	
MR	45 (88)	27 (93)	18 (82)	0.8
Mild	18 (35)	14 (48)	4 (18)	
Moderate	18 (35)	7 (24)	11 (50)	
Severe	9 (18)	6 (21)	3 (14)	
TR	45 (88)	25 (86)	20 (91)	0.8
Mild	22 (43)	11 (38)	11 (50)	
Moderate	21 (41)	13 (45)	8 (36)	
Severe	2 (4)	1 (3)	1 (5)	

Data presented as mean (standard deviation) for continuous variables and count (%) for categorical variables.

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; AI, aortic insufficiency; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CI, cardiac index; CMP, cardiomyopathy; COP, cardiac output; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; DM, diabetes mellitus; HLP, hyperlipidaemia; HTN; hypertension; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; PVR, pulmonary vascular resistance; PW, pulmonary wedge pressure; RHC, right heart catheterisation; RV, right ventricular; TPG, transpulmonary gradient; TR, tricuspid regurgitation.

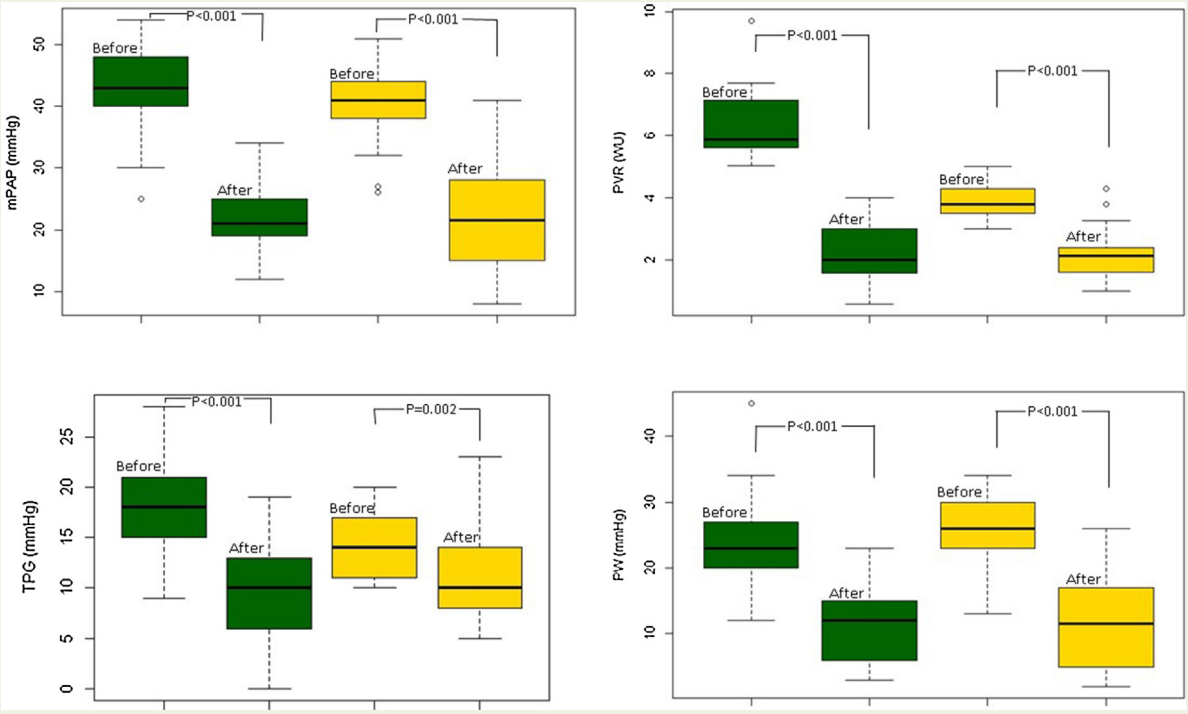

Figure 1 Changes in pulmonary haemodynamics post LVAD placement in the high vs. low PVR groups. Haemodynamic parameters post LVAD placement compared to baseline in both the high (green) and low (yellow) PVR groups.
Abbreviations: PAP, pulmonary artery pressure (mean); PVR, pulmonary vascular resistance; PW, pulmonary wedge pressure; TPG, transpulmonary gradient; LVAD, left ventricular assist devices

Table 2 Comparison of haemodynamics of the 2 groups, both before and after LVAD.

	Before LVAD placement			After LVAD placement		
	PVR 3-5 group	PVR > 5 group	P-value	PVR 3-5 group	PVR > 5 group	P-value
mPAP (mmHg)	40 (6)	43 (7)	0.13	23 (9)	22 (6)	0.47
PW (mmHg)	26 (5)	25 (7)	0.53	12 (7)	11 (7)	0.74
TPG (mmHg)	14 (3)	18 (5)	0.001	11 (4)	10 (5)	0.52
PVR (Wood Unit)	3.8 (0.5)	6.3 (1.2)	<0.001	2.2 (0.8)	2.2 (1)	0.94
*Use of pulmonary vasodilators	0	0	-	2 (7)	1 (5)	1.0

Table comparing the haemodynamic measurements between the 2 study groups, both at baseline and after the implantation of LVAD. Results are presented as mean (SD) for the continuous variables, and as no (%) for the categorical variables.
Abbreviations: mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PW, pulmonary wedge pressure; TR, tricuspid regurgitation; LVAD, left ventricular assist device
*Include inhaled nitrate, phosphodiesterase 5 inhibitors, endothelin receptor antagonists, prostacyclin agonist, and guanylate cyclase stimulators.

Tertile Analysis

We divided all patients with PVR ≥ 3 WU into three tertiles; T1: PVR = 3.0–3.8, T2: PVR = 3.81–5.18, and T3: PVR = 5.19–9.7. Haemodynamic measurements improved in all patients' tertile after LVAD placement (Table 3). Kaplan Meier analysis was done to compare the time-to-normalisation of PVR, defined as PVR < 3.0 WU, with log rank test performed and showed no significant difference between three groups (Figure 3).

PVR Post Cardiac Transplantation

We studied a subgroup of 14 patients who had cardiac transplant done after LVAD, all of whom belonged to the higher PVR group. Pulmonary vascular resistance less than 3 WU was maintained in all patients on a RHC done one year post cardiac transplant (mean PVR 1.6 ± 0.5).

Discussion

Intrinsic pulmonary vascular disease with pulmonary hypertension is a known complication of long-standing left ventricular failure. Several approaches have been used to slow the rate of pulmonary vascular remodelling in these patients, including optimisation of heart failure treatment regimen

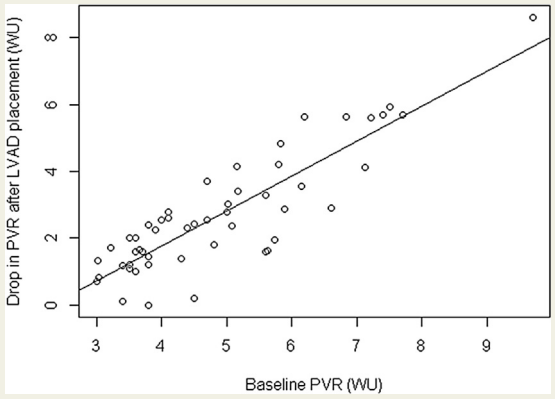

Figure 2 Relationship between baseline PVR and the drop in PVR post LVAD placement. Relationship between baseline PVR and the drop in PVR post LVAD placement.Y = −2.4 + 1.04*X. WU; Wood unit. R = 0.87, p-value <0.001.
Abbreviations: PVR, pulmonary vascular resistance; LVAD, left ventricular assist devices

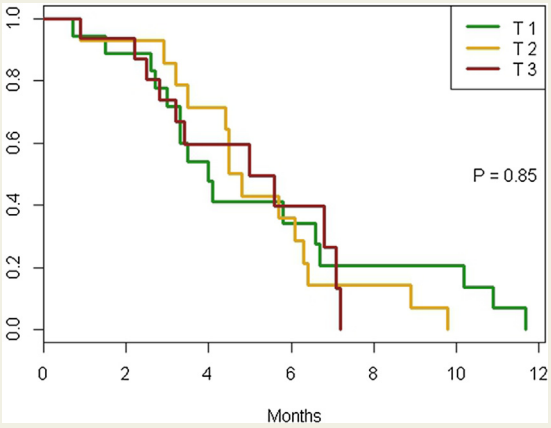

Figure 3 Time to normalisation of pulmonary vascular resistance: A comparison between the 3 patient tertiles. Kaplan Meier curve comparing the 3 tertiles of patients for their time to achieve normalised PVR (<3 Wood units). T1: first tertile (PVR = 3.0–3.8 WU), T2: second tertile(PVR = 3.81–5.18 WU), T3: third tertile (PVR = 5.19–9.7 WU).
Abbreviations: PVR, pulmonary vascular resistance

and correction of mitral valve pathology (i.e. functional valve regurgitation), although the evidence of their favourable effect on PH is still questionable [14]. Multiple pulmonary vasodilators were also investigated as a potential treatment for pulmonary hypertension secondary to LV failure with limited or no success [15,16]. For example, both riociguat (a guanylate cyclase stimulator) and epoprostenol (a prostacyclin) did not show improvement in outcomes in patients with HF and PH [17,18].

In fact, the FIRST trial, which investigated the use of epoprostenol in this group of patients was prematurely terminated because of a trend towards increased mortality. On the other hand, sildenafil, a phosphodiesterase 5 inhibitor, showed symptomatic improvement in HFrEF patients with PH in multiple small size studies [19,20], although these outcomes were not validated in a large, randomised trial.

In our study, we showed that pulmonary hypertension with advanced pulmonary vascular disease can benefit significantly from LVAD placement. Most importantly, we showed that the normalisation of mPAP and PVR persists after cardiac transplantation is performed. Based on the most recent guidelines from the International Society for Heart Lung Transplantation, an elevated PVR that is refractory to medical therapy may be considered as a contraindication to OHT depending on its severity [21], with the reason being the high likelihood of right ventricular failure after OHT. On the other hand, the diagnosis of severe PH is not considered a contraindication for the implantation of LVAD, unless if complicated by severe right ventricular failure [5].

Table 3 **Changes in pulmonary haemodynamics in the different tertiles.**

	T1 (PVR 3.0–3.8)		T2 (PVR 3.9–5.2)		T3 (PVR 5.3–9.7)	
	N = 18		N = 16		N = 17	
	Before	After	Before	After	Before	After
mPAP (mmHg)	39 (6.1)	23 (9.4)*	43 (5.3)	23 (7.4)*	43 (6.9)	21 (5.1)*
PW (mmHg)	26 (6)	12 (7)*	27 (6.3)	13 (7.9)*	24 (5.8)	11 (6.1)*
TPG (mmHg)	13 (2.7)	11 (3.7)	16 (3.1)	11 (4.6)*	19 (4.4)	10 (5.1)*
PVR (Wood Unit)	3.5 (0.3)	2.2 (0.6)*	4.6 (0.43)	2.1 (0.85)*	6.6 (1.1)	2.3 (1.1)*
RV dysfunction at baseline	15 (83)		12 (75)		13 (77)	
Time to repeat RHC (days)	146 (96)		137 (80)		119 (62)	

Table showing the changes in haemodynamic parameters post LVAD placement (after) compared to baseline (before) in all patient tertiles. Results are presented as mean (SD) for continuous variables, and number (%) for RV dysfunction at baseline.
Abbreviations: mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PW, pulmonary wedge pressure; RHC, right heart catheterisation; RV, right ventricle; TR, tricuspid regurgitation; LVAD, left ventricular assist device
*Statistically significant ($p \leq 0.05$).

The reversibility of PH with elevated PVR after the placement of an LVAD was studied before. Nevertheless, most of these studies have used a PVR cut-off of 2.5–3.0 WU for patients' inclusion. For example, Kettner et al. performed a prospective study that included 11 patients with PVR $\geq$ 3.0 WU, with no evidence of reversibility using increasing doses of IV prostaglandin E1. Patients had VAD implanted (three pulsatile biventricular VAD and eight continuous flow LVADs) and showed a reduction of PVR in all patients at 3 months post implantation [22]. Similarly, Kutty et al. retrospectively investigated the use of centrifugal LVAD in 17 HF patients with PH as a bridge to transplant in a group of patients with a baseline PVR of 5.1 WU. They showed an improvement in PVR post LVAD and favourable survival at one year post cardiac transplant [11]. On the other hand, Mikus et al. investigated the time needed for the normalisation of PVR post LVAD placement in a study that included 27 fixed PH patients with PVR$\geq$ 2.5 WU at baseline. The study concluded that the improvement in haemodynamic parameters post LVAD takes place entirely in the first 6 months, with no further improvement observed past this window [10]. Al-Kindi et al. compared the impact of LVAD versus intravenous (IV) inotropes in 1,016 patients listed on the United Network for Organ Sharing (UNOS) registry as class 1A, 1B or class 7, and have PVR $>$ 5 WU [13]. They found no difference in the drop of PVR between the 393 patients who received LVAD treatment and the rest of the study patients who received IV inotropes. The study also reported a relationship between the wait time post placement of LVAD/inotropes and the achievement of normalisation of PVR, as well as a lack of relationship between baseline PVR and the likelihood of normalising PVR post LVAD, both of which are consistent with our findings.

In our study, we tried to answer a clinically-relevant question by investigating the effect of LVAD on patients with severely elevated PVR; a group of patients that used to be excluded from consideration for cardiac transplantation before the era of LVAD.

This study also shows that the relationship between the baseline PVR and the drop in PVR post LVAD is linear, which indicates a full recovery regardless of the degree of pulmonary vascular bed remodelling, and suggests that baseline PVR could be taken completely out of the equation as a risk factor for cardiac transplantation once LVAD is used for bridging. The post-cardiac transplant follow-up confirms the sustainability of PVR normalisation, and validates the use of LVAD to treat PH prior to cardiac transplant. Our tertile analysis confirms the former findings and proves that out of proportion PH with significantly elevated PVR will progress towards recovery within the same time frame, and regardless of the baseline PVR.

Study Limitations

Given its retrospective nature, this study is limited by the usual constraints of such design including selection bias, the lack of information about the patients volume status at the time of right heart catheterisation, and the lack of uniformity of the time patients spent on LVAD before haemodynamic measurements took place, which makes it difficult to obtain an accurate estimate of the percentage of patients that recovered from PH at a certain time point. Also, pulmonary vascular reactivity data at baseline was only available in less than half of the study population, with a subgroup analysis showing that over one-fifth of the subjects have a reversible PVR. Nevertheless, because the drop in PVR post LVAD was consistent in all patients, with normalisation took place in all of those tested at 6 months or more after the placement of LVAD, we believe it is less likely for this group of patients with non-fixed PH to be the main driver of our findings. In addition, being a single centre study with a white male prevalence might limit the generalisability of its conclusions.

Conclusion

Our study shows that patients with pulmonary hypertension secondary to an elevated left-sided pressure (WHO Group 2) could be bridged to complete recovery by LVAD regardless of their baseline PVR. The time to achieve normal PVR was not dependent on the baseline PVR. We believe a prospective study should be planned to confirm these findings, and to investigate the long-term outcomes after LVAD placement in patients with significant pulmonary vascular disease.

Declaration

None of the authors have a conflict of interest or financial relationships to disclose.

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