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European Journal of Cardio-thoracic Surgery 40 (2011) 971–977

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Reversibility of fixed pulmonary hypertension in left ventricular assist device support recipients

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Received 10 October 2010; received in revised form 3 January 2011; accepted 4 January 2011; Available online 26 February 2011

Abstract

Objective: Conflicting data still exist concerning the reversibility of secondary severe 'fixed' pulmonary hypertension (PH) by the use of left ventricular assist device (LVAD) support in terms of time necessary to provide a bridge to 'transplantability'. **Methods:** We retrospectively reviewed 145 patients with heart failure and severe PH treated by LVAD support between 2000 and 2009. There were 133 men (91.7%) and 12 women (8.3%) with a mean age of 52.95 ± 12.01 years. Patients were divided into two groups depending on preoperative PH reversibility. Fixed PH was defined by a mean pulmonary arterial pressure (mPAP) >25 mmHg, a pulmonary vascular resistance (PVR) >2.5 Wood Unit (WU) and a transpulmonary gradient (TPG) >12 mmHg, despite pharmacological treatment. **Results:** Fifty-six patients had fixed PH (group A) and 89 reversible PH (group B). Only 27 patients of group A underwent right heart catheterization evaluation during LVAD support; the remaining 29 patients had other contraindications to heart transplantation (HTx). The 27 patients were divided into three subgroups on the basis of examination time during LVAD support: <6 months (11 patients), between 6 and 12 months (six patients) and >12 months (10 patients). The mPAP, PVR, and TPG decreased significantly during LVAD support (mPAP, 37.26 ± 6.35 mmHg vs 21.00 ± 7.51 mmHg, $p = 0.007$; PVR, 3.49 ± 1.47 WU vs 1.53 ± 0.66 WU, $p = 0.000$; and TPG, 15.04 ± 5.22 mmHg vs 7.78 ± 3.21 mmHg, $p = 0.019$). A significant reduction of all parameters was observed during the first 6 months and later on there was no further decrease. There were no significant differences between the three subgroups (mPAP, $p = 0.680$; PVR, $p = 0.723$; and TPG, $p = 0.679$) in terms of time of reversibility. LVAD support allowed 19 patients to be transplanted. **Conclusions:** Patients with fixed PH can be treated with LVAD support. Our data suggest that 6 months after LVAD implantation it is possible to observe an important reduction of PH and evaluate the potential transplantability of patients. Longer support does not add any effect of LVAD on PH.

Keywords: Ventricular assist device; Transplantability; Fixed pulmonary hypertension; Transpulmonary gradient; Pulmonary vascular resistance

1. Introduction

Heart transplantation (HTx) is the gold standard treatment for end-stage heart failure (HF). The first consequence of the small number of heart donors is the careful selection of candidates. Pulmonary hypertension (PH), defined as mean pulmonary pressure >25 mmHg at rest [1], affects about 72% of patients with end-stage HF [2]. Secondary PH is, at the beginning, reversible, but gradually it can become fixed due to the remodeling process of the pulmonary vascular system. The limit between fixed and reversible PH is still not well defined and there is no agreement on the time needed to reach the level of theoretical irreversibility and the best parameters to define this status. Only the pharmacological tests currently available can play a role as guides to distinguish between reversible and fixed PH.

Data reported by other authors confirm that PH can be considered a risk factor for early and late morbidity and mortality after HTx [3–5]. According to these results, patients with fixed PH, defined by American Heart Association guidelines [3] as mean pulmonary artery pressure (mPAP) >25 mmHg, pulmonary vascular resistance (PVR) >2.5 Wood Unit (WU), and transpulmonary gradient (TPG) >12 mmHg after pharmacological tests or continuous administration of inotropic drugs, are currently excluded from the HTx waiting list.

Since 1991, the idea that left ventricular assist devices (LVADs) could play a crucial role in the treatment of end-stage HF for patients with fixed or not immediately reversible PH has been introduced [6]. Later, many authors approved and confirmed this initial advice [7–21]. Nowadays, it is quite clear that even secondary 'fixed' PH can be reversible by

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[1] This study was carried out within Dr Mikus's Research Fellowship Program 'Technologies and Advanced Therapies in Surgery' awarded by Tor Vergata University, Rome, Italy, directed by Professor Dr Tommaso Claudio Mineo, and Dr Loforte's PhD Program in 'Transplantation' awarded by Tor Vergata University, Rome, Italy, in cooperation with the Deutsches Herzzentrum Berlin, Germany.

1010-7940/$ – see front matter
doi:10.1016/j.ejcts.2011.01.019

means of LVAD support, thus reducing the left atrial pressure, which is the ideal approach in case of PH secondary to HF. However, the number of patients treated is small, conflicting data exist in the literature and many questions still need to be answered: Does fixed PH secondary to HF exist or is it reversible in time in all patients? How much time is necessary for PH reversibility by the use of LVAD support and does the time allow a possible bridge to 'transplantability' strategy [15]?

The aim of this study is to try to give an answer to these questions through a literature review and a retrospective analysis of Deutsches Herzzentrum Berlin (DHZB) data.

2. Material and methods

2.1. Patient population

We retrospectively reviewed a total of 145 patients with secondary severe PH who were treated at the DHZB with LVAD implantation between January 2000 and March 2009. There were 133 men (91.7%) and 12 women (8.3%) with a mean age of 52.95 ± 12.01 years.

Patients were divided into two groups depending on the preoperative PH reversibility grade; the criteria used to define fixed PH were mPAP > 25 mmHg, PVR > 2.5 WU, and TPG > 12 mmHg, despite continuous administration of dobutamine for at least 4 days (137 patients, 94.5%) or by usage of iloprost (eight patients, 5.5%) as mentioned elsewhere [21]. The first group (group A) consisted of 56 patients with fixed PH, the second (group B) of 89 patients with reversible pulmonary hemodynamic parameters.

The main etiologies of end-stage HF were idiopathic dilated cardiomyopathy (CMP) (62 patients, 42.76%), ischemic CMP (60 patients, 41.38%).

In both groups, there was a very similar percentage of critical patients, defined as those in INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) [22] levels 1 and 2: 57.3% for group B, and 57.1% for group A.

Preoperatively, 134 patients (92.41%) required high doses of catecholamines. An overview of the patient population of the two groups is shown in Tables 1 and 2. All patients underwent preoperative transthoracic and/or transesophageal echocardiography studies to evaluate the right ventricular function (Table 2).

All patients received LVAD support and none of the 145 patients needed a right ventricular assist device. The majority of patients had a continuous-flow device. Incor and HeartMate II were the devices mainly used: the former in 76 patients (52.4%) and the latter in 21 patients (14.5%). The other devices used were Berlin Heart Excor in 17 patients (11.7%), De Bakey I in 10 patients (6.9%), Novacor in nine patients (6.2%), DuraHeart in six patients (4.1%), Jarvik 2000 in four patients (2.8%), Abiomed in one patient (0.7%), and LionHeart in one patient (0.7%).

Table 1 shows an overview of patient's hemodynamic parameters.

2.2. Statistical analysis

Statistical analysis was performed using SPSS 12.0 for Windows (SPSS, Inc, Chicago, IL, USA). Categorical variables are expressed as proportions and continuous variables as mean values ± standard deviation.

Table 1. Demographic, clinical and hemodynamic parameters before LVAD implantation in the two groups.

Parameter	Reversible PH (n = 89)	Fixed PH (n = 56)
Age (years)	54.00 ± 11.28	51.29 ± 13.02
Gender (male/female)	84/5	49/7
BSA (m^2)	1.99 ± 0.20	1.91 ± 0.19
DCMP	32 (35.9%)	26 (46.4%)
Ischemic CMP	42 (47.2%)	19 (33.9%)
Post myocarditis CMP	11 (12.4%)	10 (17.9%)
Post chemotherapy CMP	4 (4.5%)	1 (1.8%)
NYHA IV	72 (80.9%)	47 (83.9%)
INTERMACS level		
I	27 (30.3%)	12 (21.4%)
II	24 (27%)	20 (35.7%)
III	32 (36%)	24 (42.9%)
IV	6 (6.7%)	0 (0%)
AICD	48 (53.9%)	37 (66%)
Reoperation	26 (29.2%)	10 (17.8%)
CVA	10 (11.2%)	10 (17.9%)
DM	28 (31.5%)	13 (23.2%)
COPD	12 (13.5%)	4 (7.1%)
Dyslipidemia	26 (29.2%)	20 (35.6%)
Systolic AP (mmHg)	102.15 ± 15.43	104.85 ± 16.11
Systolic PAP (mmHg)	49.63 ± 10.70	55.30 ± 12.55
Diastolic PAP (mmHg)	25.39 ± 5.53	26.32 ± 7.49
Mean PAP (mmHg)	34.80 ± 6.04	37.88 ± 8.23
CVP (mmHg)	11.84 ± 5.96	11.69 ± 6.70
PVR (Wood Unit)	2.30 ± 1.19	3.61 ± 1.62
TPG (mmHg)	8.74 ± 3.20	15.21 ± 3.16
CI ($l/min/m^2$)	2.15 ± 0.65	2.34 ± 0.69

All values are presented as mean and standard deviation or as percentage. AICD: automatic implantable cardioverter defibrillator; AP: systemic arterial pressure; BSA: boy surface area; CI: cardiac index; CMP: cardiomyopathy; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; CVP: central venous pressure; DCMP: dilatative cardiomyopathy; DM: diabetes mellitus types I and II; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support levels [25]; LVAD: left ventricular assist device; NYHA: New York Heart Association class; PAP: pulmonary arterial pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; and TPG: transpulmonary gradient.

This has been a retrospective study. Patient selection has been based on the defined PH parameters (mPAP, PVR, and TPG) in patients with end-stage HF. This is not a frequent condition, thus a randomized study was not really possible.

Box plots have been used to compare the course of different pulmonary hemodynamic parameters before and after LVAD implantation in patients with fixed PH. A p value <0.05 was considered statistically significant.

The nonparametric Wilcoxon test has been applied to check the differences between T_1 (before LVAD support) and T_2 (after LVAD support) for each pulmonary parameter (mPAP, PVR, and TPG).

3. Results

3.1. Subgroups

In group A, 29 patients (51.8%) had several contraindications to HTx: age in five patients, complication assist related in four patients, comorbidities in three patients, tumor in two patients, patient's wish in two cases, social problems in one patient, and to be evaluated in three cases,

Table 2. Laboratory and echocardiographic values before LVAD implantation in the two groups.

Parameter	Reversible PH	Fixed PH	$p < 0.05$
Mean INR	1.68 ± 0.97	1.52 ± 0.50	0.201
Mean PT (%)	63.89 ± 21.59	32.75 ± 18.42	0.758
Mean aPTT (s)	44.91 ± 17.76	44.00 ± 10.93	0.703
Mean Hb (g/dl)	12.07 ± 1.82	11.67 ± 1.88	0.205
Mean Hct (%)	35.59 ± 5.72	34.51 ± 5.27	0.247
Median WBC (k/μl)	10.3 (2.04–21.2)	9.38 (4.76–17)	0.099
Mean platelets (k/μl)	197.88 ± 89.75	197.26 ± 104.13	0.971
Mean BUN (mg/dl)	69.27 ± 47.71	54.85 ± 36.27	0.042
Median LDH	283 (151–9660)	309 (138–5490)	0,637
Median total bilirubin (mmol/l)	1.245 (0.3–6.89)	1.625 (0.52–7.69)	0.186
Median CRP (mg/dl)	3.125 (0.29–22.57)	3.3 (0.3–19.8)	0.564
Median NT-Pro BNP (mg/dl)	5203 (589–37700)	6101 (1244–48407)	0.523
Median creatinine (mg/dl)	1.35 (0.57–7.08)	1.13 (0.67–4.71)	0.055
Mean albumin (g/dl)	3.27 ± 0.55	3.10 ± 0.53	0.092
Mean LVEDD (mm)	72.92 ± 9.57	69.70 ± 9.36	0.049
Mean LVEF (%)	16.97 ± 6.41	16.75 ± 5.45	0.827
Mean RVEDD (mm)	35.35 ± 5.64	34.98 ± 4.99	0.691
Mean RVEF (%)	34.30 ± 11.08	32.57 ± 10.31	0.344
AR (grade)			0.316
0	81 (91%)	52 (92.9%)	
I	8 (9%)	3 (5.3%)	
II	0 (0%)	1 (1.8%)	
MR (grade)			0.250
0	9 (10.1%)	2 (3.6%)	
I	30 (33.7%)	17 (30.4%)	
II	41 (46.1%)	26 (46.4%)	
III	9 (10.1%)	11 (19.6)	
TR (grade)			0.349
0	16 (18%)	4 (7.1%)	
I	38 (42.7%)	25 (44.6%)	
II	31 (34.8%)	22 (39.4%)	
III	4 (4.5%)	5 (8.9%)	

All values are presented as mean and standard deviation or as median and ranges.
aPTT: activated partial thromboplastin time; AR: aortic valve regurgitation; BUN: blood urea nitrogen; CRP: C-reactive protein; Hb: hemoglobin; Hct: hematocrit; INR: international normalized ratio; LDH: L-lactate dehydrogenase; LVAD: left ventricular assist device; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; MR: mitral valve regurgitation; NT-Pro BNP: N-terminal pro-B type natriuretic peptide; PH: pulmonary hypertension; PT: prothrombin time; RVEDD: right ventricular end-diastolic dimension; RVEF: right ventricular ejection fraction; TR: tricuspid valve regurgitation; and WBC: white blood cell count.

while nine patients died during hospital stay. In the remaining 27 patients (48.2%), severe PH was the only contraindication. All these 27 patients underwent right heart catheterization examinations during LVAD support (continuous-flow LVAD, $n = 20$; pulsatile flow LVAD, $n = 7$) to evaluate any further reduction of pulmonary pressure and to consider a possible transplantability concept.

To understand the time of PH reversibility, we decided to divide the previous 27 patients (group A) into three subgroups on the basis of timing of right heart catheterization examinations during LVAD support: less than 6 months (11 patients), between 6 and 12 months (six patients), and more than 12 months (10 patients). The main parameters used to compare the data after pharmacological tests, before LVAD support (T_1) and during assist device support (T_2) were mPAP, PVR, and TPG, according to literature data (Table 3).

3.2. Hemodynamic parameters' behavior

The hemodynamic parameters of PH in the 27 studied patients were compared before (T_1) and during (T_2) LVAD support (Table 3): mPAP decreased from 37.26 ± 6.358 to 21.00 ± 7.514 mmHg ($p = 0.007$), PVR decreased from 3.49 ± 1.470 to 1.53 ± 0.669 WU ($p = 0.000$), and TPG

Table 3. Hemodynamic parameters in patients with fixed PH before LVAD implantation (T_1) and during assist support (T_2).

	Group 1 ($n = 11$ patients)		Group 2 ($n = 6$ patients)		Group 3 ($n = 10$ patients)		Total = 27 patients	
	Pre T_1	Post T_2	Pre T_1	Post T_2	Pre T_1	Post T_2	Pre T_1	Post T_2
mPAP (mmHg)	37.7 ± 5.0	20.4 ± 7.9	36.5 ± 7.6	24.3 ± 8.3	37.2 ± 7.4	19.6 ± 6.6	37.3 ± 6.4 $p = 0.007$	21.0 ± 7.5
PVR (WU)	3.5 ± 1.5	1.5 ± 0.7	3.5 ± 1.6	1.4 ± 0.7	3.4 ± 1.5	1.7 ± 0.6	3.5 ± 1.5 $p = 0.000$	1.5 ± 0.7
TPG (mmHg)	15.6 ± 5.9	7.6 ± 2.9	16.8 ± 5.3	7.5 ± 3.9	13.4 ± 4.3	8.1 ± 3.3	15.0 ± 5.2 $p = 0.019$	7.8 ± 3.2

All values are presented as mean and standard deviation.
LVAD: left ventricular assist device; mPAP: mean pulmonary pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; and TPG: transpulmonary gradient.

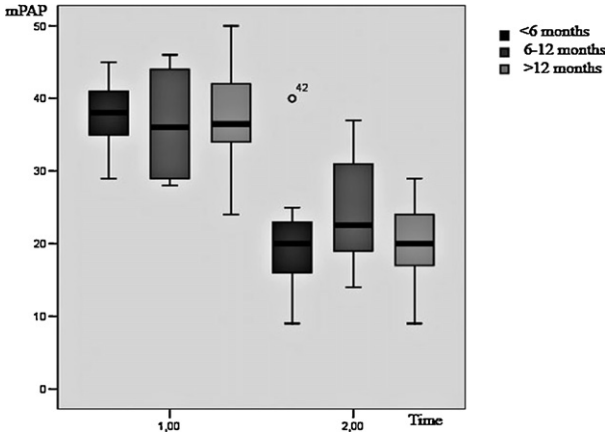

Fig. 1. Mean pulmonary artery pressure (mPAP) trend before and during LVAD support in the three groups.

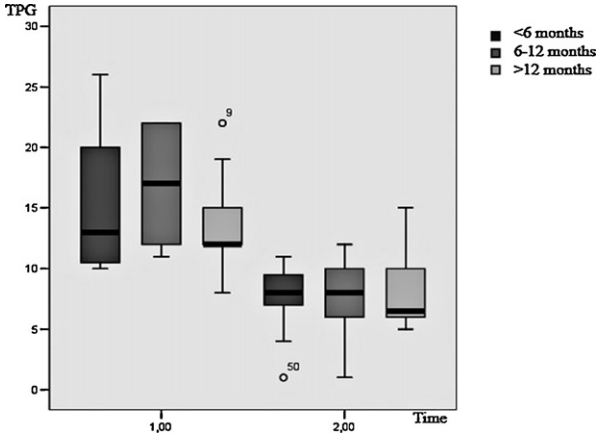

Fig. 3. Reduction of transpulmonary gradient (TPG) during LVAD support in the three groups (<6 months, between 6 and 12 months and >12 months).

decreased from 15.04 ± 5.229 to 7.78 ± 3.215 mmHg ($p = 0.019$) (Figs. 1–3). No statistical differences between the three subgroups for each parameter (mPAP, $p = 0.680$; PVR, $p = 0.723$; TPG, $p = 0.679$) were observed, thus showing that a significant reduction of all parameters can be observed even during the first 6 months, and that later on there is no important further decrease. By comparing the results between T_1 and T_2, we observed a mean reduction of 42.4% of mPAP (47.1% in <6 months, 30.5% between 6 and 12 months, and 45% in >12 months), a mean decrease of 50.9% of PVR (51.1% in <6 months, 58.3% between 6 and 12 months, and 45.7% in >12 months), and a mean decrease of 41.9% of TPG (44.6% in <6 months, 54.1% between 6 and 12 months, and 30.9% in >12 months).

By analyzing the patients who reached conditions of transplantability, we observed 22 patients (81.48%) with mPAP $\leq$ 25 mmHg, 24 patients (88.88%) with PVR $\leq$ 2.5 WU, and 26 patients (96.29%) with TPG $\leq$ 12 mmHg. A total of 19 patients (70.37%) had all three pulmonary hemodynamic parameters compatible with HTx. The results obtained were not significantly statistically correlated to the type of device used, whether continuous or pulsatile flow LVAD support.

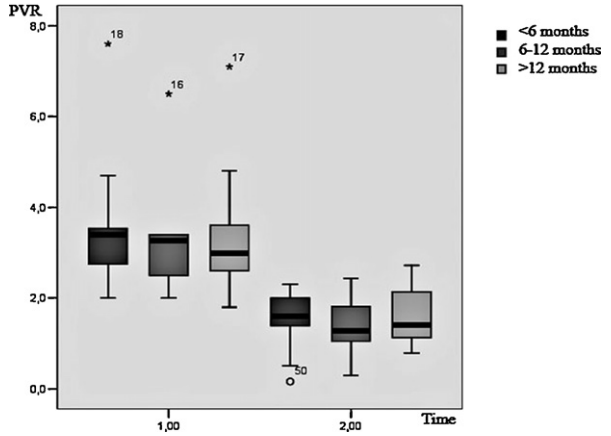

Fig. 2. Reduction of pulmonary vascular resistance (PVR) during LVAD support in the three groups (<6 months, between 6 and 12 months and >12 months).

3.3. Outcome and comparison between groups

Procedural success was defined as HTx (overall 40 patients), weaning (overall two patients), or prolonged LVAD support with discharge home (overall 38 patients), and it was reached in 55.2% of the overall population.

Procedural success of group A compared with group B was 66.0% versus 48.3%, respectively ($p = 0.037$), which was correlated to more device-related negative events of first-generation pulsatile blood pumps in group B. Thirty-day mortality was 7.2% (four patients) in patients with fixed PH, despite use of drugs and 15.7% (14 patients) in patients with reversible PH (Table 4); seven patients presented INTERMACS class 1, eight patients presented INTERMACS class 2, and three patients class 3.

A total of 40 patients underwent HTx: 19 patients (33.9%) in group A and 21 (23.60%) in group B. In group A, these patients received HTx after an average time of LVAD support of 564 ± 292 days ($n = 10$, continuous-flow LVAD; and $n = 7$, pulsatile flow LVAD). Two of them died: after 8 days and 32 days, respectively, both of sepsis (hospital mortality: 10.5%). In group B, the hospital mortality rate after HTx was 14.28% (3 of 21 patients, died respectively after 2, 28, and 58 days).

Post-HTx right heart catheterizations performed after a mean time of 564 ± 292 days in group A patients showed no

Table 4. Outcome of patients after LVAD implantation in the two groups.

	Fixed PH with drugs (56 patients)	Reversible PH with drugs (89 patients)	$p < 0.01$
Hospital mortality	9 (16.1%)	30 (33.7%)	0.02
<30 days	4 (7.2%)	14 (15.7%)	
>30 days	5 (8.9%)	16 (18%)	
Death after discharged at home	10 (17.9%)	16 (18%)	0.985
Procedural success	37 (66.0%)	43 (48.3%)	0.036
HTx	19 (33.9%)	21 (23.6%)	
On device	18 (32.1%)	20 (22.5%)	
Recovery	0 (0.0%)	2 (2.2%)	

All values are presented as percentage.
HTx: heart transplantation; LVAD: Left ventricular assist device; and PH: pulmonary hypertension.

evidence of significant statistical difference for each parameter evaluation (mPAP, $p = 0.27$; PVR, $p = 0.44$; and TPG, $p = 0.32$) if compared with the period of mechanical LVAD support.

Even in this case, the results were independent of the type of device used, whether continuous or pulsatile pre-Htx VAD support.

Medium-term post-transplant survival of patients with fixed PH treated by an LVAD (group A) was similar to that of patients with reversible PH in LVAD support (group B).

4. Discussion

PH unresponsive to vasodilator treatment is considered a contraindication for orthotropic cardiac transplantation. The reason for this is the unacceptably high risk of fatal right HF and the high mortality rate [3–5,18].

PH and increased PVR are often a consequence of end-stage HF, affecting about 72% of patients with chronic left ventricular failure [2]. In these patients, the increase of left ventricle pressure leads to a passive increase in postcapillary pressure in the pulmonary circulation. The consequence is an endothelial dysfunction, increased production of thromboxane A2 and endothelin 1, and lower availability of nitric oxide and prostacyclin. The activity of serine elastase is growth-causing glycoprotein deposition and smooth muscle cell hypertrophy and hyperplasia.

Pulmonary venous congestion is often associated with a reactive increase in PVR. The result is an increase of TPG. At the beginning, PH is due to pulmonary vasoconstriction followed by the remodeling of the arterial wall, which is characterized by medial hypertrophy and intimal fibrosis.

The fixed PH is not rapidly reversible by pharmacological treatment. The aim of treatment of secondary PH is to normalize the wedge pressure, and, consequently, LVAD support can play a crucial role. Since the beginning of the 1990s, many authors have shown a decrease of PH during LVAD support [6–21]. Table 5 shows an overview of all literature data and results.

It is important to notice that in the literature not all patients treated with LVAD support were unresponsive to medical treatment and pharmacological tests. Some authors, such as Martin et al. [13], Etz et al. [11] and Zimpfer et al. [18], considered only patients who did not respond to drugs, and others, such as Smedira et al. [17] and Liden et al. [12], gave a cutoff in terms of pulmonary hemodynamic parameters values to define a clinical scenario of severe PH. Consequently, we decided to divide our patient population into two different groups: responders and non-responders to inotrope therapy.

Usually, in such patients, PH is considered an indicator of expected absence of right ventricular failure after LVAD implantation [23] and our decision making for BVAD or LVAD support is mainly based on the geometry of the RV according to the DHZB protocol for BVAD implantation [24]; at our institution, thanks to this recent algorithm, it is possible to better control the risk of RV failure after LVAD implantation. Actually, the incidence of RV failure has been reduced to less than 10%.

Table 5. Literature data overview.

	N° of patients	Device	Time of support (days)	PVR (WU)		mPAP (mmHg)		TPG (mmHg)	
				Pre LVAD	Post LVAD	Pre LVAD	Post LVAD	Pre LVAD	Post LVAD
Gallagher et al. [6]	4	Novacor	61	7.2 ± 2.2	2.0 ± 0.8	–	–	23 ± 2	12 ± 2
Smedira et al. [17]	47	HeartMate (pneumatic and electric)	71	5	3.7 on device	41	30 on device	16	19 on device
Adamson et al. [7]	1	HeartMate TCI	70	6.6	2.3 on device	43	19 on device	28	15 on device
Nguyen et al. [14]	3	HeartMate TCI	180	6.3	3.6	56	26	22	14
Martin et al. [13]	6	Jarvik 2000, HeartMate TCI, Novacor	191 ± 86	5.7 ± 0.7	2.0 ± 1.2	46 ± 11	21 ± 3	–	–
Al-Khaldi et al. [8]	1	Novacor	330	7.1	1.2	60	26	22	6
Salzeberg et al. [16]	6	MicroMed De Bakey	42	4.97	2.08	–	–	–	–
Choong et al. [10]	5	HeartMate XVE	243	5.5	2.1	46	23	–	–
Etz et al. [11]	10	Incor and MicroMed De Bakey	182 ± 118	4.8 ± 1.8	2.2 ± 0.8	42 ± 13	24 ± 5	20 ± 6	11 ± 5
Zimpfer et al. [18]	35	MicroMed De Bakey and DuraHeart Novacor Jarvik 2000	42	5.1 ± 2.6	2.0 ± 0.8	44 ± 6	18.4 ± 4	–	–
Andrea et al. [9]	1	Berlin Heart Incor	131	6.5	2.8	29	18	23	12
Liden et al. [12]	11	De Bakey, HeartMateVE, Jarvik 2000, VentrAssist	239	4.3 ± 1.6	2.0 ± 0.6	37 ± 10	–	–	–
Torre-Amione et al. [19]	9	Novacor, Thoratec, De Bakey/Noon	59 ± 36			39 ± 7	31 ± 5	19 ± 3	13 ± 4
Deutsches Herzzentrum Berlin [21,25]	27	Pulsatile and non-pulsatile devices	342 ± 343	3.5 ± 1.5	1.5 ± 0.7	37 ± 6.4	21 ± 7.5	15 ± 5.2	8 ± 3.2

LVAD: left ventricular assist device; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; and TPG: transpulmonary gradient.

All patients were treated with an LVAD support and in none a temporary or permanent right ventricular assist device implantation was necessary.

The modality of support, continuous or pulsatile flow, seems to be a less important factor in the reversibility of PH [13,16]. In a recent study by Drews et al. [25], continuous and pulsatile devices were compared. No differences in terms of reduction of mean pulmonary arterial pressure, pulmonary vascular resistance, or transpulmonary gradient were found. Although continuous-flow devices typically unload the LV to a lesser degree than pulsatile devices, the reduction in pulmonary artery pressures does not appear to depend on the reduction of LV size but rather on the ability of the device to reduce intracardiac pressure. Other authors [19] have demonstrated a greater reduction in LV end-diastolic dimension after pulsatile LVAD support in comparison with an axial-flow LVAD; however, the change in dimensions had no effect on the effect in pulmonary pressures. The findings of our study are consistent with these observations, although the present study was not intended to compare device types but rather to present evidence of their effect on pulmonary hemodynamics.

In our data, we had 56 patients with secondary fixed PH, but only 27 underwent right heart catheterization. The remaining patients had several types of contraindication to HTx as described above.

The population consisted of a small number of selected patients but the study presents a cohort of patients within the same institution who were similarly treated with either a pulsatile or a continuous-flow device.

According to the results, an important reduction of PH during mechanical LVAD support occurred within 6 months, and 70.37% of our patients became transplantable for all three analyzed pulmonary hemodynamic parameters. Consequently, LVAD support allowed us, in a large percentage, to successfully bridge patients to HTx, who were previously excluded from the waiting list due to severe fixed PH. Post-HTx right heart catheterization procedures showed no evidence of significant statistical difference for each parameter evaluation (mPAP, $p = 0.27$; PVR, $p = 0.44$; and TPG, $p = 0.32$) if compared with the period of mechanical LVAD support, similar to other authors' studies [12,13,18].

The procedural success, defined as HTx, weaning or prolonged LVAD support with discharge home, was reached in 55.2% of the overall population. By comparing group A (fixed PH patients) to group B (reversible PH patients), success was achieved in 66.0% versus 48.3%, respectively ($p = 0.037$) (Table 4), thus giving the evidence of LVAD efficacy even in case of severe PH even if more device-correlated negative events of first-generation pulsatile blood pumps eventually occurred in group B.

Long-term post-transplant survival of patients with fixed PH treated by an LVAD (group A) was similar to that of patients with pharmacologically reversible PH and supported with an LVAD (group B), similar to some results data of literature [18,19].

Consequently, although PH remains a risk factor for early death after HTx, the equivalence of long-term survival after transplantation between LVAD patients with and without reversible PH suggests that, in most patients, mechanical unloading results in lasting effects on pulmonary vascular resistance.

The present study increases the body of clinical work that demonstrates that PH associated with chronic end-stage HF is reversible by chronic mechanical unloading with a pulsatile or an axial-flow LVAD, despite the possible complications while on device which could occur in all treated patients, considering in literature a described mortality rate on LVAD support of 10–30% [11,18].

Therefore, heterotopic cardiac transplantation and right ventricle sparing transplant techniques, which have been used in cardiac transplant candidates with fixed PH in the past, in which the donor heart acts as a biological assist device, are the subject of a variety of major limitations and high mortality rates [18].

Despite the small cohort of patients, our study provides data on pulmonary hemodynamics before LVAD insertion and after HTx. The ideal study to determine whether VAD therapy should be used in patients with secondary PH will be a larger, randomized controlled trial of aggressive medical therapy versus LVAD therapy, even if this is difficult to conduct and will take a long time to complete.

Our study confirms the crucial role of mechanical LVAD support in the case of fixed PH treatment. A reduction of PH has been observed during 6 months of support. After this time, no further improvement in pulmonary hemodynamics has been observed. Consequently, in our institution, patients with secondary fixed PH can be judged to be candidates for LVAD implantation and a right heart catheterization evaluation is currently performed after 6 months to assess a possible transplantability.

4.1. Study limitations

The first limitation of this study is the retrospective nature of the analysis and consequent selection bias. There has been no protocol management concerning the timing of evaluation of PH during LVAD support before the results of the present study. Right heart catheterization has been performed when patients were judged to be candidates for HTx for good clinical status or patients' own decision to be listed for HTx.

No complete analysis concerning PH behavior during the first 3 months of LVAD support could be possible.

Thereafter, it must be remembered that right heart catheterization studies are invasive procedures and should/could not be routinely performed in non-transplantable patients. Moreover, it can be argued that such a small cohort of patients with secondary fixed PH after right heart catheterization may mask a real behavior. Further and larger studies are consequently necessary to support our initial results.

Acknowledgments

The authors thank Julia Stein and Bacchi Reggiani for statistical analysis and Anne Gale for editorial assistance.

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