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Left ventricular assist device or heart transplantation: impact of transpulmonary gradient and pulmonary vascular resistance on decision making☆

Elisa Mikus*, Alexander Stepanenko, Thomas Krabatsch, Michael Dandel, Hans Brendan Lehmkuhl, Antonio Loforte, Roland Hetzer, Evgenij V. Potapov

Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin, Berlin, Germany

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Abstract

Objectives: Fixed pulmonary hypertension is a contraindication for heart transplantation. Left ventricular assist device support may lower it and bridge patients to heart transplantation. The aim of the study was to investigate the optimal parameters for treatment decisions and the time course of their potential reversal to normal values during preoperative inotropic support. **Methods:** Mean pulmonary arterial pressure, pulmonary vascular resistance and transpulmonary gradient were retrospectively analysed in 120 heart failure patients with severe pulmonary hypertension (mean age 51.7 ± 1.1 years, 93.3% males) treated between 2000 and 2009 with inotropes before left ventricular assist device implantation. The population was divided into three groups: patients with mean pulmonary arterial pressure > 25 mm Hg (group A, $n = 113$), patients with pulmonary vascular resistance > 2.5 Wood units (WU) (group B, $n = 75$) and patients with transpulmonary gradient > 12 mm Hg (group C, $n = 55$). Patients could be assigned to more than one group. **Results:** After 24 h of inotropic support, pulmonary vascular resistance decreased (4.1 ± 0.2 to 3 ± 0.1, −25%, $p < 0.001$), as did the transpulmonary gradient (17 ± 0.5 to 14 ± 0.7, −18%, $p < 0.001$). There was no significant decrease of mean pulmonary arterial pressure. Fifty percent of patients presented transpulmonary gradient < 12 mm Hg on the 3rd day and pulmonary vascular resistance < 2.5 WU on the 4th day. No further changes were observed in the following days. Left ventricular assist device support allowed 63 patients to be listed for heart transplantation and 40 received transplantation. A 30-day mortality after heart transplantation was higher in patients with fixed pulmonary hypertension, despite inotropes, than in those with reversible hypertension in groups B and C (12.5% and 11.1% vs 0%, respectively). **Conclusions:** Transpulmonary gradient and pulmonary vascular resistance, but not mean pulmonary arterial pressure, are predictive parameters for successful heart transplantation in cases of severe postcapillary pulmonary hypertension. When no significant decrease in pulmonary vascular resistance and transpulmonary gradient after 3—4 days of pharmacological therapy is observed, mechanical circulatory support is the only option to bridge end-stage heart failure patients to heart transplantation. Survival after heart transplantation is strictly related to the reversibility of pulmonary vascular resistance and transpulmonary gradient before assist implantation, but not related to mean pulmonary artery pressure.

Keywords: Pulmonary vascular resistance; Transpulmonary gradient; Left ventricular assist device; Inotropic drugs; Heart transplantation

1. Introduction

Fixed pulmonary hypertension (PH) is considered a crucial risk factor for mortality and morbidity following orthotopic heart transplantation (HTx) and a contraindication for it [1—3]. Pulmonary hypertension is defined by a mean pulmonary pressure (mPAP) > 25 mm Hg at rest or > 30 mm Hg during exercise [4]. A secondary, postcapillary PH is frequently present in patients affected by end-stage heart failure (HF), caused by the pulmonary venous pressure increase. Over time, the venous hypertension may produce remodelling of the arterial wall characterised by intimal fibrosis and medial hypertrophy. This stage is known as fixed PH because it is not immediately reversible with pharmacological testing; on the other hand, since 1991 various authors have reported delayed reversibility of postcapillary PH after left ventricular assist device (LVAD) support [5—10].

It is clear that preoperative response to drugs has a crucial role in predicting the outcome after HTx. Guidelines approved by the American Heart Association Science Advisory

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* Corresponding author. Address: Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. Tel.: +49 30 4593 2000; fax: +49 30 4593 2100.

E-mail address: elisamikus@yahoo.it (E. Mikus).

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Coordinating Committee recommend HTx if elevated pulmonary vascular resistance (PVR) is reversible below 2.5 Woods unit (WU) and transpulmonary gradient (TPG) is less than 12 mm Hg [11]. Presently, the optimal drug for the pharmacological test is still being discussed and the pulmonary haemodynamic parameters to predict outcome after HTx have not been well defined: mPAP, PVR and TPG are the most used, but no clear consensus is present about their real predictive value. There are several protocols for the diagnosis and treatment of PH secondary to HF, but conflicting data still exist [12–16].

The aim of the study was to investigate the optimal pulmonary haemodynamic parameters for treatment decisions and the time course of their potential reversal to normal values during preoperative inotropic support.

2. Material and methods

2.1. Selection of patients

A retrospective analysis of changes in pulmonary haemodynamic parameters was carried out in 120 end-stage heart failure patients with severe postcapillary PH between 2000 and 2009 at the Deutsches Herzzentrum Berlin. All patients were supported preoperatively with inotropes for more than 1 week and judged to be candidates for LVAD placement. There were 112 males (93.3%) and eight females (6.7%) with a mean age of 51.7 ± 1.1 years.

The aetiology was idiopathic dilated cardiomyopathy (DCMP) (48 patients, 40%), ischaemic DCMP (47 patients, 39.2%), post-myocarditis DCMP (20 patients, 16.6%) and post-chemotherapy DCMP (five patients, 4.2%). A previous cardiac operation had been performed in 27 patients (22.5%). All patients were in New York Heart Association (NYHA) class III (22 patients, 18.3%) or intravenous (IV) (98 patients, 81.7%). All patients were, at least, in Interagency Registry for Mechanically Assisted Circulatory Support levels [17] (INTERMACS) level 3 and 15% (18 patients) were in level 1, calculated just before assist implantation. The inotropic score [18,19] was used to render the population therapy homogeneous. Inclusion criteria were at least one elevated value at admission: mPAP > 25 mm Hg (group A, $n = 113$), PVR > 2.5 WU (group B, $n = 75$) or TPG > 12 mm Hg (group C, $n = 55$). Patients could be included in more than one group depending on the pulmonary parameters.

Clinical characteristics of the patients, based on the group to which they belong, are shown in Table 1.

2.2. Haemodynamic evaluation

Each patient was monitored for invasive systemic pressure by continuous measurement through the radial or femoral

Table 1. Demographic and clinical laboratory parameters before LVAD Implantation on intravenous inotropic therapy in the three groups.

Parameter	Group A ($n = 113$)	Group B ($n = 75$)	Group C ($n = 55$)
Median age (years)	51.71 ± 12.23	51.6 ± 12.49	50.56 ± 11.73
Gender (male/female)	104/9 (92%)	69/6 (92%)	51/4 (92.7%)
BSA (m^2)	1.953 ± 0.19	1.92 ± 0.18	1.95 ± 0.17
DCMP	44 (39%)	28 (37.3%)	22 (40%)
Ischaemic CMP	45 (39.8%)	28 (37.3%)	20 (36.4%)
Post-myocarditis CMP	20 (17.7%)	15 (20%)	9 (16.3%)
Post-chemotherapy CMP	4 (3.5%)	4 (5.4%)	4 (7.3%)
NYHA class IV	93 (82.3%)	58 (77.3%)	45 (81.8%)
INTERMACS levels			
I	41.9%	36.7%	33.6%
II	42.2%	48.7%	55.5%
III	15.9%	14.6%	10.9%
AICD	64 (56.7%)	41 (54.7%)	35 (63.3%)
Reoperation	26 (23%)	14 (18.7%)	11 (20%)
CVA	17 (15%)	14 (18.7%)	8 (14.5%)
DM	27 (23.9%)	19 (25.3%)	18 (32.7%)
Inotropic score[a]	10.62 ± 14.62	10.29 ± 14.62	10.59 ± 16.72
INR	1.67 ± 0.87	1.63 ± 0.82	1.58 ± 0.87
PT (%)	61.12 ± 19.63	61.75 ± 19.40	63.69 ± 19.10
PTT (or aPTT) (s)	45.18 ± 16.89	43.761 ± 9.59	43.49 ± 10.72
Hb (g/dl)	11.82 ± 1.91	11.97 ± 1.88	11.96 ± 1.85
Hct (%)	34.83 ± 5.85	35.34 ± 5.29	34.83 ± 6.19
WBC (K/μl)	10.53 ± 3.81	10.22 ± 3.78	10.25 ± 4.21
Platelets (K/μl)	188.76 ± 94.20	185.0 ± 90.15	175.56 ± 83.48
BUN (mg/dl)	63.15 ± 46.15	56.97 ± 34.16	55.90 ± 30.08
LDH	549.54 ± 1175.56	451.86 ± 674.45	356.61 ± 183.01
Total bilirubin (mmol/l)	2.03 ± 1.67	2.26 ± 1.52	2.24 ± 1.64
CRP (mg/dl)	5.17 ± 1.43	5.50 ± 5.10	4.88 ± 4.73
NT-Pro BNP (mg/dl)	9767.7 ± 10503.64	10668.42 ± 10860.99	8210.69 ± 8597.31
Creatinine (mg/dl)	1.49 ± 0.99	1.31 ± 0.54	1.29 ± 0.54

All values are presented as mean and standard deviation. AICD, automatic implantable cardioverter defibrillator; BSA, boy surface area; BUN, blood urea nitrogen; CMP, cardiomyopathy; CRP, C-reactive protein; CVA, cerebrovascular accident; DCMP, dilatative cardiomyopathy; DM, diabetes mellitus type I and II; Hb, haemoglobin; Hct, haematocrit; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support levels; INR, international normalized ratio; LDH, L-lactate dehydrogenase; LVAD, left ventricular assist device; NYHA, New York Heart Association class; NT-Pro BNP, N-terminal pro-B type natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell count.

[a] Definition is given by Potapov and Kormos [18,19].

Table 2. Echocardiographic and haemodynamic parameters before LVAD implantation on intravenous inotropic therapy in the three groups.

Parameter	Group A (n = 113)	Group B (n = 75)	Group C (n = 55)
LVEDD (mm)	71.50 ± 10.05	70.64 ± 9.04	71.54 ± 8.71
LV EF (%)	16.78 ± 6.11	16.88 ± 6.19	17.40 ± 5.89
RVDD (mm)	35.00 ± 5.48	35.74 ± 5.23	36.04 ± 4.91
RVEF (%)	32.93 ± 11.34	31.57 ± 11.09	31.62 ± 10.89
AR (grade)			
0	104 (92%)	67 (89.4%)	48 (87.3%)
I	8 (7%)	7 (9.3%)	6 (10.9%)
II	1 (1%)	1 (1.3%)	1 (1.8%)
MR (grade)			
0	8 (7%)	4 (5.3%)	4 (7.3%)
I	39 (34.6%)	23 (30.7%)	14 (25.5%)
II	52 (46%)	39 (52%)	29 (52.7%)
III	14 (12.4%)	9 (12%)	8 (14.5%)
TR (grade)			
0	15 (13.3%)	6 (8%)	6 (10.9%)
I	51 (45.1%)	31 (41.3%)	24 (43.6%)
II	38 (33.6%)	31 (41.3%)	20 (36.4%)
III	9 (8%)	7 (9.4%)	5 (9.1%)
Systolic PAP (mm Hg)	54.90 ± 10.08	55.09 ± 10.59	58.07 ± 11.06
Diastolic PAP (mm Hg)	29.05 ± 6.66	28.36 ± 6.23	28.53 ± 6.45
Mean PAP (mm Hg)	39.62 ± 7.28	39.29 ± 6.91	40.58 ± 7.35
CVP (mm Hg)	13.6 ± 6.29	12.32 ± 5.67	12.4 ± 6.23
PVR (Wood units)	3.5 ± 1.60	4.07 ± 1.44	4.21 ± 1.67
PCWP (mm Hg)	22.45 ± 6.60	20.92 ± 6.40	20.88 ± 6.63
TPG (mm Hg)	12.95 ± 4.67	14.27 ± 4.54	16.82 ± 3.50
CO (l/min)	4.17 ± 1.48	3.74 ± 1.25	4.39 ± 1.33

All values are presented as mean and standard deviation. AR, aortic valve regurgitation; CO, cardiac output; CVP, central venous pressure; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVEDD, right ventricular end-diastolic dimension; RVEF, right ventricular ejection fraction; TPG, transpulmonary gradient; TR, tricuspid valve regurgitation.

artery; a central venous catheter was inserted in the jugular vein.

A Swan–Ganz catheter was placed in the main pulmonary trunk through cannulation of the internal jugular vein. Cardiac output (CO) was obtained with thermodilution technique. Central venous pressure (CVP), pulmonary pressure (systolic, diastolic and mean) and pulmonary capillary wedge pressure (PCWP) were measured and recorded. TPG was defined, as is usual, as the difference between mPAP and PCWP, whereas the PVR was obtained by dividing TPG by CO.

Transthoracic echocardiography was performed preoperatively, during intravenous inotropic therapy, in all patients to evaluate left and right ventricular function and geometry (left ventricular diastolic dimension (LVDD), left ventricular ejection fraction (LVEF), right ventricular diastolic dimension (RVDD) and right ventricular ejection fraction (RVEF)) and valve incompetence. Haemodynamic measurements were recorded every day from the beginning of the administration of inotropic drugs until LVAD implantation. An overview of pre-treatment echocardiographic and haemodynamic data is shown in Table 2.

2.3. Pharmacological support

All patients were receiving standard medical therapy and intravenous inotropic drugs at the time of haemodynamic evaluation. Dobutamine was administered in 116 patients (96.66%); the other inotropic drugs used were dopamine (58 patients, 48.3%), enoximone (44 patients 36.66%), epinephrine (32 patients, 26.66%), milrinone (25 patients, 20.8%) and levosimendan (23 patients, 19.2%). In only four patients (3.3%), norepinephrine was used. Almost all patients (n = 118, 95%) were treated with two or more inotropic agents. The trend in the haemodynamic parameters was evaluated according to the inotropic score. The inotropic score is obtained by the pharmacologic dose in micrograms per kilo body weight per minute: the doses of dopamine, dobutamine and enoximone were added. The doses of levosimendan were multiplied by 10; those of epinephrine and norepinephrine were multiplied by 100 and then added [19].

In 40 patients (30%), a low vasodilator dose (nitroglycerin 1.1 mg h^{-1} or sodium nitroprusside used in only four patients with mean dose of 1.4 mg h^{-1}) was administered, depending on the haemodynamic stability of the patients.

2.4. 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. Pulmonary haemodynamic values were analysed by the paired t-test.

Box plots have been used to compare the course of different parameters day by day after the use of inotropic drugs. $p < 0.05$ was considered statistically significant.

3. Results

Since January 2000, 120 patients have been monitored with Swan–Ganz catheter and all haemodynamic parameters recorded (Table 2). All patients were treated with inotropic

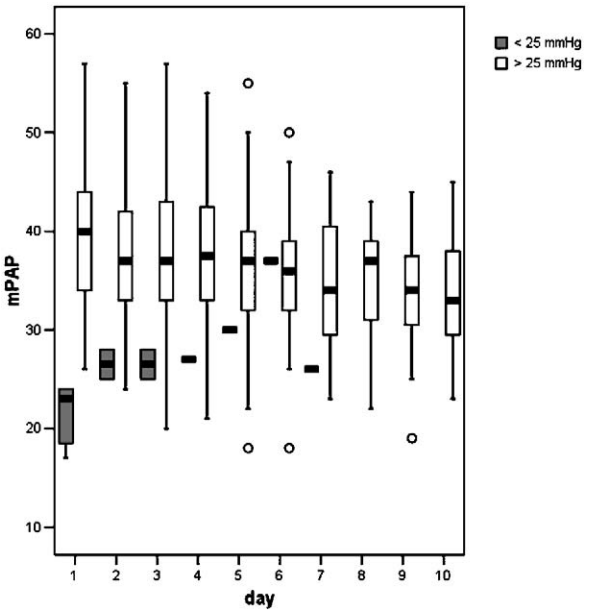

Fig. 1. Mean pulmonary artery pressure (mPAP) trend day by day (from 1st to 10th). White boxes: patients with mPAP > 25 mm Hg; grey boxes: patients with mPAP < 25 mm Hg.

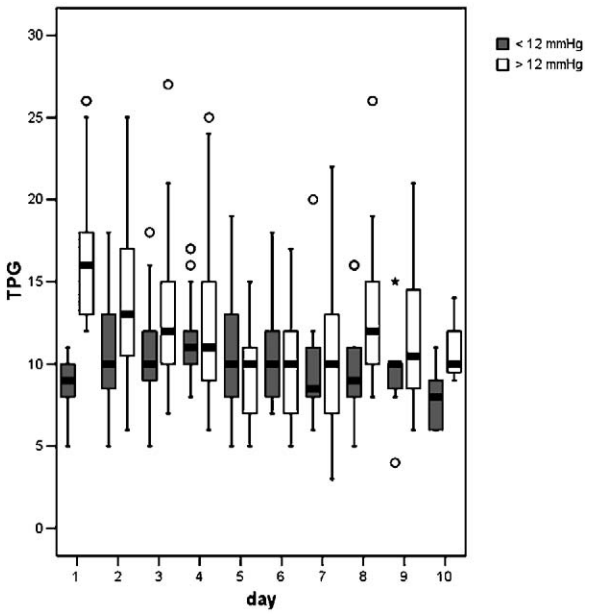

Fig. 3. Transpulmonary gradient (TPG) trend day by day (from 1st to 10th). White boxes: patients with TPG > 12 mm Hg; grey boxes: patients with TPG < 12 mm Hg.

drugs. In general, 113 patients had mPAP > 25 mm Hg, (group A), 75 patients had PVR > 2.5 WU (group B) and 55 patients had TPG > 12 mm Hg (group C).

3.1. Haemodynamic data

First, patients with low values at admission (mPAP < 25 mm Hg, seven patients; PVR < 2.5 WU, 45 patients and TPG < 12 mm Hg, 65 patients) were analysed. There were no significant changes in pulmonary haemodynamic parameters in spite of inotropic treatment (Figs. 1–3).

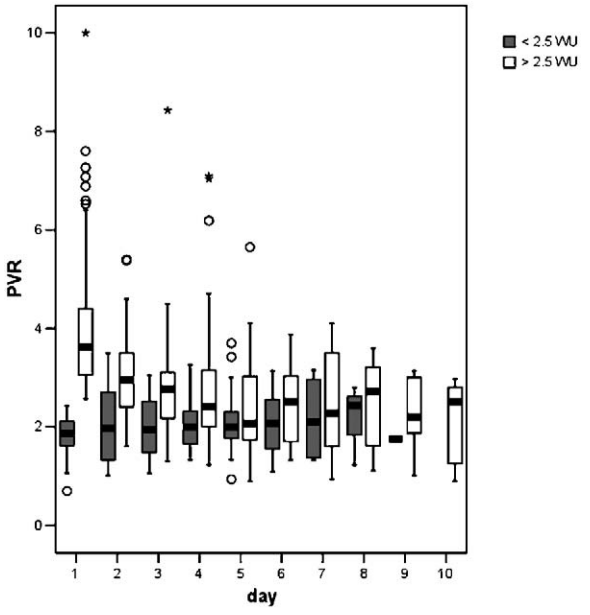

Fig. 2. Pulmonary vascular resistance (PVR) trend day by day (from 1st to 10th). White boxes: patients with PVR > 2.5 Wood units; grey boxes: patients with PVR < 2.5 Wood units.

No statistically significant increase was observed in a small cohort of seven patients only with evidence of mPAP < 25 mm Hg (Fig. 1). Second, patients with high pulmonary haemodynamic parameters were analysed. Group A (mPAP > 25 mm Hg) did not show any important change (Fig. 1). Group B (PVR > 2.5 WU) showed a significant decrease already after the first day of inotropic support: PVR dropped from 4.1 ± 0.2 to 3 ± 0.1 (−25%, $p < 0.001$) (Fig. 2). A similar decrease was noted in group C (TPG > 12 mm Hg): TPG dropped from 17 ± 0.5 to 14 ± 0.7 (−18%, $p < 0.001$) (Fig. 3). Fifty percent of patients presented TPG < 12 mm Hg on the 3rd day and 50% had a PVR < 2.5 WU on the 4th day. No further changes were observed in the following days for each parameter.

3.2. Outcome

All patients were treated with an LVAD and in none was an RVAD implantation necessary; in the postoperative period also no cases of right ventricle failure occurred. The majority (78.3%) of patients were treated with a continuous flow device. Devices used were Incor (64 patients), Berlin Heart Excor (17 patients), HeartMate II (14 patients), Novacor (nine patients), DeBakey (nine patients) DuraHeart (four patients), Jarvik 2000 (two patients) and Ventrassist (one patient).

Procedural success was defined as heart transplantation (40 patients), weaning (two patients) or continued ventricular assist device (VAD) support, but discharge home (23 patients) was reached in 54.2%. The procedural success for groups A, B and C was 53.1%, 57.3% and 52.7%, respectively (Tables 3 and 4).

LVAD support allowed overall 63 patients to be listed for HTx and 40 received transplantation after an average time of 458.225 ± 242.49 days: 38 patients (33.6%) in group A (20 patients with fixed PH with drugs and 18 patients with reversible PH with drugs), 27 patients (36%) in group B

Table 3. Outcome of patients with reversible PH after LVAD implantation.

PH reversible with drugs	Group A (65 pts)	Group B (38 pts)	Group C (30 pts)
Death	35 pts (53.8%)	19 pts (50%)	17 pts (56.7%)
<30 days	12 pts (18.4%)	8 pts (21.1%)	8 pts (26.7%)
>30 days	10 pts (15.4%)	5 pts (13.1%)	3 pts (10%)
Discharged	13 pts (20%)	6 pts (15.8%)	6 pts (20%)
Procedural success	30 pts (46.2%)	19 pts (50%)	13 pts (43.3%)
HTx	18 pts (27.7%)	11 pts (28.9%)	7 pts (23.3%)
On device	10 pts (15.4%)	6 pts (15.8%)	5 pts (16.7%)
Recovery	2 pts (3.1%)	2 pts (5.3%)	1 pts (3.3%)

HTx, heart transplantation; LVAD, left ventricular assist device; PH, pulmonary hypertension.

Table 4. Outcome of patients with fixed PH despite drugs after LVAD implantation.

PH fixed with drugs	Group A (48 pts)	Group B (37 pts)	Group C (25 pts)
Death	18 pts (37.5%)	13 pts (35.1%)	9 pts (36%)
<30 days	4 pts (8.3%)	3 pts (8.1%)	2 pts (8%)
>30 days	5 pts (10.4%)	5 pts (13.5%)	2 pts (8%)
Discharged	9 pts (18.8%)	5 pts (13.5%)	5 pts (20%)
Procedural success	30 pts (62.5%)	24 pts (64.9%)	16 pts (64%)
HTx	20 pts (41.7%)	16 pts (43.3%)	9 pts (36%)
On device	10 pts (20.8%)	8 pts (21.6%)	7 pts (28%)
Recovery	0 pts (0.0%)	0 pts (0.0%)	0 pts (0.0%)

HTx, heart transplantation; LVAD, left ventricular assist device; PH, pulmonary hypertension.

Table 5. Outcome of patients after HTx.

	Group A (mPAP)	Group B (PVR)	Group C (TPG)
HTx (*n*)	38	27	16
HTx in patients with PH fixed on inotropes (*n*)	20 (52.6%)	16 (59.3%)	9 (56.2%)
HTx in patients with PH reversible on inotropes (*n*)	18 (47.4%)	11 (40.7%)	7 (43.8%)
30-day mortality in patients with PH fixed on inotropes (*n*)	2 (10%)	2 (12.5%)	1 (11.1%)
30-day mortality in patients with PH reversible on inotropes (*n*)	2 (11.1%)	0 (0%)	0 (0%)

HTx, heart transplantation; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient.

(16 patients with fixed PH with drugs and 11 patients with reversible PH with drugs) and 16 patients (29.1%) in group C (nine patients with fixed PH with drugs and seven patients with reversible PH with drugs) (Table 5). Mortality after HTx was lower in patients with reversible PH by inotropes than in patients with fixed PH despite drugs, before LVAD implantation in groups B and C (0% vs 12.5% and 0% vs 11.1%, respectively) (Table 5). Group A showed slightly higher survival, without statistical significance, in patients with fixed PH despite drugs (90% fixed PH vs 88.9% reversible PH).

4. Discussion

The study showed that TPG and PVR, but not mPAP, are predictive parameters for successful HTx in the case of severe postcapillary PH. In patients with inotropic-dependent end-stage heart failure without significant decrease in PVR and/or TPG after 3–4 days of inotropic support therapy, primary HTx is still not possible and LVAD as a bridge to 'transplantability' is the only option [9]. Survival after HTx is related to the reversibility of PVR and TPG before LVAD. The aetiology of PH also plays a crucial role: our patients can be treated with LVAD because all are affected by a PH secondary to heart disease. In the case of severe right ventricular dysfunction, a biventricular assist device (BVAD) must be implanted [20].

Since 2000, the registry of the International Society for Heart and Lung Transplantation (ISHLT) has acknowledged the linear relationship between PVR and mortality after HTx [21]. However, there is no agreement about the role of TPG and PAP regarding the degree of PH associated with poor prognosis [1,21].

At present, there is also no clear consensus on the best drug available to reverse PH clinically (even during pharmacological tests): inotropes (dobutamine, enoximone and milrinone) and vasodilators (nitroglycerin, sodium nitroprusside, nitric oxide and prostacyclin,) have been used [12–16]. Vasodilators are mostly used but the risk of systemic hypotension in end-stage HF patients, who are candidates for LVAD support, is real. Nitric oxide appears to be safer but in patients with instable haemodynamics, it may have a negative effect due to the risk of pulmonary overflow and oedema. Torre Machos et al. demonstrated that comparable dosages of different inotropes or non-selective vasodilators or prostacyclin can achieve the same effective results in the treatment of patients with secondary severe PH [12].

PH secondary to HF is due to an increase in the venous pressure and so it is typically postcapillary hypertension; treatment of this kind of PH aims to normalise the wedge pressure. For this reason, LVAD implantation plays a role in the

treatment of patients with PH as a bridge to transplantability [5–10] ISHLT guidelines for the care of cardiac transplant candidates recommend LVAD implantation in the case of fixed PH as a bridge to eventual HTx [22]. Inotropes improve the CO and reduce the wedge pressure and, therefore, may test the reversibility of PH. However, the delayed reduction of PVR on the LVAD in patients previously identified as having fixed PH means that the 'fixed' component of PH probably just needs more time to normalise.

All patients were treated with an LVAD and no right ventricular assist device (RVAD) implantation was necessary. On the other hand, some authors believe that PH protects the patient from right ventricular failure after LVAD implantation [20,23]. Low mPAP reflects low right ventricular contractility, according to the results of a Columbia University group [24]. In our study, all patients with the risk of right ventricular failure after LVAD implantation, calculated according to the institutional algorithm, were treated with a BVAD [20]. Consequently, patients with severe right ventricular dysfunction were excluded from the patient population of this study. That it is the correct indication to treat this kind of patient with LVAD (and not BVAD) is confirmed by the absence of right ventricular failure in the postoperative period.

It would be very interesting to analyse patients with fixed PH and mPAP < 25 mm Hg pre-LVAD implantation but, in our study, these patients were few (seven patients) and all had reversible PH.

In our data, group C is the smallest one, the reason probably being that in the case of postcapillary PH, we primarily observe an increase in pulmonary artery pressure proportional to the increase in wedge pressure. At this moment, PVR and TPG are normal, but long-standing wedge pressure elevation leads to an increase in PVR; this elevation determines an increase in pulmonary artery pressure disproportionate to the wedge. The consequence is the increase of TPG also, as the last step.

It is quite clear that unresponsive PH is associated with higher mortality post-transplant than rapidly reversible PH [1–3] and knowing whether PH is reversible or not is crucial. The role of pharmacological therapy to test PH reversibility is essential for decision making. In this study, the mortality after HTx was strictly related to the pre- LVAD implantation value of PVR and TPG. The mPAP has no role in the prediction of survival in these patients.

Our study showed that most changes in pulmonary haemodynamics under inotropic support appear during the first 4 days of treatment with inotropes: in the case of lack of normalisation of the PVR and TPG values, the treatment of choice is LVAD implantation and waiting for delayed reversibility of the PH parameters. In the case of reversibility with inotropic drugs, it is possible to proceed with high urgent listing for HTx.

Since the number of patients with congestive heart failure and secondary PH is increasing, these patients may, in the future, represent a group that will need specific treatment in this regard, for example, VAD support of failing Fontan haemodynamics or of a failing single ventricle. Additional oral administration of drugs to decrease pulmonary hypertension (e.g., sildenafil or bosentan) may be of value in such cases.

The 30-day mortality after HTx in patients with fixed PH before LVAD implantation is higher than in patients with reversible PH, but still comparable with the results recorded in the ISHLT database (30-day survival 90.58%) [25]. Patients with reversible PH were transplanted earlier (389.00 ± 163.554 days) than patients with fixed PH (527.45 ± 289.593 days). Patients with PH existing despite long-term LVAD treatment have at least a similar risk profile. Therefore, the mortality of patients with PH on LVAD or primarily transplanted is also similar. Moreover, fixed PH on LVAD may be a marker for a sicker, high-risk population.

In conclusion, this study shows the importance of TPG and PVR, but not mPAP, as useful criteria in patient selection for HTx versus LVAD implantation. In patients with inotrope-dependent end-stage heart failure and without significant decrease in PVR and/or TPG after 3–4 days, the LVAD is an option to treat PH, waiting for a possible reduction of the PVR or TPG and to bridge patients to transplantability status [9].

4.1. Study limitations

The first limitation of this study is the retrospective nature of the analysis. There was not a protocol-driven management of inotropes. Moreover, it is important to argue that the small number of transplanted patients may mask any true difference in survival between patients with fixed PH and patients with reversible PH, despite medical treatment.

We focussed on pulmonary parameters only, thus dividing our patient population into three probably 'virtual' groups. It could happen that some of the same patients belonged to different groups and the result is three overlapping classes that could make the data difficult to interpret. In our opinion, this was the only way to analyse each parameter separately. Our goal was the analysis of patients with different situations regarding the complex 'pulmonary vascular resistance–right ventricle–left ventricle (end diastolic pressure)' in a quite homogeneous patient population.

This study could suffer from a patient 'overpopulation' but might help in the establishment of pulmonary parameter predictors.

Therefore, despite the fixed relationship between the three analysed parameters, it is well known that in the calculation for both TPG and PVR the wedge pressure measurement is essential but not in the case of mPAP. We studied quantitatively by haemodynamic evaluations what could happen to the three parameters if considered alone in patients under inotropic treatment, following them up to the clinical outcome (despite any patient 'overpopulation'). It was expected that mPAP would not be a predictive factor for the decision making but, in our experience, the grade of variability of the parameters and the time needed for any such variability were not known. Postcapillary PH secondary to HF is characterised by the increase of wedge pressure: for this reason, it was intuitive that TPG and PVR were the main parameters to consider as predictors of reversibility.

In conclusion, the literature data are still few, and a prospective multicentric, randomised controlled trial of aggressive medical therapy versus LVAD therapy would be important, but it is fundamental to remember that the indication for LVAD implantation in our study is based on the patients' clinical condition, and not on their PH.

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References

[1] Delgado JF, Gomez-Sanchez MA, Saenz de la Calzada C, Sanchez V, Escribano P, Hernandez-Afonso J, Tello R, Gomez de la Camara A, Rodriguez E, Rufilanchas JJ. Impact of mild pulmonary hypertension on mortality and pulmonary artery pressure profile after heart transplantation. J Heart Lung Transplant 2001;20(9):942—8.

[2] Kirklin JK, Naftel DC, Bourge RC, McGiffin DC, Hill JA, Rodeheffer RJ, Jaski BE, Haptman PJ, Weston M, White-Williams C. Evolving trends in risk profiles and causes of death after heart transplantation: a ten-year multi-institutional study. J Thorac Cardiovasc Surg 2003;125(4):881—90.

[3] Goland S, Czer LS, Kass RM, De Robertis MA, Mirocha J, Coleman B, Capelli C, Raissi S, Cheng W, Fontana G, Trento A. Pre-existing pulmonary hypertension in patients with end-stage heart failure: impact on clinical outcome and hemodynamic follow-up after orthotopic heart transplantation. J Heart Lung Transplant 2007;26(4):312—8.

[4] Hatano SST. Primary pulmonary hypertension. Geneva: World Health Organization; 1975.

[5] Adamson RM, Dembitsky WP, Jaski BE, Daily PO, Moreno R, Kim JC, Sono J, Akasaka T, Hoagland PM, Gordon JB. Left ventricular assist device support of medically unresponsive pulmonary hypertension and aortic insufficiency. ASAIO J 1997;43(4):365—9.

[6] Gallagher RC, Kormos RL, Gasior T, Murali S, Griffith BP, Hardesty RL. Univentricular support results in reduction of pulmonary resistance and improved right ventricular function. ASAIO 1991;37:287—8.

[7] Liden H, Haraldsson A, Ricksten SE, Kjellman U, Wiklund L. Does pretransplant left ventricular assist device therapy improve results after heart transplantation in patients with elevated pulmonary vascular resistance? Eur J Cardiothorac Surg 2009;35(6):1029—34 [Discussion 34—5].

[8] Martin J, Siegenthaler MP, Friesewinkel O, Fader T, van de Loo A, Trummer G, Berchtold-Herz M, Beyersdorf F. Implantable left ventricular assist device for treatment of pulmonary hypertension in candidates for orthotopic heart transplantation—a preliminary study. Eur J Cardiothorac Surg 2004;25(6):971—7.

[9] Potapov EV, Weng Y, Jurmann M, Lehmkuhl H, Hetzer R. Bridging to transplantability with a ventricular assist device. J Thorac Cardiovasc Surg 2005;130(3):930.

[10] Zimpfer D, Zrunek P, Sandner S, Schima H, Grimm M, Zuckermann A, Wolner E, Wieselthaler G. Post-transplant survival after lowering fixed pulmonary hypertension using left ventricular assist devices. Eur J Cardiothorac Surg 2007;31(4):698—702.

[11] Costanzo MR, Augustine S, Bourge R, Bristow M, O'Connell J, Driscoll D, Rose E. Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. Circulation 1995;92(December (12)):3593—612.

[12] Torres Macho J, Delgado Jimenez JF, Sanz Salvo J, Gonzalez Mansilla A, Sanchez Sanchez V, Gamez Diez S, Escribano Subias P, Saenz de la Calzada C. Effect of different pharmacologic agents to reverse severe pulmonary hypertension among end-stage heart failure patients. Transplant Proceed 2009;41:2477—9.

[13] Givertz MM, Hare JM, Loh E, Gauthier DF, Colucci WS. Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: a rapid test for reversibility of pulmonary hypertension. J Am Coll Cardiol 1996;28(7):1775—80.

[14] Radovancevic B, Vrtovec B, Thomas CD, Croitoru M, Myers TJ, Radovancevic R, Khan T, Massin EK, Frazier OH. Nitric oxide versus prostaglandin E1 for reduction of pulmonary hypertension in heart transplant candidates. J Heart Lung Transplant 2005;24:690—5.

[15] Klotz S, Wenzelburger F, Stypmann J, Welp H, Drees G, Schmid C, Scheld H. Reversible pulmonary hypertension in heart transplant candidates: to transplant or not to transplant. Ann Thorac Surg 2006;82(November (5)):1770—3.

[16] Von Scheidt W, Costard-Jaeckle A, Stempfle HU, Deng M, Schwaab B, Haaff B, Naegele H, Nohacsi P, Trautnitz M. Prostaglandin E1 testing in heart failure-associated pulmonary hypertension enables transplantation: the PROPHET study. J Heart Lung Transplant 2006;25(September (9)):1070—6.

[17] Stevenson LW, Pagani FD, Young JB, Jessup M, Miller L, Kormos RL, Naftel DC, Ulisney K, Desvigne-Nickens P, Kirklin JK. INTERMACS profiles of advanced heart failure the current picture. J Heart Lung Transplant 2009;28(6):535—41.

[18] Kormos RL, Gasior TA, Kawai A, Pham SM, Murali S, Hattler BG, Griffith. Transplant candidate's clinical status rather than right ventricular function defines need for univentricular versus biventricular support. J Thorac Cardiovasc Surg 1996;111(4):773—82 [Discussion 782—3].

[19] Potapov EV, Henning F, Wagner FD, Volk HD, Sodian R, Hausmann H, Lehmkuhl HB, Hetzer R. Natriuretic peptides and e-selectin as predictors of acute deterioration in patients with inotrope-dependent heart failure. Eur J Cardiothorac Surg 2005;27(5):899—905.

[20] Potapov EV, Stepanenko A, Dandel M, Kukucka M, Lehmkuhl HB, Weng Y, Hennig F, Krabatsch T, Hetzer R. Tricuspid incompetence and geometry of the right ventricle as predictors of right ventricular function after implantation of a left ventricular assist device. J Heart Lung Transplant 2008;27(12):1275—81.

[21] Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report-2000. J Heart Lung Transplant 2000;19(10):909—31.

[22] Gronda E, Bourge RC, Costanzo MR, Deng M, Mancini D, Martinelli L, Torre-Amoine G, O'Hara ML, Chambers S. Heart rhythm considerations in heart transplant candidates and considerations for ventricular assist devices: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates — 2006. J Heart Lung Transplant 2006;25(9):1043—56.

[23] Ochiai Y, McCarthy PM, Smedira NG, Banbury MK, Navia JL, Feng J, Hsu AP, Yeager ML, Buda T, Hoercher KJ, Howard MW, Takagaki M, Doi K, Fukamachi K. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. Circulation 2002;106(September (12 Suppl. 1)):I198—202.

[24] Levin HR, Burkhoff D, Chen J, Oz MC, Packer M, Rose EA. Right ventricular performance (but not outflow resistance) is a major pre-operative determinant of right heart failure in patients with chronic heart failure who receive a left ventricular assist device. J Am Coll Cardiol 1994;1A—484A [Abstract 838—6].

[25] Taylor DO, Stehlik J, Edwards LB, Aurora P, Christie J, Dobbels F, Kirk R, Kucheryavaya A, Rahmel A, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: twenty-sixth Official adult Heart Transplant Report-2009. J Heart Lung Transplant 2009;28:1007—22.