Effect of pulmonary vascular resistance before left ventricular assist device implantation on short- and long-term post-transplant survival

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ABSTRACT

Objectives: Pulmonary hypertension is often considered a contraindication to orthotopic heart transplantation. Left ventricular assist device support may improve pulmonary hypertension by unloading the left ventricle, making patients eligible for transplantation. We sought to investigate the effect of continuous-flow left ventricular assist device support on pulmonary hypertension and compare post-transplantation outcomes in patients with preexisting pulmonary hypertension.

Methods: Between March 2004 and December 2013, 256 potential orthotopic heart transplantation candidates underwent continuous-flow left ventricular assist device implantation at Columbia University. Preimplantation right heart catheterization data were available for 227 patients. Patients were divided into 2 groups on the basis of preimplantation pulmonary vascular resistance: low (<5 Wood units) (n = 182) and high (≥5 Wood units) (n = 45). Postimplantation and post-transplantation outcomes were compared between the groups.

Results: Pulmonary vascular resistance in the high resistance group decreased significantly during left ventricular assist device support ($P < .001$). Post-transplantation in-hospital mortality was significantly higher in patients with high vascular resistance ($P < .05$). However, 3-year survival after transplantation was similar between groups (85.0% and 79.0% for low and high vascular resistance, respectively; $P = .45$).

Conclusions: Continuous-flow left ventricular assist device therapy reduced pulmonary vascular resistance. Subsequent orthotopic heart transplantation in patients with significantly elevated pulmonary vascular resistance resulted in higher in-hospital mortality but similar 3-year survival. (J Thorac Cardiovasc Surg 2015;150:1352-61)

Hemodynamic parameters pre- and post-LVAD support.

Central Message

Heart transplantation in patients with pHTN results in a good outcome after LVAD support.

Perspective

CF-LVADs can reverse pHTN and render patients with heart failure with severe pHTN eligible for heart transplantation with reasonable survival during support. Although in-hospital mortality is higher, long-term post-transplant survival in these patients is comparable to that in patients with less PVR.

See Editorial Commentary page 1362.

Supplemental material is available online.

Pulmonary hypertension (pHTN) refractory to medical treatment is often considered a contraindication to orthotopic heart transplantation (OHT) because of an increased

risk of right ventricular heart failure in the immediate post-operative period.¹ However, secondary pHTN has developed in approximately two thirds of transplant candidates at the time of evaluation.² It is well known that in certain cases pHTN can be reversed with medical treatment (eg, sodium nitroprusside, milrinone, inhaled nitric oxide, and prostaglandin I₂ inhibitor), and these patients are

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Abbreviations and Acronyms

CF	= continuous flow
CO	= cardiac output
LVAD	= left ventricular assist device
OHT	= orthotopic heart transplantation
PAP	= pulmonary artery pressure
PCWP	= pulmonary capillary wedge pressure
pHTN	= pulmonary hypertension
PVR	= pulmonary vascular resistance
TPG	= transpulmonary pressure gradient
WU	= Wood units

considered to have reversible pHTN. In contrast, some cases cannot be readily reversed by these pharmacologic treatments and are considered to have fixed or irreversible pHTN.³ The physiologic mechanism underlying reversibility has not been fully elucidated.

Previous studies have demonstrated that left ventricular assist device (LVAD) implantation can decrease pulmonary vascular resistance (PVR) by unloading the left ventricle, reducing filling pressures, and augmenting cardiac output (CO), and can therefore render even certain patients with pHTN refractory to medical treatment eligible for OHT.⁴⁻⁹ However, these were mostly small studies that combined various types of LVAD devices used (pulsatile and continuous flow [CF]). Given the shortage of donor organs, it is particularly important to investigate whether contemporary LVAD implantation can reverse pHTN, to what extent if it does so, and whether such reversal affects patients' eligibility for heart transplantation and the post-transplant outcomes. Therefore, we investigated the effect of CF-LVAD support on the reversal of pHTN and analyzed post-OHT outcomes in patients with an LVAD and preexisting elevated PVR.

MATERIALS AND METHODS

From March 2004 to December 2013, 340 patients at Columbia University underwent CF-LVAD insertion. Of these patients, 256 were potential heart transplantation candidates. Pre-LVAD right heart catheterization data were available for analysis in 227 of 256 patients. Clinical records of those 227 patients, including demographics, right heart catheterization data (pre-LVAD, post-LVAD, and post-OHT), intraoperative data regarding LVAD insertion and OHT, and postoperative data, were retrospectively reviewed. The Columbia University Institutional Review Board approved this study. The requirement for informed consent was waived because of the retrospective nature of the study.

Right Heart Catheterization

Hemodynamic variables, including systemic blood pressure, central venous pressure (mm Hg), pulmonary artery pressure (PAP) (mm Hg), mean pulmonary capillary wedge pressure (PCWP) (mm Hg), transpulmonary pressure gradient (TPG) (mm Hg, calculated as mean PAP-PCWP), and CO (L/min) were recorded. CO and mixed venous oxygen saturation were obtained using a continuous CO pulmonary artery catheter and confirmed using measured oxygen tension and manual calculation of

CO. PVR (Wood units [WU]) was calculated as TPG/CO . Right ventricular stroke work index ($g \cdot m/m^2/beat$) was calculated as stroke volume index $\times$ (mean PAP-central venous pressure) $\times$ 0.0136. When PVR was greater than 3.0 and the patient's hemodynamic state was deemed to tolerate it, a pulmonary vasodilator challenge was performed using sodium nitroprusside, milrinone, or inhaled nitric oxide. If pulmonary vasodilator challenge was performed, the hemodynamic parameters obtained under those medications were used for this analysis, because those were considered to represent intrinsic pulmonary vascular elasticity. Pre-LVAD hemodynamic variables were acquired immediately before LVAD implantation. Post-LVAD hemodynamic variables were acquired at a time chosen at the discretion of the heart failure cardiologists. Post-OHT right heart catheterizations were performed at 1, 2, 4, and 6 weeks; 2, 3, and 6 months; and 1, 2, 3, 4, and 5 years after OHT for all survivors. Patients were divided into 2 groups according to their postpharmacologic challenge PVR scores. A total of 182 patients had low PVR (<5 WU), and 45 patients had high PVR (≥ 5 WU).

Management of Pulmonary Hypertension

On the basis of our institutional criteria, patients with PVR 6 WU or more despite pulmonary vasodilators are excluded from OHT. These patients receive pulmonary vasodilator therapy and, if indicated, undergo LVAD implantation as destination therapy. During LVAD support, vasodilator therapy is continued, and PVR is monitored with serial right heart catheterization studies. If the PVR is decreased, the patient is reconsidered for OHT. PVR continues to be monitored while the patient is on the waiting list. Patients with low pre-LVAD PVR also underwent post-LVAD right heart catheterization if right ventricular dysfunction or device thrombosis developed. Donor hearts for these patients are selected with special attention to size and sex matching.

Statistical Analysis

Categorical variables are presented as proportions, and continuous variables are expressed as the mean $\pm$ standard deviation for parametric analysis and as the median with interquartile range for nonparametric analysis. Differences between groups were analyzed using Pearson's chi-square test for categorical variables and the Kruskal-Wallis test for nonparametric analysis of continuous and ordinal variables. Actuarial survival during LVAD support and 3-year survival after OHT were assessed by Kaplan-Meier analysis, and the log-rank test was used for comparisons between groups. Univariate logistic regression was used to analyze the potential factors affecting early survival, and variables tested in the univariate analysis with P value less than .2 were entered into the multivariate logistic regression. The statistical analyses were performed with STATA 13.1 (StataCorp LP, College Station, Tex).

RESULTS

Patient Characteristics and Hemodynamic Data before Left Ventricular Assist Device Insertion

The patients' characteristics before LVAD insertion showed that patients in the high PVR group were more likely to be female ($P < .05$) and to have lower body surface area ($P < .01$) than the patients in the low PVR groups (Table 1). There was no statistical difference in heart failure cause, medical history, preoperative dependence on mechanical ventilation, or preoperative need for inotropes or intra-aortic balloon pump between groups. Patients with high PVR were more likely to have undergone mitral or tricuspid valve surgery ($P < .01$). The use of preoperative

TABLE 1. Pre-left ventricular assist device patient characteristics and hemodynamic data

Variables	All patients	Low PVR	High PVR	P value
Basic patient characteristics				
Patients (n)	227	182	45	
Age (y)	53.4 ± 12.5	53.3 ± 12.5	53.8 ± 12.3	.82
Female sex	41 (18.1%)	28 (15.4%)	13 (28.9%)	.035
BMI	26.4 ± 5.3	26.5 ± 5.3	26.2 ± 5.4	.7
BSA	1.97 ± 0.3	1.99 ± 0.26	1.87 ± 0.25	.005
Cause of HF				
ICM	83 (36.6%)	68 (37.4%)	15 (33.3%)	.39
DCM	129 (56.8%)	104 (57.1%)	25 (55.6%)	
Others	15 (6.6%)	10 (5.5%)	5 (11.1%)	
CAD	89 (39.2%)	73 (40.1%)	16 (35.6%)	.58
MI	73 (32.2%)	59 (32.4%)	14 (31.1%)	.87
CVA	27 (11.9%)	18 (9.9%)	9 (20.0%)	.06
DM	75 (33.0%)	64 (35.2%)	11 (24.4%)	.17
HTN	104 (45.8%)	81 (44.5%)	23 (51.1%)	.43
PVD	15 (6.6%)	10 (5.5%)	5 (11.1%)	.17
Smoking	93 (41.0%)	74 (40.7%)	19 (42.2%)	.85
COPD	17 (7.5%)	11 (6.0%)	6 (13.3%)	.1
Preoperative inotropes	200 (88.1%)	159 (87.4%)	41 (91.1%)	.49
Preoperative MCS	22 (9.7%)	18 (9.9%)	4 (8.9%)	.84
Preoperative IABP	58 (25.6%)	48 (26.4%)	10 (22.2%)	.57
Preoperative ventilator support	7 (3.2%)	6 (3.3%)	1 (2.5%)	.71
Previous cardiac surgery	42 (18.5%)	29 (15.9%)	13 (28.9%)	.045
CABG	34 (15.0%)	27 (14.8%)	7 (15.6%)	.9
Mitral valve	13 (5.7%)	6 (3.3%)	7 (15.6%)	.002
Tricuspid valve	3 (1.3%)	0 (0.0%)	3 (6.7%)	.0001
Aortic valve	4 (1.8%)	4 (2.2%)	0 (0.0%)	.32
Congenital	2 (0.90%)	1 (0.6%)	1 (2.2%)	.28
Hemodynamic data				
LVEF (%)	15.2 ± 6.1	15.2 ± 6.3	15.2 ± 5.2	.7
Mean PAP (mm Hg)	36.2 ± 10.4	34.7 ± 9.8	42.3 ± 10.4	.0001
PCWP (mm Hg)	24.1 ± 8.5	24.3 ± 8.7	23.0 ± 7.9	.56
TPG (mm Hg)	12.1 ± 6.5	10.3 ± 5.2	19.2 ± 6.4	.0001
CO (L/min)	3.30 ± 1.02	3.50 ± 0.98	2.57 ± 0.83	.0001
PVR (wood units)	3.59 ± 2.23	2.71 ± 1.12	7.13 ± 2.09	.0001
RVSWI (g·m/m ² /beat)	6.98 ± 3.55	7.00 ± 3.54	6.93 ± 3.61	.81

Data are expressed as means ± standard deviations or as n (%). Differences were considered significant at $P < .05$, and these values are listed in bold. *BMI*, Body mass index; *BSA*, body surface area (m²); *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CO*, cardiac output; *COPD*, chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *DCM*, dilated cardiomyopathy; *DM*, diabetes mellitus; *HF*, heart failure; *HTN*, hypertension; *IABP*, intra-aortic balloon pump; *ICM*, ischemic cardiomyopathy; *LVEF*, left ventricular ejection fraction; *MCS*, mechanical circulatory support; *MI*, myocardial infarction; *PAP*, pulmonary artery pressure; *PCWP*, pulmonary capillary wedge pressure; *PVD*, peripheral vascular disease; *PVR*, pulmonary vascular resistance; *RVSWI*, right ventricular stroke work index; *TPG*, transpulmonary pressure gradient.

mechanical circulatory support was not different between groups ($P = .84$).

There was a significant difference in PVR between groups (2.71 ± 1.12 WU and 7.13 ± 2.09 WU for the

low PVR and high PVR groups, respectively, $P < .001$). The high PVR group included patients with severe pHTN, ranging from 5.07 to 14.38 WU. In the high PVR group, the mean PAP was significantly higher than in the low PVR group (34.7 ± 9.8 mm Hg and 42.3 ± 10.4 mm Hg for the low PVR and high PVR groups, respectively, $P < .001$). TPG was also higher (10.3 ± 5.2 mm Hg and 19.2 ± 6.4 mm Hg for the low PVR and high PVR groups, respectively, $P < .001$). In contrast, CO was significantly lower in the high PVR group than in the low PVR group (3.50 ± 0.98 L/min and 2.57 ± 0.83 L/min for the low PVR and high PVR groups, respectively, $P < .001$). There was no statistical difference in PCWP ($P = .56$) or right ventricular stroke work index ($P = .81$) between groups.

Intraoperative and Postoperative Data at Left Ventricular Assist Device Implantation

CF-LVADs used were the HeartMate II (Thoratec Corp, Pleasanton, Calif), HeartWare (HeartWare Inc, Framingham, Mass), DuraHeart (Terumo Heart Inc, Ann Arbor, Mich), DeBakey (MicroMed Cardiovascular, Inc, Houston, Tex), VentrAssist (Ventracor Limited, Chatswood, Australia), or Jarvik 2000 (Jarvik Heart, Inc, New York, NY). There was no statistical difference in cardiopulmonary bypass time or the need for aortic crossclamp between groups (Table 2). The number of patients for whom each type of LVAD was implanted is summarized in Table 2. The HeartMate II device was used for most patients (81.1%), although a higher rate of use of the HeartWare device in the high PVR group was noted (7.1% and 15.6% for the low PVR and high PVR groups, respectively, $P < .01$). Concomitant valve procedures were performed as follows: aortic valve procedures in 32 patients (14.1%), mitral valve procedures in 26 patients (11.5%), and tricuspid procedures in 55 patients (24.2%). There was no statistical difference in the proportion of patients who underwent concomitant valve procedures between groups.

Length of intensive care unit stay, in-hospital mortality, and incidence of adverse events were comparable between groups after LVAD implantation. Right ventricular assist device implantation was needed in 7.7% of the low PVR group and 4.4% of the high PVR group ($P = .45$). One-year survival during LVAD support was 81.9% and 90.3% in the low PVR and high PVR groups, respectively ($P = .16$). Figure 1 shows the Kaplan–Meier survival curve during LVAD support (transplant recipients were censored). There was no difference in survival during LVAD support between groups ($P = .14$), and there was no statistical difference in the percentage of patient outcomes for OHT, cardiac recovery, or ongoing LVAD support ($P = .24$). In the low PVR group, 120 patients (65.9%) underwent heart transplant, 2 patients (1.1%) recovered and underwent LVAD explant, and 30 patients (16.5%) were on the waiting list at the time of last

TABLE 2. Intraoperative and postoperative data for left ventricular assist device insertion

Variables	All patients (n = 227)	Low PVR (n = 182)	High PVR (n = 45)	P value
Intraoperative data				
CPB time (min)	89.5 ± 50.3	88.8 ± 52.0	92.5 ± 42.8	.36
Aortic crossclamp	39 (17.2%)	29 (15.9%)	10 (22.2%)	.32
Device type				
HeartMate II (Thoratec Corp, Pleasanton, Calif)	184 (81.1%)	151 (83.0%)	33 (73.3%)	.009
HeartWare (HeartWare Inc, Framingham, Mass)	20 (8.8%)	13 (7.1%)	7 (15.6%)	
VentrAssist (Ventricor Limited, Chatswood, Australia)	8 (3.5%)	4 (2.2%)	4 (8.9%)	
DeBakey (MicroMed Cardiovascular, Inc, Houston, Tex)	6 (2.6%)	6 (3.3%)	0 (0.0%)	
Dura Heart (Terumo Heart Inc, Ann Arbor, Mich)	8 (3.5%)	8 (4.4%)	0 (0.0%)	
Jarvik 2000 (Jarvik Heart, Inc, New York, NY)	1 (0.4%)	0 (0.0%)	1 (2.2%)	
Concomitant procedure				
Aortic valve	32 (14.1%)	24 (13.2%)	8 (17.8%)	.43
Mitral valve	26 (11.5%)	18 (9.9%)	8 (17.8%)	.14
Tricuspid valve	55 (24.2%)	46 (25.3%)	9 (20.0%)	.46
Postoperative data				
iNO use	82 (36.1%)	60 (33.0%)	22 (48.9%)	.046
ICU stay (d) [IQR]	7 [5-11]	7 [5-10]	7 [6-12]	.18
In-hospital mortality	15 (6.6%)	13 (7.1%)	2 (4.4%)	.51
CVA	12 (5.3%)	9 (5.0%)	3 (6.7%)	.64
HD/CVVH	22 (9.7%)	20 (11.0%)	2 (4.4%)	.18
Tracheotomy	6 (2.6%)	4 (2.2%)	2 (4.4%)	.4
RVAD support	16 (7.1%)	14 (7.7%)	2 (4.4%)	.45
Bleeding/take-back	43 (18.9%)	37 (20.3%)	6 (13.3%)	.28
Bridge to				
OHT	150 (66.1%)	120 (65.9%)	30 (66.7%)	.24
Recovery	2 (0.9%)	2 (1.1%)	0 (0.0%)	
Ongoing support	42 (18.5%)	30 (16.5%)	12 (26.7%)	

Differences were considered significant at $P < .05$, and these values are listed in bold. CPB, Cardiopulmonary bypass; CVA, cerebrovascular accident; HD/CVVH, hemodialysis/continuous veno-venous hemofiltration; ICU, intensive care unit; iNO, inhaled nitric oxide; IQR, interquartile range; OHT, orthotopic heart transplantation; PVR, pulmonary vascular resistance; RVAD, right ventricular assist device.

follow-up. In the high PVR group, 30 patients (66.7%) underwent heart transplant and 12 patients (26.7%) were on LVAD support. In the high PVR group, 1 patient died of respiratory arrest, 1 patient died of cerebrovascular accident, and 1 patient died of multiorgan failure after device exchange.

Changes Over Time in Pulmonary Vascular Resistance

After LVAD implantation, PVR in the high PVR group decreased significantly (7.13 ± 2.09 WU to 2.82 ± 1.46 WU, $P < .001$) to a level similar that in the low PVR group (2.70 ± 1.20 WU, $P = .91$) and remained low after heart transplantation (Figure 2). No patient in the high PVR group had the PVR increased after the LVAD was implanted. Figure E1 shows the change in each hemodynamic variable pre- and post-LVAD. In the high PVR group, mean PAP, PCWP, and TPG were reduced significantly, and CO improved. Although the median interval between the LVAD implantation and the post-LVAD hemodynamic measurement was lower in the high PVR group, there was no statistical difference ($P = .3$) (363 days [interquartile range, 140-566] in the low PVR group and 152 days [interquartile range, 96-438] in the high PVR group). The prevalence of

chronic pulmonary vasodilator treatment (eg, sildenafil or tadalafil) at the time of the post-LVAD hemodynamic measurement was 19% and 40% in the low PVR and high PVR groups, respectively ($P = .17$).

Intraoperative and Postoperative Data at Orthotopic Heart Transplantation Surgery

For 150 patients who underwent heart transplant, donor data (age, ABO compatibility, and donor-recipient weight ratio) and intra- and postoperative data were analyzed (Table 3). There was no statistical difference in donor characteristics between groups. For those who underwent heart transplantation, the duration of LVAD support was not significantly different between groups (median, 211 and 229.5 days for low PVR and high PVR groups, respectively, $P = .53$). Cardiopulmonary bypass time and donor heart ischemic time were similar between groups. There was no significant difference in the incidence of major complications, such as cerebrovascular accident, renal failure requiring hemodialysis, and respiratory failure between groups. The mean follow-up period after OHT was 3.5 ± 2.4 years (range, 1 month to 9.3 years). In-hospital mortality after OHT was significantly higher in the high PVR than in

FIGURE 1. Kaplan–Meier survival curve during LVAD support. Survival at each time point is shown with 95% confidence interval in the table. *CI*, Confidence interval; *LVAD*, left ventricular assist device; *PVR*, pulmonary vascular resistance.

the low PVR group (5.8% and 20.7% in the low PVR and high PVR groups, respectively, $P < .05$). Of 6 deaths in the high PVR group, 4 patients died as a result of primary graft failure (defined as the need for mechanical circulatory support in the immediate post-transplant period). All 4 patients needed a biventricular assist device. There was only 1 patient who died of primary graft failure in the low PVR group. There was no statistical difference in the dosage of post-OHT inotropes, blood transfusions, and the length of hospital stay between groups (data not shown). All causes of post-OHT mortality during follow-up are shown in Table E1. The Kaplan–Meier 3-year survival curve after OHT is shown in Figure 3. The log-rank test showed no statistical difference in survival between groups ($P = .26$). The survival at 3 years post-OHT was 85.0% and 79.0% for the low PVR and high PVR groups, respectively ($P = .45$).

Univariate and multivariate logistic regression analyses were performed for 30-day post-OHT survival (Table 4). The multivariate analysis revealed that pre-LVAD PVR 5 or greater was strongly associated with early mortality (odds ratio, 5.99; 95% confidence interval, 1.25-28.9;

$P < .05$). Post-LVAD PVR was not associated with short-term mortality after OHT.

DISCUSSION

The present study is a retrospective, single-institution study on patients with end-stage heart failure who underwent LVAD insertion that especially focused on preexisting pHTN. To our knowledge, this is the largest study ever reported with regard to the effects of preexisting pHTN on OHT outcomes in patients bridged with CF-LVAD. In this study, we found 3 interesting findings: (1) PVR decreased after LVAD implantation even in patients with severe pHTN refractory to pulmonary vasodilators; (2) despite the improvement in PVR, patients with high PVR still had higher early mortality; and (3) the long-term survival (mean follow-up 3.5 years) was not different among groups.

Secondary pHTN due to an elevation in left ventricular filling pressure and subsequent increase in PVR develop in approximately two thirds of patients with heart failure and reduced ejection fraction.² Long-standing elevation of PCWP results in pulmonary vascular disease with vasoconstriction and remodeling of the pulmonary arterial bed,

FIGURE 2. Chronologic change in PVR after LVAD insertion. Numbers in the table represent the number of patients who underwent right heart catheterization at each time point. *LVAD*, Left ventricular assist device; *OHT*, orthotopic heart transplantation; *PVR*, pulmonary vascular resistance.

which manifests as increased PVR and TPG. This phenomenon was also shown in our study. Pre-LVAD right heart catheterization data showed no statistical difference in PCWP, regardless of the severity of PVR. This observation suggests that once heart failure reached the end stage, the elevation of PAP is caused not by further elevation of PCWP but by the elevation of TPG secondary to pulmonary vascular remodeling. The presence of elevated PVR is

TABLE 3. Intraoperative and postoperative data for orthotopic heart transplantation

Variables	All patients (n = 150)	Low PVR (n = 120)	High PVR (n = 30)	P value
Donor data				
Age	29.7 ± 9.5	29.2 ± 9.2	31.8 ± 11.0	.38
ABO identical	88.5%	89.0 %	86.7%	.72
ABO compatible	11.5%	11.0%	13.3%	
Donor/recipient weight	0.99 ± 0.17	0.98 ± 0.16	1.03 ± 0.18	.19
Recipient data				
LVAD duration (d) [IQR]	219 [110-359]	211 [105.5-356]	229.5 [134-397]	.53
Intraoperative data				
CPB time (min)	176 ± 54	174 ± 47	184 ± 74	.90
Ischemic time (min)	189 ± 51	188 ± 50	192 ± 54	.80
Postoperative data				
iNO use	49 (33.8%)	37 (31.1%)	13 (44.8%)	.16
In-hospital mortality	13 (8.7%)	7 (5.8%)	6 (20.0%)	.014
CVA	8 (5.4%)	6 (5.1%)	2 (6.7%)	.73
HD/CVVH	24 (16.2%)	19 (16.1%)	5 (16.7%)	.94
Tracheotomy	10 (6.8%)	8 (6.8%)	2 (6.7%)	.98
Bleeding	32 (21.6%)	25 (21.2%)	7 (23.3 %)	.80
Primary graft failure	12 (8.1%)	8 (6.8%)	4 (13.3%)	.24

Differences were considered significant at $P < .05$, and these values are listed in bold. *CPB*, Cardiopulmonary bypass; *CVA*, cerebrovascular accident; *HD/CVVH*, hemodialysis/continuous veno-venous hemofiltration; *iNO*, inhaled nitric oxide; *IQR*, interquartile range; *LVAD*, left ventricular assist device; *PVR*, pulmonary vascular resistance; *ABO*, blood type.

FIGURE 3. Kaplan–Meier survival curve after heart transplantation. Survival at each time point is shown with 95% confidence interval in the table. *CI*, Confidence interval; *PVR*, pulmonary vascular resistance.

found in approximately one third of patients with heart failure with reduced ejection fraction and is often associated with mortality and morbidity.¹⁰

Secondary pHTN can be treated by pulmonary vasodilators, such as nitroglycerine, prostaglandins, milrinone, sildenafil, and inhaled nitric oxide. These pharmacologic agents have improved pulmonary hemodynamics and outcomes of OHT.^{11–14} However, pHTN may not be readily reversible and may even be irreversible by pharmacologic treatment, and for patients with progressive, decompensated heart failure, long-term administration of vasodilators are of limited use because of the risk of systemic hypotension. OHT is the most effective therapeutic alternative for end-stage heart failure. However, OHT in the patients with fixed pHTN is contraindicated because of unacceptably high risks of right ventricular failure and the associated high mortality rate.¹⁵ Current guidelines recommend that PVR greater than 5 WU, indexed PVR greater than 6 WU/m², or TPG greater than 16 to 20 mm Hg, despite an aggressive challenge with 1 or more vasodilators or inotropic agents, represents a relative contraindication to OHT.¹⁶

LVAD therapy is one treatment option for pHTN associated with heart failure. By unloading the left ventricle, it reduces the postcapillary downstream pressure, and, with time, it can lower TPG and PVR. In the current study, we found that LVAD support reduced PVR significantly. After LVAD insertion, PVR in the high PVR group decreased to a level comparable to that in the low PVR group, suggesting that LVAD can reverse even severe pHTN refractory to medical treatment. PVR remained low even after OHT in survivors. The long-term survival after OHT was also comparable, regardless of pHTN severity. This observation was consistent with previous studies.^{4–7} Mikus and colleagues⁴ reported a significant reduction of mean PAP, TPG, and PVR in 27 patients with preexisting fixed pHTN with LVAD support. Etz and colleagues⁵ also showed a similar reduction of PVR in 10 patients with severe pHTN refractory to medical treatment undergoing LVAD insertion with no significant increase in PAP, TPG, or PVR after the heart transplantation.

Although the time interval between LVAD implantation and post-LVAD hemodynamic measurement in our study is variable, the PVR in the high PVR group decreased as

TABLE 4. Univariate and multivariate logistic regression analyses of the short-term survival post-orthotopic heart transplantation

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.03	0.96-1.10	.44			
Sex (male)	1.40	0.16-12.2	.76			
BMI	0.92	0.78-1.08	.30			
ICM	0.76	0.14-4.06	.75			
COPD	2.2	0.24-20.1	.49			
HTN	3.05	0.57-16.2	.19	2.86	0.52-15.7	.23
HeartMate II (vs others)	0.48	0.09-2.64	.40			
Preoperative MCS	1.98	0.22-18.0	.54			
LVAD support duration	1.002	0.99-1.00	.10	1.00	0.99-1.00	.72
Interval between post-LVAD RHC and OHT	1.006	0.99-1.01	.11	1.00	0.99-1.02	.35
Pre-LVAD PVR >5	6.00	1.26-28.4	.02	5.99	1.25-28.9	.03
Smoking	1.88	0.40-8.70	.42			
Post-LVAD PVR >3	0.58	0.05-6.35	.65			

Differences were considered significant at $P < .05$, and these values are listed in bold. *BMI*, Body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *HTN*, hypertension; *ICM*, ischemic cardiomyopathy; *LVAD*, left ventricular assist device; *MCS*, mechanical circulatory support; *OHT*, orthotopic heart transplantation; *OR*, odds ratio; *PVR*, pulmonary vascular resistance; *RHC*, right heart catheterization.

early as 37 days post-LVAD implantation. Zimpfer and colleagues⁸ reported important findings regarding time required post-LVAD implantation to see a reduction in PVR. They analyzed hemodynamic variables pre- and post-LVAD implantation (3 days and 6 weeks post-LVAD) in 35 patients with pHTN refractory to medical treatment. They found a significant reduction in PVR (from 5.1 pre-LVAD to 2.9 at the 3-day follow-up and to 2.0 at the 6-week follow-up) after LVAD implantation. Mikus and colleagues⁴ reported that the reduction in PVR occurs in the first 6 months of LVAD support and that longer support does not add any effect on pHTN. These data, including ours, suggest that the reduction in PVR after LVAD implantation may be seen in early-stage post-LVAD.

One of the unique aspects of this study is the severity of pHTN. We have been aggressive in the management of end-stage heart failure and have bridged patients with markedly elevated PVR to OHT. In our study, 66.7% of patients with pre-LVAD PVR 5 WU or greater reached OHT after a support interval that was comparable to that in patients with lower PVR. Post-OHT 3-year survival of these patients was 79.0%, similar to survival of patients with lower PVR. These numbers are consistent with previous reports regarding OHT outcomes for patients bridged to transplantation with or without preexisting pHTN.^{17,18}

In our study, in-hospital mortality of the high PVR group was 3-fold higher than in the low PVR group, and

pre-LVAD PVR 5 or greater was a potent predictor of early mortality after OHT. All post-OHT mortality in the high PVR group occurred while the patients were in the hospital. Alba and colleagues¹⁹ also reported a higher peritransplant mortality in the pre-LVAD fixed pHTN group than in the nonfixed pHTN group (18% vs 0%). Torre-Amione and colleagues²⁰ reported on 9 patients with heart failure with secondary pHTN (TPG >15 mm Hg) who underwent LVAD implantation. After LVAD support, the TPG in these patients decreased significantly and 1-year Kaplan-Meier survival curve for OHT was similar to that in patients with pre-LVAD TPG less than 15 mm Hg. However, there was 1 early mortality (11%) due to primary graft failure in the high TPG group. Torre-Amione and colleagues also conducted an analysis of the data obtained from the Organ Procurement and Transplantation Network database, which is a large multi-institutional cohort. Of note, 30-day mortality was significantly higher in patients with elevated TPG (13.2 % vs 6.7%) than in those with lower TPG. One of the possible reasons for the higher early mortality in the high PVR group is that although PVR decreases with the aid of LVAD support, reversal of pulmonary vascular remodeling is heterogeneous or incomplete, and the pulmonary arterioles that have not been reverse remodeled may be susceptible to early postoperative insults, such as myocardial ischemia, metabolic acidosis, hypoxemia, or inflammatory response imposed by cardiopulmonary bypass, infection, or blood transfusion. Although PVR in the high PVR group was reduced significantly with LVAD support (mean, 7.1-2.8 WU) to a level comparable to that in the low PVR group, it is speculated that in a subset of patients, PVR might not have reduced to the level that the right ventricle is able to eject blood against. It is well known that the normal thin-wall right ventricle is exquisitely afterload-sensitive and cannot tolerate abrupt increases in afterload, even with mild pHTN.²¹ However, our study failed to demonstrate a correlation between post-LVAD PVR and early mortality after OHT. Another possibility is that because the hemodynamic data were not collected immediately before OHT, those numbers do not reflect the actual patient hemodynamics at the time of OHT. Further investigation is warranted to ascertain the cause of high early mortality post-OHT in patients with pre-LVAD pHTN.

Study Limitations

The main limitation of the present study is that this is a retrospective and nonrandomized study at a single institution. However, comparing OHT outcomes by randomizing patients with heart failure with pHTN with a group with or without LVAD support would be clinically impractical. We believe that given the paucity of data regarding the effect of preexisting pHTN on the outcome of OHT in patients bridged to transplantation, this large study provides data with statistical strength that are less biased by preoperative

risk characteristics and types of LVAD device implanted. The second limitation is that not all patients underwent right heart catheterization after LVAD insertion or OHT surgery because of anticoagulation or a patient health condition not amenable to invasive hemodynamic study, or other reasons. It is possible that patients who did not undergo right heart catheterization and died during LVAD support or after OHT had persistently high PVR despite LV unloading. Also, the timing of hemodynamic measurement relative to LVAD implantation and OHT was not uniform and was potentially dynamic. Because of the retrospective nature of this study, survival comparisons are unadjusted comparisons.

CONCLUSIONS

LVAD therapy significantly reduced PVR even in patients with severely elevated PVR. Although the early post-OHT mortality in LVAD recipients with high PVR was high, their long-term survival was comparable to that for patients with lower PVR. For patients with end-stage heart failure who used to be deemed ineligible for OHT because of severe pHTN, LVAD therapy as a bridge to transplant may be a reasonable strategy.

Conflict of Interest Statement

Y.N. has received consulting fees from Thoratec Corp. All other authors have nothing to disclose with regard to commercial support.

You can watch a Webcast of this AATS meeting presentation by going to: http://webcast.aats.org/2015/Video/Tuesday/04-28-15_607_0810_Tsukashita.mp4

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Key Words: pulmonary hypertension, ventricular assist device, heart transplantation

Discussion

Dr A. Babu (Aurora, Colo). Dr Tsukashita, excellent presentation. Your series adds to the literature on PVR reduction affected by a LVAD. A couple of questions.

What is unique about your series is the correlation of these groups of patients to their post-heart transplant outcome, and clearly you showed a relatively high acute mortality rate after transplant in the patients who previously had a high PVR, and the question is, why do these patients have a higher mortality? You talk about them having a higher incidence of primary graft dysfunction. Was this right ventricular failure, and if so, is there anything we can do in this group of patients to have a lower threshold to place early mechanical support?

Dr Tsukashita. Of 29 patients whose PVR was high, 6 patients died postoperatively, I mean, after heart

transplantation, and of 6 patients who died, 4 patients had primary graft failure. So the primary cause of death in the high PVR group was primary graft failure. All those 4 patients required a biventricular assist device intraoperatively, and echocardiography showed biventricular dysfunction, not only right ventricular dysfunction.

Dr M. Acker (*Philadelphia, Pa*). But you didn't modify your donor selection in that group, because you assumed and showed that the PVR went down. Do you think going on that if you actually selected a bigger heart, one more robust, that that would modify your primary graft dysfunction? This is a very important question.

Dr Tsukashita. We didn't see a difference.

Dr Acker. I know. What I am suggesting, looking at these results going forward, maybe that would make the difference and decrease your primary graft dysfunction. Yoshi?

Dr Y. Naka (*New York, NY*). We attempted to choose the larger donor or the male donor, but often we were not able to achieve it, and the recipient is having device-related complications and they tend to stay, like the device. So the complication rate is maybe a bit higher, too.

Dr Acker. We didn't want to usurp our primary discussant's podium, so go ahead, second question.

Dr Babu. We do know that the HeartWare ventricular assist device probably affects less decompression of the ventricle and perhaps less decompression of mitral regurgitation, and that may have an effect on PVR decrease over time. I know your percentage of HeartWare ventricular assist device is small, but I wanted to know if you had any observations in regard to that.

I noticed a group of your patients received mitral valve repair at the time of LVAD implant, and perhaps that may have an effect on PVR reduction over time as well. Can you comment on those 2 groups?

Dr Tsukashita. We have seen more reduction in PVR after LVAD implantation in the patients, particularly in those who received a mitral valve repair concomitantly than in those who did not. But we didn't specifically look at the post-heart transplant data on the patients who received a HeartWare device.

Dr M. Ruel (*Ottawa, Ontario, Canada*). Do we really know when these patients are ready for transplant? We occasionally all get burned with this situation. We do a right heart catheterization at 6 months on the ventricular assist device, the PVR goes from 8 to 3, and we're all happy, we clap our hands, and still we occasionally get in trouble at the time of transplant.

You have 20% mortality in this population; this is high in a transplant series. Again, do we really have the right technology and approach to test these patients?

There are 2 components to PVR: the venous component and the arterial component. The venous component quickly disappears with any LVAD that works well. But occasionally there's still an important arterial component, and we get burned by it. Again, do we have the right evaluation?

Dr Tsukashita. For those patients who died with primary graft failure after heart transplantation in the high PVR group, we have the post-LVAD right heart catheterization data, which show that the PVR was less than 3. So we really don't know the cause of primary graft failure after heart transplant.

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FIGURE E1. Hemodynamic variables pre- and post-LVAD implantation. * $P < .05$ pre-LVAD versus post-LVAD parameters. CO, Cardiac output; LVAD, left ventricular assist device; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TPG, trans-pulmonary pressure gradient.

TABLE E1. All causes of post-orthotopic heart transplantation mortality during follow-up

Cause of death	Low PVR	High PVR	Total
Primary graft failure	1 (1, 0)	4 (4, 0)	5
Late graft failure	2 (1,1)		2
Rejection	1 (0, 1)		1
Sepsis	6 (4, 2)	1 (1, 0)	7
Pneumonia	1 (0, 1)		1
Cardiac tamponade	1 (1, 0)		1
Stroke		1 (1, 0)	1
Cancer	1 (0, 1)		1
Gastroenteritis	1 (0, 1)		1
<i>Clostridium difficile</i> colitis	1 (0, 1)		1
Unknown	5 (1, 4)		5
total	20 (7, 13)	6 (6, 0)	26

Data are presented as n. The numbers in parentheses represent the early and late mortality, respectively. PVR, Pulmonary vascular resistance.