

Long-Term Effects of Left Ventricular Assist Device Therapy on Pulmonary Vascular Resistance in Patients Bridged to Heart Transplant

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Abstract

Background: Elevated pulmonary vascular resistance (PVR) is a relative contraindication to cardiac transplantation. Bridge-to-transplant with LVAD may reduce PVR, though its efficacy and long-term outcomes post-transplant are unknown.

Methods & Results: Retrospective review was performed with selection of patients who received LVADs for BTT indication from May 2008 to November 2016. Subjects were divided into two groups based on pre-VAD hemodynamics: PVR ≥ 3 and PVR < 3 . 83 BTT patients received HeartMate II (n=53) or HeartWare (n=32) with a mean PVR of 2.7 ± 1.6 Woods units (W.U.). Thirty-five patients (42%) had PVR ≥ 3 . A total of 44 patients (53%) successfully underwent OHT. Pre-implant PVR did not affect likelihood of undergoing OHT (49% vs 51%, p=ns). VAD support as BTT successfully reduced PVR across the entire cohort (2.7 ± 1.6 to 1.2 ± 0.6 W.U. p<0.01). HMII and HVAD were equally effective in decreasing post-OHT PVR in the long-term (1.2 ± 0.5 vs 1.3 ± 0.5 W.U. p=0.5). Having PVR >3 pre-VAD did not influence post-OHT PVR, both at immediate post-operative (1.2 ± 0.5 vs 1.2 ± 0.6 W.U. p=0.8) and at 2-years follow-up time points (1.2 ± 0.4 vs 1.4 ± 0.6 W.U. p=0.2). Kaplan Meier analysis demonstrated similar survival post-OHT at 30 days (88% vs. 96%) and 6 years (62% vs. 74%, p=0.2), and similar incidence of moderate or greater RV failure post-OHT (p=0.4).

Conclusion: VAD support successfully reduces PVR among BTT patients, and does not appear to increase the incidence of adverse events or reduce survival.

Keywords

Left ventricular assist device therapy; Pulmonary vascular resistance; Heart transplant

Introduction

Severely elevated pulmonary vascular resistance (PVR) is contraindicated in orthotopic heart transplant (OHT) due to increased risk of right heart failure [1-4]. While institutions vary in their policies, most centers consider a PVR greater than three on maximal medical therapy an absolute contraindication [5]. Historically, no surgical intervention was available for these patients, whose advanced heart failure and chronic pulmonary congestion led to adverse cardiac remodeling and pulmonary hypertension (PH). The maturation of mechanical circulatory support technology has led to the development of new management and optimization strategies for these challenging patients. In addition to destination therapy (DT), short-term use of ventricular assist devices (VAD) as bridge-to-transplant (BTT) has been shown to be effective in normalizing PVR for many patients with advanced heart failure and PH, rendering them eligible for OHT [6,7].

Despite these benefits in bridging patients to transplantation, the long-term efficacy and durability of reducing PVR with mechanical circulatory support are not yet fully understood. Therefore, this study aimed to better characterize patients' pulmonary vascular profiles as they progressed from end-stage heart failure to VAD therapy then ultimately to OHT. We stratified patients based on their PVR prior to VAD implantation and evaluated the effects of mechanical circulatory support on PVR and incidence of adverse events in the long-term following successful transplantation.

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Materials & Methods

Patient Selection

The Institutional Review Board (IRB) at the Hospital of the University of Pennsylvania approved this study. Patients who received HeartMate II (HMII) (Thoratec Corp., Pleasanton, CA, USA) or HeartWare (HVAD) (HeartWare International Inc., Framingham, MA, USA) as bridge-to-transplant (BTT) indications between the time period May 2008 to November 2016 were identified from the institutional MCS database. Patients who required bi-ventricular support during their index operations were excluded. Based on their PVR values immediately prior to VAD implantation, patients were divided into two groups: "Elevated PVR," denoting PVR \geq 3, and "Normal PVR," denoting PVR $<$ 3. LVAD settings at time of implantation were titrated to adequate ventricular unloading based on echocardiographic findings and hemodynamic profiles, as per standard practice protocol. A subset of patients who successfully underwent OHT during the study period were identified.

Variable Selection

Primary outcome was defined as survival at both 30 days and most recent follow-up date after OHT. Secondary outcomes were defined as incidence of right heart failure and PVR post-OHT. Patient demographics and implant characteristics, including hemodynamic and laboratory profiles, were compared between groups. Patients underwent formal right heart catheterization studies (RHC) at following time points: prior to VAD implantation, within 30 days after OHT, and at the most recent follow-up time point after OHT. These studies recorded mean arterial pressure (MAP), mean pulmonary arterial pressures (mPAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), index (CI) and central venous pressure (CVP), which were used to calculate PVR. Pulmonary arterial pressure recordings while on VAD support were derived from post-operative Swan-Ganz measurements within 7 days after VAD implantation.

Adverse events post-VAD implantation and post-OHT, including right ventricular (RV) failure, gastrointestinal bleeding, stroke, transient ischemic attacks, renal failure requiring hemodialysis, concern for pump thrombosis, and major infection requiring oral or IV antibiotic therapy, were also assessed. RV failure at any time point during VAD support were included, defined as requiring right ventricular assist device (RVAD) support, severe RV dysfunction on echocardiography or inotropic therapy for longer than 14 days post-operatively as per INTERMACS.

Statistical Analysis

Continuous variables were reported as mean \pm standard

deviation and non-parametric variables were reported as median and interquartile range. All statistical analyses were conducted using GraphPad Prism (La Jolla, CA) and Stata software 14 (College Station, Tx). Patient demographics and baseline characteristics were compared using univariable analysis. Differences in hemodynamic profiles at varied time points between the two groups were compared using T-tests. Longitudinal progression of PVR within the cohort at pre-VAD, pre-OHT, and post-OHT time points were compared using paired-t-test. Categorical variables were compared by chi-square analysis. Survival at 30 days and 1 year were compared using Kaplan-Meier curves and log-rank tests. For all analyses, values of p greater than 0.05 were considered not significant (NS).

Results

During the study period, 235 patients received LVADs with a mean mechanical support duration of 470 ± 570 days. Baseline cohort statistics are outlined in Table 1. Of the total, 83 patients received HeartMate II (n=51) or HVAD (n=32) for BTT indications. Prior to VAD implantation, the median PVR in the overall cohort was 2.7 (1.5-4.0) Woods units (W.U.). Thirty-five patients (42%) had PVR \geq 3 with a median of 4.6 (4.0-5.0) W.U, while 48 (58%) patients had normal PVR with a median of 1.8 (1.2-2.5) W.U prior to VAD implantation. Patients with elevated PVR had higher mPAP (36.9 [32.9-43.55] vs. 33.2[26.6-37.1] mmHg, $p < 0.05$) and lower cardiac output values (3.5 [2.8-4.5] vs. 4.3 [3.5-4.1] l/min, $p < 0.05$, Table 2). Other hemodynamic parameters including MAP and CVP were comparable. There were no differences between the groups in terms of demographic and laboratory variables.

While on VAD support, there was no difference in the incidence of right heart failure (11.4% vs 6.3%, $p 0.4$), ventricular tachyarrhythmia (8.6% vs. 4.2%, $p 0.4$) or neurologic events (5.7% vs. 14.6% $p 0.2$, Table 3) between the elevated and normal PVR cohorts. There was no statistically significant difference in incidence of death while on VAD (14.3% vs. 8.3%, $p 0.5$). Both groups were successfully bridged to OHT at equal proportions (n=17 [49%] vs. n=27 [51%], $p 1.0$).

Of the total of 83 patients implanted with VAD for BTT indication, 44 patients (53%) successfully underwent OHT during the study period, 17 of whom had elevated and 27 of whom had normal pre-VAD PVR values. These patients were supported on VAD for similar durations prior to OHT (229 ± 226 days vs 185 ± 232 , $p 0.4$). No difference in donor characteristics such as age, etiology of injury and mismatch in size were observed.

As a whole cohort, these patients had normalized PVR values at immediate post-OHT (3.0 ± 1.8 vs. 1.2 ± 0.6 W.U. $p < 0.01$), and at long-term follow-up time points (3.0 ± 1.8 vs. 1.3 ± 0.5 W.U. $p < 0.01$).

	Elevated PVR (n=35)	p-value	Normal PVR (n=48)	Aggregate Cohort (BTT LVADs) (n=83)
Age (years)	57 (45-65)	0.9	58 (48-64)	57 (48-64)
Male	85.70%	1	85.40%	84.70%
Caucasian	54.50%	0.9	64.60%	60.00%
Body Mass Index	28.8 (24.1-35.7)	0.5	28.7 (24.5-33.6)	28.8 (24.5-33.6)
HeartMate II	65.70%	0.5	58.30%	62.40%
HVAD	34.30%	0.5	41.70%	37.70%
ICM	30.40%	0.2	35.70%	33.30%
Smoker (past & current)	45.70%	0.3	58.30%	51.70%
IABP	20.00%	1.0	20.80%	21.20%
Intubation	20.00%	0.9	12.50%	15.30%
Feeding Tube	2.90%	0.05	2.10%	2.40%
Infusions				
Milrinone	96.70	0.7	91.90	94.20
Epinephrine	40.00	0.2	45.90	43.50
Norepinephrine	0.00	0.7	2.10	1.20

ICM: Ischemic cardiomyopathy; IABP: Intra-aortic balloon pump; RV: Right ventricular

Table 1: Baseline demographics prior to VAD implantation-compares basic demographic information among the Elevated PVR and Normal PVR groups prior to VAD-implant

Hemodynamics	Elevated PVR (n=35)	P-Value	Normal PVR (n=48)	Aggregate Cohort (BTT LVADs) (n=83)
Mean Arterial Pressure (mmHg)	75 (66-80)	0.9	74 (66.8-82.8)	75 (66.7-82.3)
Cardiac Output (L/min)	3.5 (2.8-4.5)	<0.05	4.3 (3.5-4.1)	3.91 (3.1-4.9)
Central Venous Pressure (mmHg)	11 (6-14)	0.3	8.5 (6-11)	10 (6-13)
Systolic PAP(mmHg)	56 (50-68)	<0.05	49.5 (41-56)	52 (44-59)
Mean PAP(mmHg)	36.9 (32.9-43.6)	<0.05	33.2 (26.6-37.1)	34.9 (28.9-38.6)
PVR (WU)	4.6 (4.0-5.0)	<0.05	1.8 (1.2-2.5)	2.7 (1.5-4.0)
Laboratory Values				
Sodium (mg/dL)	136 (132-138)	0.3	134.5 (131-137.5)	135 (132-138)
Potassium(mg/dL)	4.2 (3.7-4.5)	0.4	4.2 (4.0-4.45)	4.2 (3.8-4.5)
White Blood Cells (x10 ⁹ /L)	8.5 (7.2-10.6)	0.1	7.95 (6.4-9.6)	8.2 (6.6-9.9)
Hemoglobin (x10 ⁹ /L)	11 (9.3-13.1)	0.4	10.95 (9.6-12)	11 (9-12.3)
Platelet (x10 ⁹ /L)	219 (168-298)	0.1	185.5 (130-251)	204 (154-258)
Blood Urea Nitrogen (mg/dL)	20 (16-32)	0.2	25 (14.5-44.5)	23 (15-38)
Creatinine (mg/dL)	1.3 (0.9-1.3)	0.9	1.39 (1-1.7)	1.31 (0.99-1.7)
Albumin (mg/dL)	3.3 (2.5-3.7)	0.08	3.6 (3.3-3.9)	3.5 (2.8-3.8)
Pre-albumin (mg/dL)	17.5 (14.6-24.8)	0.4	21 (16.1-26.1)	20 (15.9-25.1)
ALT (mg/dL)	25 (18-41)	0.4	24 (15-37)	25 (16-39)
AST (mg/dL)	28 (21-41)	0.1	26 (18.5-34)	27.5 (20.5-35.5)
Total Bilirubin (umol/L)	1 (0.7-1.3)	0.5	1.1 (0.7-1.3)	1 (0.7-1.3)

PAP: Pulmonary arterial pressure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PVR: Pulmonary vascular resistance; WU: Woods unit

Table 2: Hemodynamic and end-organ profiles prior to VAD implantation

Complications on LVAD	Elevated PVR (n=35)	Normal PVR (n=48)	p
Heart failure (%)	5 (14.3)	2 (4.2)	0.1
Right Ventricular failure (%)	4 (11.4)	3 (6.3)	0.4
Ventricular Tachyarrhythmia (%)	3 (8.6)	2 (4.2)	0.4
Acute kidney injury (%)	2 (5.7)	0 (0)	0.1
Gastrointestinal Bleed (%)	5 (14.3)	7 (14.6)	1
Major Infection (Pneumonia, DLI) (%)	4 (11.3)	9 (11.4)	0.4
Device Thrombosis& Dysfunction (%)	6 (17.1)	4 (8.3)	0.2
Neurologic (Stroke, TIA) (%)	2 (5.7)	7 (14.6)	0.2
Death on VAD support prior to OHT (%)	5 (14.3%)	4 (8.3%)	0.5

DLI: Driveline infection; TIA: Transient ischemic attack

The table delineates various complications associated with LVAD therapy based on patients' pre-implantation PVR profiles. RV failure was defined as inotropic requirement greater than 2 weeks or RVAD requirement.

Table 3: Incidence of complications while on VAD support prior to OHT

These 44 patients also demonstrated lasting improvements in right-heart hemodynamic parameters: Progressive reductions in mean pulmonary arterial pressures (pre-LVAD 34.6 ± 8.3 vs. LVAD 23.7 ± 7.5 vs. OHT 18.7 ± 6 mmHg) and improvements in cardiac index (pre-LVAD 1.9 ± 0.5 vs. LVAD 2.8 ± 0.9 vs. OHT 3.1 ± 0.8) were observed (Table 4).

Regardless of having normal (PVR<3) or elevated (PVR ≥ 3) values prior to VAD implantation, both groups had comparable survival outcomes post-OHT at 30 days (88% vs. 96%, p=0.9) and 5 years (62% vs. 74%, p=0.2) (Figure 1). There was no difference in the incidence of moderate or greater right ventricular failure post-OHT (p=0.4). Both groups also had comparable PVR values post-OHT, both at immediate post-operative (1.2 ± 0.6 vs. 1.2 ± 0.5 W.U. p=0.8) and at long-term follow-up time points (1.4 ± 0.6 vs. 1.2 ± 0.4 W.U. p=0.2) (Figure 2a).

Device Type Analysis

Both HeartMate II and HVAD groups had elevated PVR values prior to VAD implantation (3.3 ± 1.9 vs. 2.6 ± 1.7 W.U. p=0.5). Both device

types were equally effective in mitigating pulmonary hypertension, as evidenced in their normalized PVR values both at immediate post-operative (1.2 ± 0.5 vs. 1.3 ± 0.6 W.U. p=1) and at long-term follow-up after OHT (1.2 ± 0.5 vs. 1.3 ± 0.5 W.U. p=1) (Figure 2b).

Discussion

In this study, our goal was to investigate the efficacy and durability of using mechanical circulatory support to reduce PVR among patients listed for heart transplant. Our principal findings are as follows.

1. VAD therapy successfully reverses elevated PVR in patients who are bridged-to-transplant
2. Benefits of reduced PVR are equal among those with elevated and normal PVR values prior to VAD implantation

Patients with advanced heart failure with long-standing pulmonary congestion, vasoconstriction and adverse remodeling often have concomitant pulmonary hypertension (PH). The severity as well as the reversibility of PH has been shown to have prognostic implications [8]. Due to increased risk of right heart failure after OHT,

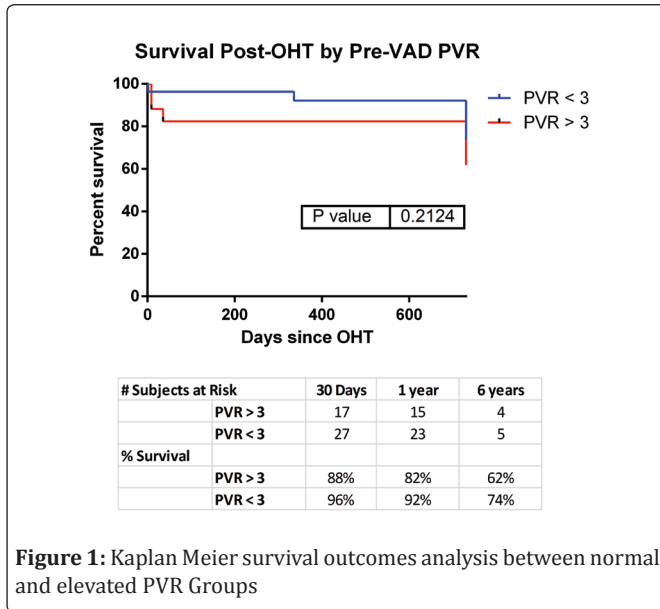


Figure 1: Kaplan Meier survival outcomes analysis between normal and elevated PVR Groups

irreversible elevated PVR is a well-established contraindication with varying degrees of stringency across institutions [9].

At our institution, PVR ≥ 4 is an absolute contraindication for transplant and PVR between 3 and 4 on optimal medical therapy is a relative contraindication. Therefore, hemodynamic optimization prior to OHT, especially mitigating PH using inotropic support, pulmonary vasodilators or mechanical circulatory support, remains crucial. In our study, approximately 40% of all BTT patients had PVR above 3 at the time of implantation, indicating the high prevalence of and the importance in further understanding this patient population’s long-term outcomes.

Landmark clinical trials have demonstrated the efficacy of VAD therapy in restoring hemodynamic stability in patients with end-stage heart failure with excellent long-term outcomes [10-12]. In addition to restoring cardiac output, various studies have shown the efficacy of using mechanical circulatory support to mitigate PH and optimize right heart function [6,7,13]. Particularly for potential OHT candidates who are contraindicated based on their fixed PH diagnoses, VAD therapy as BTT indication may render them eligible upon repeat right heart catheterization in as short as 3 to 6 months. According to the 2016 International Society for Heart Lung Transplantation (ISHLT) Listing Criteria, this strategy to assess the reversibility of PH is currently listed as a Class IIA recommendation [14].

In our study, the benefits of VAD support in optimizing pulmonary circulation among BTT patients were reaffirmed. While right heart catheterizations were not routinely performed in all BTT patients while on LVAD support, significant improvements in pulmonary arterial pressures, cardiac output and index were observed, consistent with previously reported findings [15]. Reassuringly, significantly elevated PVR values (≥3) prior to VAD implantation had effectively normalized by the time of transplant across the entire cohort. Moreover, these hemodynamic improvements were sustained in the long-term following OHT, suggesting stable reverse remodeling in the pulmonary vasculature. While right heart failure is a well-described adverse event after VAD implantation and OHT, especially among patients with increased PVR, its incidence was equivalent between both groups in our study [16,17].

Lastly, studies have noted the differential efficacy of axial versus centrifugal flow VADs in unloading the left ventricle [18]. Inherent differences in device capability may have implications for how effective each device type is in mitigating pulmonary hypertension and favoring reverse remodeling among BTT patients. In our study, there were no differences in survival or other adverse outcomes based on device type. Future studies that aim to understand the relationship between the type of intervention, the degree of unloading, and long-term post-OHT outcomes are warranted.

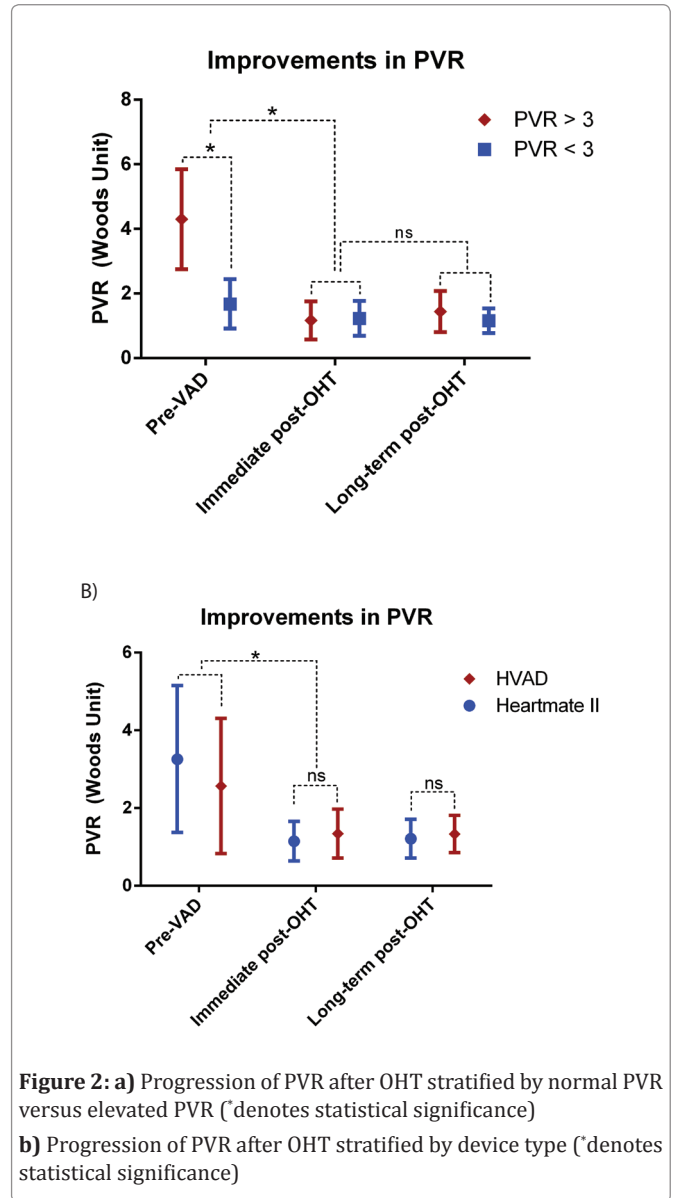


Figure 2: a) Progression of PVR after OHT stratified by normal PVR versus elevated PVR (*denotes statistical significance)

b) Progression of PVR after OHT stratified by device type (*denotes statistical significance)

Our study has several limitations. First, it is a single institutional retrospective study with a limited cohort size. Moreover, although many patients are designated as BTT prior to VAD implant, patients have varying severity of PH that may still preclude their eligibility for OHT. While all patients had bedside Swan-Ganz catheter measurements, not all patients underwent formal right heart catheterization assessments while on VAD during the study period, which limited our overall analysis. Recent evidence by Schumer et al. [19] pointed to the possibility of increased risk of adverse outcomes post-OHT for patients with persistently elevated PVR on VAD. This subset of patients with irreversible PH may need to be described separately in future studies, as right heart catheterization studies become more commonly utilized in evaluating, optimizing as well as prognosticating BTT patients. This would help avoid selection bias for patients whose PVR values were able to be reversed prior to undergoing OHT.

Furthermore, a growing body of evidence supports an equally vital role of compliance, in addition to resistance, in RVF, especially in the setting of PH [20-22]. These two parameters are inversely correlated as evidenced by the formula describe the arterial time constant, $\tau=RC$ [23]. As described by Lankhaar et al. [24], the clinical implication is that the same degree of improvement in R can lead to different degree of improvement in C depending on how severely R is elevated at baseline. As such, it points to interesting questions about therapeutic potential of LVADs based on the severity of PVR, and subsequently, the optimal timing of implantation.

	Pre-LVAD N=44	Immediate post-LVAD N=44	Immediate post-OHT N=44	Post-OHT Follow-Up N=38
sPAP (mmHg)	51.8 ± 13.5	36.9 ± 11.0	33.6 ± 10.0	31.3 ± 13.1
DPAP (mmHg)	26.1 ± 6.5	17.2 ± 6.4	11.3 ± 5.0	10.9 ± 5.6
mPAP (mmHg)	34.6 ± 8.3	23.7 ± 7.5	18.7 ± 6.0	17.6 ± 7.6
PCWP (mmHg)	24.4 ± 8.5	-	13.6 ± 5.8	12.2 ± 6.2
Cardiac Index	1.9 ± 0.5	2.8 ± 0.9	3.1 ± 0.8	2.8 ± 0.5
Cardiac Output (l/min)	3.9 ± 1.3	5.2 ± 1.7	6.3 ± 1.9	5.8 ± 1.1
PVR (W.U)	2.7 ± 1.6	-	1.2 ± 0.6	1.2 ± 0.5

sPAP: Systolic pulmonary arterial pressure; DPAP: Diastolic pulmonary arterial pressure; MPAP: Mean pulmonary arterial pressure; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; WU: Woods units

The table shows progressive changes in hemodynamic profiles in all patients who were bridged-to-transplant on LVAD across various intervention time points. Formal RHC studies were conducted at pre-lvad and post-OHT time points. Informal measurements were recorded using Swan-Ganz catheter post-VAD.

Table 4: Right Heart Catheterization Hemodynamics across various intervention time points for patients successfully bridged-to-transplant with VAD

Conclusions

In conclusion, our study reaffirms the role of mechanical circulatory support among patients with end-stage heart failure who are bridged-to-transplant. Sustained and clinically meaningful reductions in PVR were observed regardless of the degree of pulmonary hypertension prior to VAD implantation and the type of device used.

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