

# How effective are continuous flow left ventricular assist devices in lowering high pulmonary artery pressures in heart transplant candidates?

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## Abstract

**Background:** *Pulmonary hypertension (PH) is considered a risk factor for morbidity and mortality in patients undergoing heart transplantation. Medical therapy with oral and pharmacologic agents is not always effective in reducing pulmonary artery (PA) pressures. Left ventricular assist devices (LVADs) have been used to reduce PA pressures in cases of PH unresponsive to medical therapy.*

**Methods and results:** *Our study sought to evaluate the effectiveness of axial- and centrifugal-continuous flow LVADs in reversing PH in heart transplant candidates. Hemodynamics were assessed pre- and post-operatively in nine patients undergoing HeartMate II and six patients undergoing HeartWare continuous flow LVADs. Mean PA pressures were reduced from  $31.9 \pm 10.6$  mm Hg to  $22.1 \pm 6.6$  mm Hg ( $p = 0.001$ ), and pulmonary vascular resistance was reduced from  $3.08 \pm 1.6$  mm Hg to  $1.8 \pm 1.0$  mm Hg ( $p = 0.007$ ). This improvement was seen within seven days of LVAD implantation. Three of 15 patients were successfully transplanted, with 100% survival at an average of 199 days post-transplant.*

**Conclusions:** *The results of this study suggest that both axial- and centrifugal-continuous flow LVADs are effective in immediately lowering PA pressures in heart transplant candidates with PH. (Cardiol J 2012; 19, 2: 153–158)*

**Key words:** left ventricular assist devices, pulmonary hypertension, continuous flow, transplant

## Introduction

Pulmonary hypertension (PH) is common in chronic heart failure (HF) and is an established risk factor for morbidity and mortality in heart transplant patients [1, 2]. PH is defined as a mean pulmonary artery (PA) pressure  $> 25$  mm Hg, systolic PA pressure  $\geq 50$  mm Hg, pulmonary vascular resistance (PVR)  $\geq 2.5$  Wood Units (WU) and (or) a transpul-

monary gradient (TPG)  $> 12$  mm Hg [3, 4]. PH not only increases early mortality after heart transplant, but also at one year after transplant, with up to a seven-fold increase in mortality with a TPG  $> 12$  mm Hg [5, 6]. PH also increases right HF and adverse events after heart transplantation [7]. Medical therapy with intravenous pulmonary vasodilators and inotropes superimposed on maximal oral pharmacologic treatment has previously been

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**Table 1.** Effect of pulsatile and continuous flow LVADs on pulmonary hypertension.

Author (Reference #)	Year	# Patients	Devices (number)	PVR [Wood Units]		MPAP [mm Hg]	
				Before	After	Before	After
<b>Pulsatile</b>							
Gallagher et al. [30]	1991	16	Novacor	3.8	1.5	NA	NA
Smedira et al. [31]	1996	47	HeartMate XVE	5.0	3.7	NA	NA
Adamson et al. [28]	1997	1	HeartMate XVE	6.6	2.8	43	19
Bhat et al. [33]	2003	1	HeartMate XVE	5.79	4.54	49	31
Al-Khalidi et al. [29]	2004	1	Novacor	7.1	1.2	NA	NA
Nair et al. [15]	2010	58	Novacor (30) Thoratec LVAD (15) HeartMate XVE (12) Thoratec VAD (1)	2.8	1.6	35	21
<b>Pulsatile and continuous flow</b>							
Martin et al. [35]	2004	6	HeartMate XVE (4) Novacor (1) Jarvik 2000 (1)	5.7	2.0	46	21
Zimpfer et al. [17]	2007	35	Novacor (8) Micromed Debakey (24) Duraheart (3)	5.1	2.0	44	18.4
Haft et al. [36]	2007	34	HeartMate XVE (16) HeartMate II (18)	NA	NA	37	20
Torre-Amione et al. [16]	2010	9	Micromed Debakey (7) Thoratec PVAD (1) Novacor (1)	4.4	2.4	39	31
Alba et al. [34]	2010	22	HeartMate XVE (14) HeartMate II (6) Novacor (2)	4.3	NA	39	NA
<b>Continuous flow</b>							
Salzberg et al. [19]	2005	6	Micromed Debakey (17)	5	2.1	NA	NA
Etz et al. [18]	2007	10	Incor (9) Micromed Debakey (1)	4.8	2.2	42	24

LVADs — left ventricular assist devices; PVR — peripheral vascular resistance; MPAP — mean pulmonary artery pressures; NA — not applicable

used acutely to decrease PVR and PA pressures in HF patients and heart transplant candidates [2, 8–11]. Fibrosis and remodeling, including smooth muscle hypertrophy, may occur in the pulmonary vasculature of chronic HF patients [12–14]. This remodeling can result in PH that is refractory to medical therapy and which poses a high risk post-transplantation.

Several studies have shown that left ventricular assist devices (LVADs) can be used to reduce elevated PVR in HF patients, even when PH is refractory to maximal medical therapy [15–18]. Most studies have described the use of pulsatile LVADs in reversing PH. More recently, a limited number of studies have shown that continuous flow LVADs can also reverse PH (Table 1). These studies have used primarily axial-flow LVADs [16–19]. The goal of our study was to evaluate the efficacy of continuous-flow LVAD devices (both axial and centrifugal)

in lowering PA pressures in heart transplant candidates with PH.

### Methods

This was a retrospective study of 15 patients with advanced HF, a mean age of 51 years and a mean left ventricular ejection fraction of 14.9% (Table 2) undergoing continuous flow LVAD implantation as bridge to transplantation (BTT). Nine (60%) of these patients received HeartMate II (Thoratec Corp.) axial-flow LVADs (approved by the Food and Drug Administration [FDA] for BTT and destination therapy [DT]), and six (40%) patients received HeartWare (HeartWare International Inc.) centrifugal-flow LVADs (currently in clinical trials for BTT and DT). Hemodynamics, including central venous pressure (CVP), pulmonary artery systolic pressure (PAS), pulmonary artery diastolic pressure (PAD), mean

**Table 2.** Study population.

Patient	Age (years)	Gender	Ethnicity	Etiology	LVEF (%)	VAD	Type
1*	26	F	AA	NICM	10	HW	Centrifugal
2	42	M	AA	NICM	12	HW	Centrifugal
3	58	M	C	ISCM	20	HW	Centrifugal
4	55	M	C	NICM	10	HW	Centrifugal
5	63	F	C	ISCM	20	HW	Centrifugal
6	59	M	C	ISCM	17	HW	Centrifugal
7	66	F	AA	NICM	10	HMII	Axial
8	57	M	AA	NICM	15	HMII	Axial
9*	43	M	H	NICM	18	HMII	Axial
10*	55	F	C	ISCM	15	HMII	Axial
11	26	M	C	ISCM	20	HMII	Axial
12	34	M	AA	NICM	20	HMII	Axial
13	62	M	C	ISCM	15	HMII	Axial
14	60	M	AA	NICM	9	HMII	Axial
15	61	M	C	ISCM	13	HMII	Axial

\*Transplanted; AA — African-American; C — Caucasian; HMII — HeartMate II; HW — HeartWare; ISCM — ischemic cardiomyopathy; LVEF — left ventricular ejection fraction; NICM — non-ischemic cardiomyopathy; VAD — ventricular assist device

**Table 3.** Pre- and post-operative hemodynamics on right heart catheterization.

Hemodynamics	Pre-VAD	Post-VAD	P
CVP [mm Hg]	11.6 ± 6.3	10.6 ± 6.3	0.33
PAS [mm Hg]	46.1 ± 15.3	30.4 ± 10.6	< 0.001
PAD [mm Hg]	22.9 ± 8.5	15.1 ± 5.8	0.006
MPAP [mm Hg]	31.9 ± 10.6	22.1 ± 6.6	0.001
PCWP [mm Hg]	20.4 ± 8.5	11.4 ± 4.9	0.01
PVR [Wood Units]	3.08 ± 1.6	1.8 ± 1.0	0.007
CO [L/min]	4.2 ± 1.2	5.7 ± 1.1	0.003
CI [L/min/m <sup>2</sup> ]	2.0 ± 0.6	2.8 ± 0.5	0.001
SVO <sub>2</sub> [%]	57.0 ± 12.3	68.8 ± 8.2	0.03

CI — cardiac index; CO — cardiac output; CVP — central venous pressure; PAD — pulmonary artery diastolic pressure; MPAP — mean pulmonary artery pressure; PAS — pulmonary artery systolic pressure; PCWP — pulmonary capillary wedge pressure; PVR — peripheral vascular resistance; SVO<sub>2</sub> — mixed venous oxygen saturation

pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), cardiac index (CI), and mixed venous oxygen saturation (SVO<sub>2</sub>), were assessed by right heart catheterization within seven days of implantation (mean five days) pre- and post-operatively. Right heart catheterization and hemodynamics were obtained by standard techniques [20]. All the patients (15/15) were on continuous intravenous inotropic therapy prior to LVAD implantation on milrinone (average dose 0.49 µg/kg/min), and 60% (9/15) of them were on dobutamine (average dose 4.67 µg/kg/min). Two patients were also on continuous intravenous nitroglycerine at an average dose of

30 µg/min. Sixty-six per cent (10/15) of patients were maintained on oral sildenafil (average dose 74 mg/day) on discharge after LVAD implantation. All patients were otherwise considered candidates for transplantation and therefore implanted as BTT. Pre- and post-operative hemodynamic values were compared using SPSS v. 11.5 statistical software. A p value of < 0.05 was considered significant.

## Results

Pre- and post-operative hemodynamics of the entire cohort (Table 3) and based on device type (Table 4) were tabulated. There was significant

**Table 4.** Comparison of hemodynamics based on device type.

Hemodynamics	Axial pump (n = 9)		Centrifugal pump (n = 6)		P
	Pre VAD	Post VAD	Pre VAD	Post VAD	
CVP [mm Hg]	12.2 ± 7.9	12.0 ± 4.2	10.1 ± 3.7	7.3 ± 5.2	0.94
PAS [mm Hg]	48.3 ± 9.7	39.7 ± 11.5	46.5 ± 10.1	31.8 ± 7.1	0.68
PAD [mm Hg]	23.7 ± 3.5	20.0 ± 4.1	23.3 ± 8.1	18.8 ± 5.2	0.08
MPAP [mm Hg]	33.0 ± 3.4	27.6 ± 7.4	32.1 ± 15.4	24.0 ± 10.6	0.31
PCWP [mm Hg]	20.2 ± 4.2	12.5 ± 3.5	17.2 ± 12.7	9.0 ± 10.4	0.94
PVR [Wood Units]	3.3 ± 3.6	2.4 ± 2.9	3.6 ± 0.8	1.7 ± 1.1	0.27
CO [L/min]	4.0 ± 0.6	6.09 ± 1.0	4.8 ± 2.5	5.8 ± 1.7	0.62
CI [L/min/m <sup>2</sup> ]	2.0 ± 0.2	3.0 ± 0.6	2.4 ± 1.3	2.8 ± 0.3	0.55
SVO <sub>2</sub> [%]	57.6 ± 4.4	72.0 ± 7.6	56.5 ± 11.5	71.0 ± 12.7	0.88

Abbreviations as in Table 3

improvement in PAS, PAD, MPAP, PVR, TPG, CO, CI, and SVO<sub>2</sub> after LVAD implantation. This improvement was seen within seven days of implantation. Among these patients, the peak PVR was 6.9 WU (Patient #1, Table 2), and the peak MPAP was 52 mm Hg (Patient #6, Table 2). None of the patients required a right ventricular (RV) assist device after LVAD implantation.

Repeat right heart catheterization on 8/15 (53%) patients at an average of 423 days post-implantation demonstrated MPAP of 20.3 ± 7.3 mm Hg, and PVR of 1.7 ± 2.1 WU, indicating sustained improvements in PA pressures and PVR.

Three of 15 (20%) patients were successfully transplanted, with 100% survival at an average of 199 days post-transplant. Hemodynamics assessed at an average of 73 days after transplant (average 471 days after LVAD implantation) demonstrated mean MPAP of 18 ± 7 mm Hg with a mean PVR of 2.0 ± 1 WU.

### Discussion

PH is a common consequence of congestive HF, with an incidence as high as 60–80% in patients with long-standing HF [21, 22]. In HF secondary to left ventricular (LV) dysfunction, PH acutely arises secondary to increased filling pressures within the LV chamber. These increased pressures are then transmitted to the left atrium and ultimately result in an elevated PCWP and PH. Over time, chronic HF results in pulmonary vascular remodeling and fibrosis with superimposed smooth muscle hypertrophy [12–14].

PH ultimately leads to increased morbidity and mortality in patients with chronic congestive HF [23, 24]. Likewise, PH increases the risk of RV fail-

ure and complications post-heart transplant [2, 7]. PH can be treated medically using nitrates, hydralazine, phosphodiesterase (PDE-5) inhibitors such as sildenafil, and endothelin antagonists such as bosentan [8, 10, 11]. In cases of PH refractory to oral pharmacologic therapy, IV vasodilators such as milrinone, prostaglandins and nitrates can be added to test vaso-reactivity and ultimately lower PA pressures [9, 11]. In some patients however, both oral and IV vasodilator therapy may fail to lower PA pressures, resulting in what has been termed ‘fixed’ or ‘irreversible’ PH.

LVADs have now come to be an accepted form of treatment for advanced HF secondary to LV dysfunction, both as BTT and as permanent long-term support otherwise known as DT [25–27]. LVADs improve HF symptoms by unloading the LV and improving circulation to the body and perfusion to the end-organs. By volume unloading the LV, LVADs decrease LV filling pressures, and thereby improve congestion. This subsequently leads to decreased left atrial or PCWP and decreases congestion within the pulmonary vasculature. This is one of the mechanisms by which LVADs are thought to improve PA pressures.

Early case reports with LVADs and PH reported the successful lowering of medically unresponsive PH with pulsatile devices such as the HeartMate XVE (Thoratec Corp.) [28] and Novacor LVAD (WorldHeart Corp.) [29]. Likewise, a retrospective series by Gallagher et al. [30] demonstrated a reduction in the total pulmonary resistance among 16 patients undergoing implantation with the pulsatile Novacor LVAD. Smedira et al. [31] also demonstrated that the HeartMate pulsatile device could be used in patients with PH to successfully lower PA pressures and TPG, with similar out-

comes to patients without PH. The results of these early studies have been confirmed in follow-up case reports [32, 33] and a single recent large scale study by Nair et al. [15].

With the advent of continuous flow devices, studies utilizing both pulsatile and continuous flow LVADs have shown that these devices can reverse PH in patients with chronic HF [16–19, 34–36]. These studies have shown reversibility in patients previously thought to have ‘irreversible’ or ‘fixed’ PH. Two studies have utilized exclusively continuous flow devices in their series [18, 19]; however, these studies have all used axial-flow LVADs.

Our single center experience expands on the previous series of pulsatile and continuous axial-flow LVADs reversing PH in chronic HF. Our study suggests that both centrifugal and axial flow LVADs can reverse PH early after implantation in chronic advanced HF with a successful transplant outcome. This improvement in PA pressures, occurring within seven days of implantation, suggests that reversal of PH can occur immediately, allowing for decisions to be made regarding transplant candidacy. Furthermore, this improvement in PH was maintained at an average of 423 days after LVAD implantation, suggesting a sustained hemodynamic benefit long after surgery. PA pressures remained within normal limits even after heart transplant, suggesting that the improvement in PH continues even after transplantation and removal of the LVAD.

It should also be noted that despite significantly elevated pre-LVAD PA pressures, none of the patients in this study required RVADs after LVAD implantation. This is in contrast to previous studies that have demonstrated RVAD implantation in as many as 37% of patients after LVAD [37].

Our study was limited by the small number of patients involved and the fact that it was a retrospective review. The present study was not intended to compare the two devices (HeartWare and HeartMate II), but rather to describe their overall effect on PH in heart transplant candidates.

The two devices were able to significantly improve hemodynamics in chronic HF patients; however, further studies with more patients will be necessary to elucidate the mechanisms involved in this process.

**Conflict of interest:** none declared

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