

Reversal of secondary pulmonary hypertension by axial and pulsatile mechanical circulatory support

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BACKGROUND: Pulmonary hypertension associated with chronic congestive heart failure poses a significant risk of morbidity and death after heart transplantation. Isolated observations suggest that chronic ventricular unloading may lead to normalization of pulmonary pressures and thus render a patient likely to be a heart transplant candidate.

METHODS: This study is a retrospective analysis of 9 heart failure patients with secondary pulmonary hypertension (transpulmonary gradient [TPG] > 15 mm/Hg). Two were treated with a pulsatile left ventricular assist device (LVAD) and 7 with an axial-flow LVAD.

RESULTS: After LVAD support, mean pulmonary artery pressure decreased from 39 ± 7 to 31 ± 5 mm Hg, and the TPG decreased from 19 ± 3 to 13 ± 4 mm Hg ($p < 0.01$). The 1-year Kaplan–Meier survival curve for patients with pre-LVAD TPG > 15 mm Hg vs those with TPG < 15 mm Hg showed no difference in survival ($p = 0.6$). This finding was supported by analysis of a large multi-institutional cohort obtained from the Organ Procurement and Transplantation Network database, where no differences in survival were found in the same groups.

CONCLUSIONS: Pulmonary hypertension that is secondary to congestive heart failure, as defined by a TPG > 15 mm Hg can be reversed by the use of pulsatile and axial-flow LVADs; furthermore, post-transplant survival for patients with secondary pulmonary hypertension treated with an LVAD was no different than for those without pulmonary hypertension who received LVAD support.

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Pulmonary hypertension commonly occurs secondary to congestive heart failure and portends an increased mortality rate in these patients.¹ Pulmonary hypertension is defined according to the following criteria: systolic pulmonary artery pressure (SPAP) > 50 mm Hg, mean pulmonary artery pressure (MPAP) > 25 mm Hg, pulmonary vascular resis-

tance (PVR) > 4 Wood units (WU), or transpulmonary gradient (TPG) > 15 mm Hg.²

The effect of pulmonary hypertension on survival after heart transplantation has been described in 2 studies. In a study by Erickson et al³ of 109 heart transplant recipients, patients with a TPG > 12 mm Hg at the time of transplantation had a 1-year mortality 7 times greater than that of a comparable group of patients with a TPG < 12 mm Hg. In a study of 425 heart transplant recipients, Murali et al⁴ documented that patients with a TPG \geq 15 mm Hg had an early transplant mortality rate (0 to 2 days) that was 3 times higher than patients with TPG < 15 mm Hg. Thus, an

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elevated TPG has a profound effect on short-term and long-term survival⁵ and has become an established contraindication for orthotopic heart transplantation. This problem is of great concern, because it appears that the number of patients with advanced heart failure and secondary pulmonary hypertension has increased over time.

It is important to acknowledge recent observations from case reports and small series that demonstrate that in some patients with pulmonary hypertension, pulsatile-flow left ventricular assist device (LVAD) support results in normalization of pulmonary pressures.^{6,7} Al Khaldi et al⁸ reported a patient who underwent reduction in TPG from 22 to 6 mm Hg after 11 months of mechanical unloading. Adamson et al⁹ reported similar results, with a reduction of TPG from 28 to 15 mm Hg in a patient who was supported for 10 weeks. Nguyen et al¹⁰ demonstrated a dramatic lowering of the TPG in another 3 patients supported with an assist device. It thus appears that long-term mechanical unloading can normalize pulmonary hypertension as it occurs in the setting of heart failure. More recently, the phenomenon of normalization of pulmonary pressures was also observed with the use of the DeBakey VAD (MicroMed Technology, Inc, Houston, TX) axial-flow pump.¹¹

The importance of normalization of pulmonary hypertension by the use of mechanical support is that patients who would otherwise be unsuitable for orthotopic heart transplantation become acceptable candidates after LVAD support. To this end, very limited data exist; for example, in 6 patients where the mean PVR was decreased from 5.7 ± 0.7 to 2.0 ± 1.2 WU after 191 ± 86 days of support, 1 death occurred at 3 months after heart transplantation.¹²

The purpose of the present investigation was (1) to further define the effect of axial-flow and pulsatile LVAD support on pulmonary hemodynamics among patients with pulmonary hypertension secondary to chronic heart failure, and (2) to define the effect of LVAD support on survival after cardiac transplantation among patients with associated pulmonary hypertension.

Methods

Data collection

The Institutional Review Board of the Baylor College of Medicine approved the retrospective collection of patient data. Patients were included in this study if they were successfully bridged to heart transplantation by LVAD support between September 1, 2000, and January 31, 2004, and had a TPG ≥ 15 mm Hg by right heart catheterization at our institution before LVAD implantation. We identified 23 patients who were successfully bridged to transplant who underwent catheterization before LVAD implant and after transplant. Out of these 23 patients, 9 had a TPG ≥ 15 mm Hg preoperatively.

Direct measurements for SPAP, DPAP, MPAP, and pulmonary capillary wedge pressure (PCWP) were obtained during right heart catheterization. Cardiac output (CO) was deter-

mined by thermal dilution. Pulmonary vascular resistance (PVR) was calculated as $[(\text{MPAP} - \text{PCWP}) \times 79.9]/\text{CO}$. TPG was calculated as $\text{MPAP} - \text{PCWP}$. These values were recorded and calculated from the most recent right heart catheterization performed before LVAD insertion and compared with the first right heart catheterization performed after transplantation. Mean \pm SD time between catheterization and LVAD insertion was 10 ± 10 days. Mean time between transplant and catheterization was 10 ± 4 days. Patient medical records were also reviewed to determine death after heart transplantation.

Organ procurement and transplantation network data

Data from the Organ Procurement and Transplantation Network (OPTN) through May 23, 2005, were used to identify patients who underwent heart transplantation after LVAD support since January 1, 2000. Patients were included in the analysis if right heart catheterization data were recorded at the time of listing for transplant and they had received one of the following long-term device types: HeartMate LVAS, Thoratec VAD (Thoratec Corp, Pleasanton, CA), Novacor LVAS (World Heart Corp, Oakland, CA), or Micromed DeBakey VAD (Miromed Cardiovascular, Houston, TX). Patients with other devices, total artificial hearts, or unknown device types were excluded.

Of 1,521 patients with a long-term LVAD at the time of transplantation, 1,082 (71.1%) had right heart catheterization data recorded at the time of listing. The TPG for each of these patients was calculated, and patients were classified as having pulmonary hypertension if the TPG ≥ 15 mm Hg.

The data reported here were supplied by the United Network for Organ Sharing as the contractor for the OPTN. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. government.

Statistical analysis

The paired *t*-test was used to compare SPAP, DPAP, MPAP, PCWP, CO, PVR, and TPG before LVAD implantation and after transplant. The unpaired *t*-test was used to compare continuous demographic variables between patients with TPG ≥ 15 mm Hg and those with TPG < 15 mm Hg. Categorical variables were compared between these 2 groups by the Fisher exact test.

Data from our center and from OPTN were used to compare post-transplant Kaplan–Meier survival between LVAD patients with and without pulmonary hypertension using the log-rank test. OPTN data for survival 1 month and 1 year after transplant were compared between patients with and without pulmonary hypertension using the chi-square test. All analyses were performed using SPSS 11.0.1 software (SPSS Inc, Chicago, IL).

Table 1 Demographic Variables in All Patients Successfully Bridged to Heart Transplant and by Transpulmonary Gradient

Variable	All	TPG, mm Hg	
		≥15	<15
Mean ± SD, or No. (%)			
Patients	23	9	14
Age, years	52 ± 12	55 ± 10	51 ± 14
Male sex	18 (78)	7 (78)	11 (79)
Device type			
Novacor	4 (17)	1 (11)	3 (21)
HeartMate	1 (4)	0 (0)	1 (7)
Thoratec (extracorporeal)	1 (4)	1 (11)	0 (0)
DeBakey/Noon	17 (73)	7 (78)	10 (71)
Duration of support, days	46 ± 31	59 ± 36	37 ± 25

SD, standard deviation; TPG, transpulmonary gradient.

Results

Demographics

Right heart catheterization data were available for 23 patients who were successfully bridged to heart transplant with an LVAD, 9 of whom had a TPG ≥ 15 mm Hg. The demographic variables are summarized in Table 1 and compared with patients without pulmonary hypertension who were successfully bridged to transplantation by LVAD during the same period. Mean age of patients with TPG ≥ 15 was 51 ± 14 years, 7 (78%) were men, and mean duration of support was 37 ± 25 days. There was no significant difference between age, sex, or device selection between patients with TPG ≥ 15 mm Hg and those with TPG < 15 mm Hg. There was a trend toward a longer duration of support in those patients with TPG ≥ 15 mm Hg ($p = 0.1$).

Effect of axial and pulsatile VAD support on pulmonary hemodynamics

In the patients with a preoperative TPG ≥ 15 mm Hg, MPAP decreased from 39 ± 7 to 31 ± 5 mm Hg ($p = 0.02$) and TPG decreased from 19 ± 3 to 13 ± 4 mm Hg ($p < 0.01$.) The pre-LVAD and post-transplant mean values for MPAP, TPG, and PVR, as well as the values for each patient, are represented in Figure 1. There was a trend toward a decrease in SPAP from 60 ± 10 to 51 ± 10 mm Hg ($p = 0.08$). PCWP in this group of patients decreased from 20 ± 8 to 17 ± 4 mm Hg ($p = 0.5$). CO slightly increased from 4.3 ± 1.3 to 5.5 ± 1.4 liters/min ($p = 0.4$). At least a nominal decrease occurred in TPG in 8 of 9 patients (the remaining patient's TPG did not change); furthermore, 5 of the 9 patients had a TPG < 15 mm Hg after transplant.

Seven patients with pulmonary hypertension in this study received a DeBakey VAD, 1 received a Thoratec extracorporeal device, and 1 received a Novacor LVAS. Patients were grouped by axial-flow device vs pulsatile

device. The changes in right heart catheterization data from pre-LVAD measurements to post-transplant measurements in patients with pulmonary hypertension are shown in Figure 2. The small number of patients in each sub-group precludes a statistical comparison between device types. However, patients with an axial-flow device had a significant decrease in TPG from 20 ± 3 to 14 ± 4 mm Hg ($p = 0.02$).

Effect of VAD support on survival after heart transplantation. During the mean follow-up of 30 ± 16 months after transplantation, 4 patients died of the 23 initially stud-

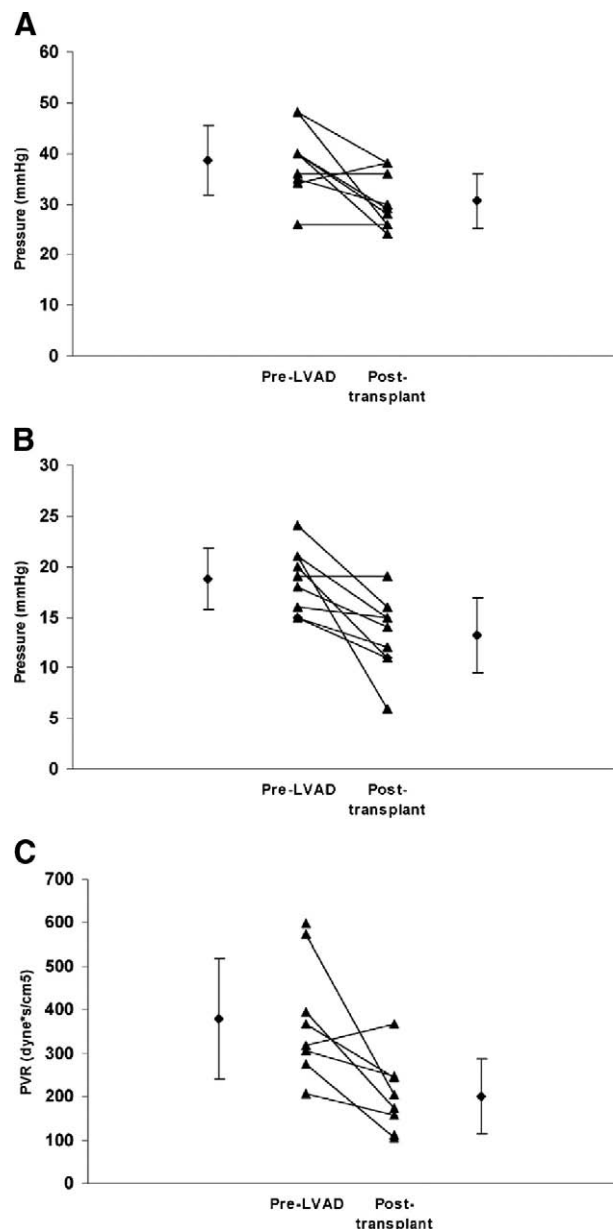


Figure 1 Effect of left ventricular assist device (LVAD) support is compared in 9 patients before LVAD support (pre-LVAD) and after transplantation (Post-transplant) for change for (A) mean pulmonary artery pressure (MPAP), (B) transpulmonary gradient (TPG), and (C) pulmonary vascular resistance (PVR). Mean values before LVAD and after transplant are also presented (squares ± standard deviation; $p < 0.05$ for all 3 variables by paired t -test).

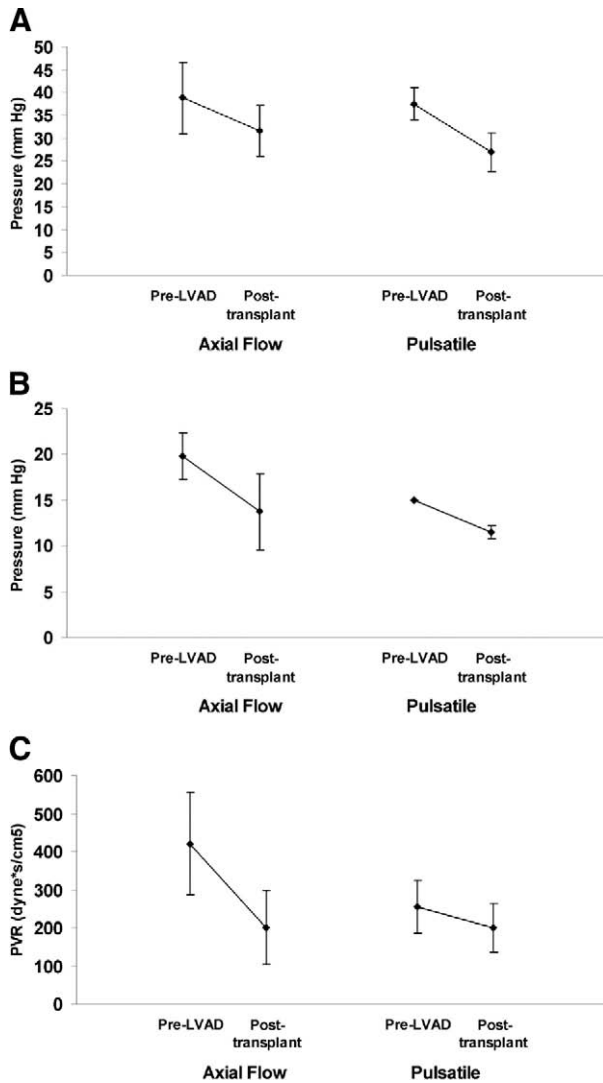


Figure 2 Effect of axial and pulsatile-type left ventricular assist device (LVAD) support is shown for (A) mean pulmonary artery pressure (MPAP), (B) transpulmonary gradient (TPG), and (C) pulmonary vascular resistance (PVR) before LVAD and after transplant. The small number of patients in each group precludes statistical comparisons between device types. Graphs represent differences in mean (standard deviation).

ied. Three of these had an initial TPG < 15 mm Hg, and all survived at least 1 year. The fourth patient who died had an initial TPG of 20 mm Hg that was reduced to 11 mm Hg after transplant; however, the patient died 34 days after transplant of primary graft failure. There was no difference in Kaplan–Meier survival between patients with TPG ≥ 15 and TPG < 15 mm Hg ($p = 0.6$; not shown). None of these patients required biventricular support before transplant or right ventricular support after transplant.

OPTN data identified 1,082 patients who received a heart transplant between January 1, 2000, and May 23, 2005, had right heart catheterization data recorded at the time of listing, and had a long-term implantable LVAD at the time of transplant. These patients were grouped according to presence of pulmonary hypertension defined as TPG ≥ 15 mm Hg. The TPG was normal in 912 patients (84.3%) and elevated in 170 (15.7%). The difference in post-transplant

Kaplan–Meier survival between the 2 groups was not significant ($p = 0.24$). However, survival at 30 days was 86.8% for LVAD patients with pulmonary hypertension vs 93.3% for LVAD patients with normal TPG ($p = 0.01$). Furthermore, there was a trend toward lower 1-year survival in patients with pulmonary hypertension (77.0% vs 83.0%, $p = 0.07$; Figure 3).

Discussion

This study has 3 important findings:

- It expands the existing evidence that pulmonary hypertension as it is observed in the context of chronic heart failure can be reversed after long-term mechanical support.
- In a similar cohort of patients, the reversibility of pulmonary hypertension can be achieved by the use of a pulsatile as well as an axial-flow LVAD.
- It suggests that long-term post-transplant survival of patients with pulmonary hypertension treated by an LVAD is similar to patients without pulmonary hypertension supported with an LVAD.

This study examined the effect of LVAD support on pulmonary hypertension (defined as TPG ≥ 15 mm Hg) in 9 patients who underwent LVAD implantation as a bridge to transplantation. TPG in 5 patients was reduced to normal levels (<15 mm Hg). In an additional 3 patients, TPG was reduced without reaching a normal pressure gradient.

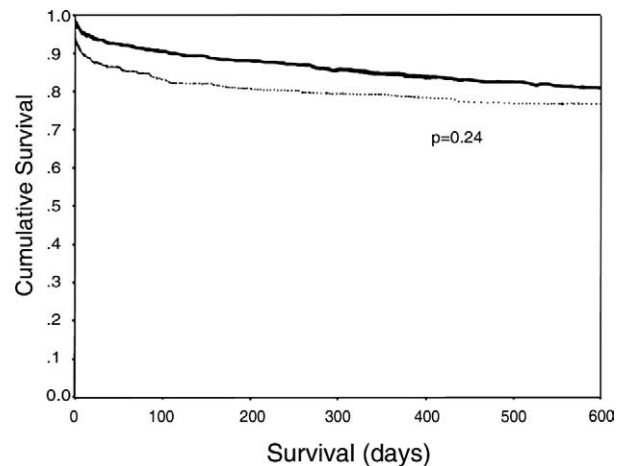


Figure 3 Post-transplant survival data in patients with and without pulmonary hypertension were compared in left ventricular assist device (LVAD) patients with a transpulmonary gradient (TPG) ≥ 15 mm Hg (dotted lines) and patients with TPG < 15 mm Hg (solid lines) who underwent cardiac transplantation and were reported to the Organ Procurement and Transplantation Network (OPTN). The difference in the overall Kaplan–Meier survival in either set of data by log-rank test was not significant; however, survival was decreased at 1 month after transplant in LVAD patients with TPG ≥ 15 mm Hg compared with patients with TPG < 15 mm Hg based on OPTN data ($p = 0.01$ by chi-square). A trend was noted toward decreased survival in these patients 1 year after transplant ($p = 0.07$ by chi-square).

These data expand the previously reported observations of other investigators that also reported in small case series that pulmonary hypertension secondary to chronic heart failure can be reversed. Martin et al¹² reported a series of 6 patients who received pulsatile devices. These patients experienced normalization of PVR during LVAD support, and all were successfully bridged to transplantation. Salzberg et al¹¹ reported 6 patients who received axial-flow devices and demonstrated a decrease with these devices as well.

Although continuous-flow devices typically unload the LV to a lesser degree than pulsatile devices, the reduction in pulmonary artery pressures does not appear to depend on the reduction of LV size but rather on the ability of the device to reduce intracardiac pressure. For example, our group¹³ previously demonstrated a greater reduction in LV end-diastolic dimension after pulsatile LVAD support comparison with an axial-flow LVAD; however, the change in dimensions had no effect on the effect in pulmonary pressures. The findings of the present study are consistent with our previous observations.

The number of patients in this study is small; however, the study presents a cohort of patients within the same institution who were similarly treated with either a pulsatile or an axial-flow device. The present study was not intended to compare device types but rather to present evidence of their effect on pulmonary hemodynamics. Because axial-flow devices are easier to implant, quieter, and smaller in size, they are potentially suitable for a larger population. Axial-flow devices can also be used among patients with secondary pulmonary hypertension. Indeed, the survival curve from our study cohort that includes 7 patients treated with an axial-flow LVAD is not significantly different from a comparable group that was treated with an LVAD but did not have pre-existing pulmonary hypertension. Thus, the data from the present study further support the use of axial-flow support for patients with advanced refractory heart failure.

It thus appears that as the number of patients with congestive heart failure and secondary pulmonary hypertension continues to increase, these patients may in the future represent a group that will need specific interventions. For example, strategies to optimize device support that specifically reduce or normalize pulmonary hypertension may be established. Indeed, we are currently prospectively evaluating continuous-flow LVAD function based on echocardiography to provide sufficient unloading to minimize the degree of mitral regurgitation, reduced LV size, and decrease pulmonary artery pressures. Data from this prospective evaluation should be forthcoming. In addition, it would be important to determine whether pharmacologic therapies can mimic the effect of mechanical support in the syndrome of pulmonary hypertension associated with congestive heart failure.

Our study is limited by the small numbers of patients, its retrospective nature, and the lack of controlled measurements; however, it does provide data on pulmonary hemodynamics before LVAD insertion and after heart transplantation. The ideal study to determine whether VAD therapy should be used in patients with secondary pulmonary hypertension will be a larger, randomized controlled trial of aggressive medical ther-

apy vs LVAD therapy. Such studies are difficult to conduct, however, and may take a long time to complete; for example, the Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) trial that defined the use of VAD for destination therapy, was completed in 7 years.¹⁴ Therefore, the findings of the present study, taking into account the retrospective and observational nature, are of significant value and may provide the basis for a larger randomized clinical trial.

In conclusion, the present study increases the body of clinical work that demonstrates that end-organ function and, specifically, pulmonary hypertension associated with heart failure, is reversible by chronic mechanical unloading with a pulsatile or an axial-flow LVAD.¹⁵ Moreover, although pulmonary hypertension remains a risk factor for early death after transplantation, the equivalence of long-term survival after transplantation between LVAD patients with and without pulmonary hypertension suggests that in most patients, mechanical unloading results in lasting effects on pulmonary vascular resistance.

Disclosure Statement

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