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Left Ventricular Assist Device to Avoid Heart-Lung Transplant in an Adolescent With Dilated Cardiomyopathy and Severely Elevated Pulmonary Vascular Resistance

Betul Yilmaz, MD^a, Warren A. Zuckerman, MD^a, Teresa M. Lee, MD^a, Kimberly D. Beddows, CPNP^a, Lisa A. Gilmore, CPNP^a, Rakesh K. Singh, MD, MS^a, Marc E. Richmond, MD, MS^a, Jonathan M. Chen, MD^b, and Linda J. Addonizio, MD^a

^aDivision of Cardiology, Department of Pediatrics, Morgan Stanley Children's Hospital, Columbia University College of Physicians and Surgeons, New York, NY

^bDepartment of Cardiothoracic Surgery, Weill Medical College of Cornell University, New York, NY

Abstract

Orthotopic heart transplantation remains the definitive treatment of choice for patients with end-stage heart failure, however, elevated pulmonary vascular resistance index (PVRI) is a reported risk factor for mortality after heart transplant, and when severely elevated, is considered an absolute contraindication. Use of a ventricular assist device has been proposed as one treatment for reducing PVRI in potential heart transplant candidates refractory to medical vasodilator therapies. We report on a teenage patient with dilated cardiomyopathy and severely elevated PVRI, unresponsive to pulmonary vasodilator therapy, who underwent left ventricular assist device implantation to safely allow for aggressive pulmonary vasodilator therapy and to decrease PVRI. The resulting dramatic improvement in PVRI in a relatively short period of time allowed for successful heart transplantation, avoiding the need for heart-lung transplant.

Clinical History

An 18-year-old female with history of idiopathic dilated cardiomyopathy was referred to our institution for evaluation of end-stage heart failure and potential orthotopic heart transplantation (OHT). She was diagnosed with dilated cardiomyopathy at age 13 years when she developed clinical signs and symptoms of congestive heart failure following a throat infection. She had been maintained on oral anti-congestive therapies since the time of diagnosis. Additionally, at age 17 years, she underwent radiofrequency ablation for atrioventricular nodal reentry tachycardia, followed by placement of a biventricular pacemaker/defibrillator in an attempt to improve her clinical symptoms.

At presentation to our institution, her symptoms included shortness of breath, nausea, abdominal pain, vomiting and lethargy with minimal activity, consistent with New York Heart Association (NYHA) functional classification III despite a medical regimen including digoxin, carvedilol, valsartan, furosemide, spironolactone, warfarin, and aspirin. Her serum B-type natriuretic peptide level (BNP) was elevated at 1800pg/mL. Other laboratory values,

Corresponding author for proofs and reprints: Betul Yilmaz, MD, Division of Pediatric Cardiology, Morgan Stanley Children's Hospital of New York-Presbyterian, 3959 Broadway, Room 2 North, New York, NY 10032, Telephone: (212) 342-0531, by2190@columbia.edu.

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including troponin and liver and renal function panels, were within normal limits. A transthoracic echocardiogram demonstrated severe left atrial and ventricular dilatation with severe, globally diminished biventricular function. Ejection fraction was estimated at 23% by Simpson's Biplane. There was moderate mitral regurgitation and mild tricuspid regurgitation. The peak pressure estimate of the regurgitant jet measured approximately 40 mmHg, with flattening of the ventricular septum in systole.

As part of her evaluation, the patient underwent right heart catheterization (table 1) that revealed a pulmonary artery saturation of 51%, and cardiac index (CI) by Fick calculation of 2.0 L/min/m². Her systolic and mean pulmonary artery pressures (PAP) were 77 mmHg and 49 mmHg, respectively, with pulmonary capillary wedge pressure (PCWP) of 20 mmHg. Pulmonary vascular resistance indexed to body surface area (PVRI) was 14.5 Wood Units (WU)×m². With initiation of 100% oxygen to assess pulmonary vasoreactivity, PCWP increased from 20 to 26 mmHg, however, PVRI decreased to 9.5 WU×m². Due to severe elevation of the filling pressures, further testing with acute vasodilator agents was not attempted, nor was she thought to be a candidate for chronic pulmonary vasodilator therapy. This severe degree of pulmonary hypertension precluded her from being listed for OHT, and a plan was developed to lower PVRI to acceptable levels. In addition to continuation of oral heart failure medications, milrinone infusion was initiated at 0.5 mcg/kg/min. Fluid status was monitored closely, and diuretics were optimized.

After one month on milrinone therapy, the patient remained NYHA functional classification III. Fluid status was well balanced, without x-ray or physical exam evidence of fluid overload. Repeat catheterization (table 1) demonstrated persistently low CI and severely elevated PVRI. Given her poor clinical status and elevated PVRI, which continued to preclude her from listing for OHT, she was placed on a Heartmate II (Thoratec Corp, Pleasanton, CA) left ventricular assistant device (LVAD) as a means of both treating her left ventricular (LV) failure and allowing for more aggressive treatment with pulmonary vasodilator therapies. In the operating room, following LVAD implantation, right ventricular (RV) function was noted to improve. In addition, mean PAP by direct measurement was in the low 40's, hence the decision was made to proceed solely with LVAD placement. Right heart failure following LVAD placement was initially managed medically with inhaled nitric oxide (iNO), then transition to oral sildenafil, while milrinone therapy was continued. With this management, she did not require the addition of RV mechanical support. After the initiation of milrinone, BNP had decreased slightly and was 1400pg/ml four days prior to the placement of LVAD. BNP decreased further to 1100pg/ml five days after LVAD placement, and continued to trend down steadily thereafter.

One month following LVAD implantation, and with continued milrinone and sildenafil, her symptoms significantly improved and she was NYHA functional classification II. Fluid status remained optimized with titrating of diuretics, and BNP was now down to 380 pg/mL. In addition, echocardiographic evidence of mitral regurgitation improved from moderate to mild, which may have contributed to improvement of the right-sided pressures. Repeat catheterization (table 1) showed remarkable improvement as there was a dramatic decline in PVRI to 5.3 WU×m², which is considered acceptable for OHT in our pediatric program. She was listed for OHT as UNOS status 1B, and upgraded to status 1A 23 days later.

After six weeks on the heart transplant wait list, a suitable donor became available and the patient underwent OHT. In the immediate post-operative period, she was maintained on continuous infusions of milrinone, dobutamine, epinephrine, and vasopressin, as well as iNO. She remained intubated and sedated for four days post-operatively, during which time inotropic and respiratory support was gradually weaned based on stabilization of right-sided pressures that were closely monitored by Swan-Ganz catheter, as well as RV size and

function monitored by echocardiogram. Right atrial pressure during that time was 15-18 mm Hg, PAP was 30-34 mmHg, and PCWP was 18-20 mmHg. CI was approximately 4.0 L/min/m², and therefore PVRI was approximately 3-4 WU×m². Sildenafil was re-started on post-operative day (POD) 3, and iNO was discontinued on POD 5. On POD 9, she underwent first post-transplant catheterization (table 1) on milrinone. Following this catheterization, she was transitioned from milrinone to oral digoxin and nifedipine XL. However, nifedipine XL was later discontinued due to lower extremity edema.

The patient was discharged on POD 21 on an oral immunosuppressive regimen, as well as digoxin and sildenafil. Transthoracic echocardiogram prior to discharge demonstrated normal LV function, and moderately dilated and mildly hypertrophied RV, with qualitatively mildly diminished systolic function. Her most recent catheterization (table 1) was performed three and a half months post-transplant, and demonstrated only mildly elevated right-sided pressures. She has no edema, is quite active, and has had no clinical signs or biopsy-evidence of graft rejection.

Discussion

Orthotopic heart transplantation remains the treatment of choice for patients with end-stage heart failure. Post-transplant RV dysfunction is a significant cause of morbidity and mortality after OHT, (1-5) and can lead to death in up to 19% of patients post-transplant. (3) Pre-operative elevation of PVRI is tightly linked to the development of post-transplant RV dysfunction, and is a major factor that precludes patients being listed for transplant. The etiology of right heart failure in such cases is due to the inability of the normal thin-walled donor RV to instantaneously compensate for the sudden increase in afterload from elevated PVRI. This can occur after implantation at discontinuation of cardiopulmonary bypass, or may occur over the first 24-48 hours after surgery. (6) Elevated PVR is generally defined as > 2.5 WU in the adult population, and > 5 WU is considered at least a relative contraindication in most adult centers. (1, 7, 8) In pediatrics, PVR is indexed to body surface area (PVRI) to allow for a better comparison of hemodynamics between disparately sized patients. (9) Although controversy exists as to what level of PVRI is an absolute contraindication for OHT, in our experience PVRI at or below the range of 6 to 9 WU×m² is acceptable for successful OHT. (9, 10) The use of preoperative pulmonary vasodilators to lower PVRI for potential transplant recipients is well-described in the literature. (11-14) In cases of long-standing pulmonary hypertension, however, vasodilator therapies often fail to decrease PVRI sufficiently, (15) and their use in patients with elevated LV filling pressures can potentially be problematic, and in fact harmful, due to resultant pulmonary edema. For this subset of patients, heart-lung transplantation is an option, but this comes with significant increases in morbidity and mortality. (16, 17)

Use of a VAD has been proposed as a method for the reduction of PVR in potential OHT candidates refractory to medical therapies. (18-20) Adult studies have demonstrated that mechanical circulatory support using LVAD alone can decrease PVR, allowing patients to become eligible for transplantation, however in most reports PVR prior to VAD implantation is in the range of 4 to 6 WU. Some of these cases reported the use of RV assist device for more severe cases, and cases with RV failure. There are also reports in pediatric and adolescent patients describing VAD as a bridge to transplant, however discussions on the role of VAD in lowering PVRI in this patient population are sporadic. There has been reported use of biventricular assist device in pediatric patients as a means of lowering resistance, including two cases with PVRI > 10 WU×m². (21, 22) To date, the use of only LVAD, along with aggressive pulmonary vasodilator therapies, as a bridge to successful OHT in our patient with refractory pulmonary hypertension, is unique due to the severity of

PVRI elevation, which is one of the highest reported in the literature, as well as her relatively young age.

Our group has previously reported that pre-transplant vasodilator testing identifies patients at highest risk of morbidity and mortality related to RV failure. This study showed that in several children with very high PVRI who did not respond to preemptive use of iNO, the mortality rate after transplant was 14%. The data on patients who are responsive to vasodilators showed no mortality. (9) In our patient, initiation of oxygen during catheterization caused an increase in PCWP. Therefore, use of iNO was limited due to the severely elevated LV filling pressures and she was thought to be a poor candidate for chronic pulmonary vasodilator therapy. In addition, she remained unresponsive to chronic milrinone therapy. LVAD implantation not only allowed for unloading of the LV with a resultant decrease in filling pressures, but also provided the opportunity for aggressive pulmonary vasodilator treatment with iNO, which was eventually transitioned to oral sildenafil. Dramatic improvement in PVRI occurred in only one month, and successful OHT was performed just over two months following LVAD implantation in this patient who was previously unable to be listed, and may have required consideration for heart-lung transplantation.

We present a case of a teenage patient with history of dilated cardiomyopathy and severely elevated PVRI refractory to medical therapy. The successful use of LVAD in an adolescent patient with PVRI as high as $14.5 \text{ WU} \times \text{m}^2$, and subsequent dramatic improvement in resistance over a short period of time, is unique in the literature. The resultant improvement in PVRI allowed for this patient to become a suitable OHT recipient, avoiding the increased morbidity and mortality of heart-lung transplantation. We believe this strategy can potentially improve access to OHT for patients with elevated PVRI, with lower associated morbidity and mortality compared to heart-lung transplantation, and also spare the use of donor lungs for other patients awaiting lung transplant.

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Table 1

Summary of catheterization data at five time points (A. at presentation to our institution; B. one month following the initiation of continuous milrinone infusion; C. one month following LVAD implantation (with concurrent milrinone infusion and oral sildenafil); D. nine days following OHT; E. at last follow-up, three and a half months following OHT

	PA Sat	mRA (mmHg)	mPAP (mmHg)	PCWP (mmHg)	TPG (mmHg)	CI (L/min/m ²)	PVRI (WU×m ²)	SVRI (WU×m ²)
RHC A	51%	15	49	20	29	2.0	14.5	25
RHC B	52%	15	57	28	29	1.9	15.3	31
RHC C	61%	10	28	11	17	3.2	5.3	18
RHC D	58%	15	29	15	14	3.0	4.7	20
RHC E	68%	3	20	7	13	3.3	3.9	22

CI cardiac index; mPAP mean pulmonary artery pressure; mRA mean right atrial pressure; PA sat pulmonary artery saturation; PCWP pulmonary capillary wedge pressure; PVRI pulmonary vascular resistance index; RHC right heart catheterization; SVRI systemic vascular resistance index; TPG transpulmonary gradient.