Beyond Berlin: Heart transplantation in the "untransplantable"

Sanjiv K. Gandhi, MD,^a R. Mark Grady, MD,^b Charles B. Huddleston, MD,^a David T. Balzer, MD,^b and Charles E. Canter, MD,^a St Louis, Mo

Severe pulmonary hypertension unresponsive to acute pulmonary vasodilators—"fixed" or "irreversible" pulmonary hypertension—has traditionally been regarded as a contraindication to an orthotopic heart transplant. We report a novel strategy of combining mechanical biventricular assist device (BiVAD) support provided by the Berlin Heart EXCOR device (Berlin Heart AG, Berlin, Germany) with medical pulmonary vasodilator therapy in the cases of 2 children initially referred to our institution for a heart–lung transplant because of heart failure and presumed irreversible pulmonary hypertension. In both cases, our approach significantly improved the pulmonary hypertension, permitting an orthotopic heart transplant alone, a procedure with a much better long-term prognosis than a heart–lung transplant.

Case Reports

PATIENT 1. Patient 1 was a 2-year-old boy with congenitally corrected transposition of the great arteries, congenital heart block, and a small ventricular septal defect. He had undergone implantation of a single-chamber epicardial pacemaker as a neonate. He was seen at 2 years with worsening ventricular failure. Cardiac catheterization at that time demonstrated a pulmonary vascular resistance (PVR) of 15 Woods units/m² and a transpulmonary gradient of 40 mm Hg, unresponsive to oxygen or inhaled nitric oxide (Table 1).

Initiation of intravenous epoprostenol therapy and placement of a dual-chamber biventricular pacemaker in an attempt to optimize ventricular function and reduce PVR were poorly tolerated and resulted in significant cardiac instability. Ultimately, the child was placed on extracorporeal membrane oxygenation support. After 8 days of extracorporeal membrane oxygenation, the patient was transitioned to mechanical BiVAD support with the EXCOR system. The patient was weaned from extracorporeal circulation without difficulty and extubated at 1 week. He was maintained on a regimen of intravenous epoprostenol (initiated at 1 ng/[kg · min] and increased to 20 ng/[kg · min] over 3 weeks), oral sildenafil citrate (INN sildenafil, 5 mg four times daily), and oxygen by nasal cannula (2 L/min, inspired oxygen fraction 100%). During the next 4 weeks, the pa-

tient's rehabilitation was optimized. Repeat cardiac catheterization at 1 month after BiVAD implantation demonstrated normal pulmonary arterial pressures and normal PVR (Table 1). The patient underwent a successful orthotopic heart transplant 1 week later. His pulmonary arterial pressures in the operating room were normal. The child was extubated on postoperative day 2 and discharged from the hospital on postoperative day 12. Epoprostenol was tapered over 2 weeks, and sildenafil citrate was tapered over 3 months. The patient has undergone numerous postoperative endomyocardial biopsies with nearly normal hemodynamics. He remains clinically well 18 months after his heart transplant.

PATIENT 2. The second patient was a 10-month-old girl with a presentation of failure to thrive who was discovered to have a restrictive cardiomyopathy and severe pulmonary hypertension. Anatomically, she had a very small left ventricle, probably representing a forme fruste of hypoplastic left heart syndrome. Cardiac catheterization demonstrated a PVR of 11 Woods units/m² and a transpulmonary gradient of 42 mm Hg, minimally responsive to a combination of oxygen and inhaled nitric oxide (Table 2). The patient was started on a regimen of intravenous epoprostenol (initiated at 1 ng/[kg · min] and titrated to 15 ng/[kg · min] over 2 weeks), milrinone (1 µg/[kg · min]), and oral sildenafil citrate (3 mg four times daily) and was also maintained on inhaled nitric oxide (20 ppm by nasal cannula). Repeat cardiac catheterization 2 weeks after the initiation of medical therapy demonstrated only minimal improvement in the pulmonary hypertension. The decision was made to implant EXCOR BiVADs. In addition to maintenance of inhaled nitric oxide therapy, the epoprostenol was aggressively upwardly titrated (to a maximum dose of 40 ng/[kg · min]) and the sildenafil dosing was increased (7 mg by mouth four times daily). At 6 postoperative weeks, the PVR had dropped to 4.6 Woods units/m² and the transpulmonary gradient had declined to 14 mm Hg. At 10 postoperative weeks, a successful orthotopic heart transplant was performed. The patient's immediate postoperative course was uneventful. Epoprostenol was tapered over 3 weeks, and she was discharged on postoperative day 25. Sildenafil citrate was tapered over 2 months. The patient's posttransplant hemodynamics normalized, and she remains clinically well 6 months after her heart transplant.

Discussion

Severe pulmonary hypertension, especially associated with congenital heart disease, has traditionally been regarded as an absolute contraindication to a cardiac transplant alone because of the prohibitive risk of right ventricular failure in the allograft.¹ The outlook for these patients has changed, however, with the advent of potent pulmonary vasodilators. Patients with heart failure and pulmonary hypertension responsive to such agents acutely in the cardiac catheterization laboratory are considered to have reversible lung disease and are thus possible candidates for a heart transplant alone. Those patients whose pulmonary pressures do not respond are considered to have "fixed" or "irreversible" lung disease and are not

From the Divisions of Pediatric Cardiothoracic Surgery^a and Pediatric Cardiology,^b Saint Louis Children's Hospital, Washington University School of Medicine, St Louis, Mo.

Received for publication Nov 14, 2007; accepted for publication Jan 9, 2008.

Address for reprints: Sanjiv K. Gandhi, MD, Division of Cardiothoracic Surgery, Saint Louis Children's Hospital, Suite 5S50, 1 Children's Place, St Louis, MO 63110 (E-mail: gandhis@wustl.edu).

J Thorac Cardiovasc Surg 2008;136:529-31

0022-5223/\$34.00

Copyright © 2008 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2008.01.032

TABLE 1. Patient 1's hemodynamic variables at baseline and after interventions

	Baseline	iNO and 100% Fl_{O_2}	After BiVADs (4 wk)	After heart transplant	
				1 wk	1 y
Systemic pressure (mm Hg)	75/47	74/47	120/80	106/66	100/45
Pulmonary arterial pressure (mm Hg)	74/36	72/47	29/10	19/11	21/11
Transpulmonary gradient (mm Hg)	40	38	4	10	9
Cardiac index (L/[min · m ²])	2.9	2.3	2.9	3.4	3.7
Pulmonary vascular resistance (Woods units/m ²)	15	17.7	1.4	1.8	1.3

iNO, Inhaled nitric oxide; Fl_{O_2} , inspired oxygen fraction; BiVADs; biventricular assist devices.

considered eligible for a heart transplant alone. The traditional tenets of PVR with regard to a heart transplant are brought into question by the 2 cases in this report. Acute irreversibility in the catheterization laboratory may not equate to irreversibility over the course of weeks to months with pulmonary vasodilator therapy, mechanical ventricular assistance, or both. In these 2 cases, we reversed what was initially designated as irreversible pulmonary hypertension by using a combined surgical and medical approach. This strategy ultimately allowed a successful isolated orthotopic heart transplant. Our results suggest that the classification of who is eligible for a heart transplant should be broadened.

Although the pathophysiology of pulmonary hypertension in patients with heart failure is complex and multifactorial, it is in large part related to elevated left atrial filling pressures, which are a consequence of impaired left (systemic) ventricular systolic and diastolic function and, in many cases, systemic atrioventricular valve pathology. Left atrial hypertension translates into increased postcapillary pressure in the pulmonary circulation, which unleashes a cascade of biochemical responses, resulting in endothelial dysfunction, intimal thickening, and smooth muscle cell proliferation and thrombosis.² Whereas in idiopathic pulmonary hypertension these derangements are seemingly progressive and unalterable, our patients and other data suggest that in patients whose lung disease is secondary to heart failure, this process can be halted or even reversed.

Continuous unloading of the left ventricle, thereby lowering left atrial pressure, is the theoretic basis for ventricular assist device implantation in these patients as a mechanism of improving their pulmonary hypertension. There is information in adults that this unloading of the left ventricle, accomplished by left ventricular assist device insertion, reduces elevated PVR over time.³ Most of these previously described adult patients have had a modest (5–6

Woods units/m²) elevation of PVR, unlike the extreme pulmonary hypertension present in the children in this report. In addition, most have not had severe right heart failure and have thus undergone isolated left ventricular assist device implantation. As recent technologic advancements have made ventricular assist devices applicable even to infants, even the smallest child with end-stage heart failure and lung disease may benefit from their use.

We combined the use of mechanical ventricular assistance with aggressive use of pulmonary vasodilators. Animal and human studies have implicated several molecular mechanisms in the development of pulmonary hypertensive changes.⁴ Such medications as inhaled nitric oxide, phosphodiesterase 5 inhibitors, endothelin receptor antagonists, and epoprostenol analogs have been shown not only to reduce pulmonary arterial pressure acutely but also to reverse some of the pathologic remodeling that has already occurred in the pulmonary vascular bed. The clinical application of combination medical pulmonary vasodilator therapy to affect chronic pulmonary hypertension is becoming more widespread⁵ and may be particularly effective in children, in whom the chronicity of vascular changes is relatively short relative to adults. This pharmacotherapy is also an important adjunct in the immediate posttransplant period, when allograft function may be compromised by even mildly elevated pulmonary arterial pressures.

Our results suggest that patients with end-stage heart disease and severe pulmonary hypertension may be successful candidates for a heart transplant alone, instead of a heart–lung transplant. When evaluating children for a heart transplant in situations where fixed pulmonary hypertension is apparently present, consideration should be given to an aggressive trial of medical pulmonary vasodilators. If these prove ineffective, implantation of BiVADs in concert with medical therapy may resurrect the potential of a heart transplant for a patient previously considered ineligible.

TABLE 2. Patient 2's hemodynamic variables at baseline and after interventions

	Baseline	iNO and 100% Fl_{O_2}	After therapy* (2 wk)	After BiVADs		After heart transplant	
				3 wk	6 wk	6 wk	6 mo
Systemic pressure (mm Hg)	80/50	67/36	96/64	100/50	105/55	114/55	110/60
Pulmonary arterial pressure (mm Hg)	96/41	58/22	80/48	57/15	48/8	18/11	30/17
Transpulmonary gradient (mm Hg)	42	23	34	21	14	8	10
Cardiac index (L/[min · m ²])	3.9	3.9	3.6	3.0	3.0	4.6	5.3
Pulmonary vascular resistance (Woods units/m ²)	11	8	9.2	7	4.6	2.1	1.9

iNO, Inhaled nitric oxide; Fl_{O_2} , inspired oxygen fraction; BiVADs; biventricular assist devices. *Therapy with epoprostenol, milrinone, sildenafil citrate [INN sildenafil], and inhaled nitric oxide.

References

- Butler J, Stankewicz MA, Wu J, Chomsky DB, Howser RL, Khadim G, et al. Pre-transplant reversible pulmonary hypertension predicts higher risk mortality after cardiac transplantation. *J Heart Lung Transplant*. 2005;24:170-7.
- Humbert M, Morrell NW, Archer SL, Stenmark KR, MacLean MR, Lang IM, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43(12 Suppl S):13S-24S.
- Haddad H, Elabbassi W, Moustafa S, Davies R, Mesana T, Hendry P, et al. Left ventricular assist devices as bridge to heart transplantation in congestive heart failure with pulmonary hypertension. *ASAIO J*. 2005;51:456-60.
- Ito T, Ozawa K, Shimada K. Current drug targets and future therapy of pulmonary arterial hypertension. *Curr Med Chem*. 2007;14:719-33.
- Mogollon MV, Lage E, Cabezon S, Hinojosa R, Ballesteros S, Aranda A, et al. Combination therapy with sildenafil and bosentan reverts severe pulmonary hypertension and allows heart transplantation: case report. *Transplant Proc*. 2006;38:2522-3.

Total resection and complete reconstruction of the tricuspid valve in acute infective endocarditis

Igor E. Konstantinov, MD, PhD, Perth, Australia

Acute infective endocarditis of the tricuspid valve (TV) in noncompliant intravenous drug abusers presents a difficult problem. Progressive sepsis despite appropriate antibiotics necessitates surgical intervention. These noncompliant patients, however, often leave the hospital against medical advice. The risk of prosthetic endocarditis in this group of patients is very high. Complete resection of the valve without replacement, although feasible, can result in progressive right-sided heart failure. Reconstruction of the TV might be an alternative option.

Clinical Summary

A 33-year-old man with a long history of intravenous drug abuse was admitted with fever and chills. He previously underwent drainage of an infected left hip joint, as well as multiple bilateral groin abscesses at the site of drug injection. Multiple blood cultures demonstrated *Staphylococcus aureus*. Despite appropriate antibiotic coverage, uncontrolled sepsis developed. Echocardiographic analysis demonstrated large multiple vegetations of the TV (Figure 1, A) and an abscess extending into the free wall of the right ventricle. This infective process involved all 3 leaflets, causing TV stenosis (Figure 1, C).

The patient underwent urgent surgical intervention. Total resection of the TV and the entire subvalvular apparatus was performed. The right ventricular abscess was drained. The entire operation was performed on the beating heart with cardiopulmonary bypass. The

TV was reconstructed with autologous pericardium soaked in rifampicin (Figure 1, B-D and E) and polytetrafluoroethylene* cords. Apart from 4-0 polytetrafluoroethylene cords and 4-0 Prolene sutures, no artificial material was used. After complete resection of all infected tissues, a distance from the papillary muscles or right ventricular wall was measured by using a Silastic tube at approximately two thirds of the distance to the TV annulus (Figure 2, A). A polytetrafluoroethylene suture was then placed through the free edge of the reconstructed leaflet, right ventricular myocardium, and pericardial pledget and introduced into the previously sized tube (Figure 2, B). The polytetrafluoroethylene cord was then tightened with the tube in place to prevent incidental shortening of the cord while tightening the knots (Figure 2, C). The tube was then removed, and the reconstructed leaflet was retracted (Figure 2, D and E). Each leaflet was suspended by 3 cords placed in a similar fashion (Figure 2, F-H). The pulmonary artery was then clamped. The newly reconstructed valve was tested with warm normal saline with the heart beating to recreate a normal anatomy of the distended right ventricle. Postoperative echocardiographic analysis demonstrated normal function of the reconstructed TV and subvalvular apparatus (Figure 1, B). The patient is asymptomatic at 3 months of follow-up yet continues to abuse drugs.

Discussion

Surgical treatment of acute right-sided endocarditis is associated with significant mortality.¹ Complete destruction of the TV in a non-compliant patient is a difficult problem. These patients often leave the hospital despite medical advice once they feel better and do not complete the full course of antibiotics. Recurrences of endocarditis are common. Replacement of the valve with a prosthesis carries a very high risk of prosthetic endocarditis, whereas valve excision results in massive tricuspid regurgitation. Although successful repair of acute TV endocarditis involving a single leaflet has been reported,² a complete reconstruction after total resection of the TV is a much more challenging procedure. A simplified technique for

From the Department of Cardiothoracic Surgery, Sir Charles Gairdner Hospital, Perth, Australia.

Received for publication Dec 20, 2007; accepted for publication Dec 24, 2007.

Address for reprints: Igor E. Konstantinov, MD, PhD, Department of Cardiothoracic Surgery, Sir Charles Gairdner Hospital, G Block, Hospital Avenue, Perth, WA 6009 Australia (E-mail: konstantinov.igor@alumni.mayo.edu).

J Thorac Cardiovasc Surg 2008;136:531-2

0022-5223/\$34.00

Copyright © 2008 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2007.12.061

*Gore-Tex cord, registered trademark of W. L. Gore & Associates, Inc, Newark, Del.