Outcome of patients with pulmonary arterial hypertension referred for lung transplantation: A 14-year single-center experience

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Objective: To analyze the outcomes of patients with pulmonary arterial hypertension referred for lung transplantation and determine the changes over time.

Methods: All patients with pulmonary arterial hypertension referred for lung transplantation in our program from January 1997 to September 2010 were reviewed. Pulmonary arterial hypertension was classified as idiopathic (n = 123) or associated with congenital heart disease (n = 77), connective tissue disease (n = 102), or chronic thromboembolic disease (n = 14).

Results: After completing their assessment, 61 patients (19%) were found to be unsuitable for lung transplantation, 38 (12%) refused lung transplantation, 65 (21%) were too early to be listed, and 48 (15%) died before their assessment (n = 34) or being listed (n = 14). Of the 100 patients listed for lung transplantation, 57 underwent bilateral lung transplantation, 22 underwent heart–lung transplantation, 18 died while waiting, and 3 were still waiting. The waiting list mortality was the greatest for patients with connective tissue disease–pulmonary arterial hypertension (34% vs 11% in the remaining patients, $P = .005$). The number of patients admitted to the hospital to be bridged to lung transplantation increased from 7% in the 1997–2004 cohort to 25% in the 2005–2010 cohort ($P = .02$). After lung transplantation, the 30-day mortality decreased from 24% in the 1997–2004 group to 6% in the 2005–2010 group ($P = .007$). The 10-year survival was worse for those with idiopathic pulmonary arterial hypertension (42% vs 70% for the remaining patients, $P = .01$). The long-term survival reached 69% at 10 years in the patients with connective tissue disease pulmonary arterial hypertension.

Conclusions: Lung transplantation is an option for about one third of the patients with pulmonary arterial hypertension referred for lung transplantation. The 30-day mortality after lung transplantation improved significantly over time, but the long-term survival remained similar between the two cohorts. Patients with connective tissue disease–pulmonary arterial hypertension have a high mortality on the waiting list but excellent long-term survival. (J Thorac Cardiovasc Surg 2012;143:910-8)

Lung transplantation is the only therapeutic option for patients with pulmonary arterial hypertension (PAH) when medical therapy fails. However, lung transplantation for patients with PAH has generally been hindered by high mortality on the waiting list and in the early post-transplant period. A recent analysis of the United Network for Organ Sharing data demonstrated that the waiting list mortality for patients with idiopathic PAH (iPAH) was 20% at 1 year after listing, and the mortality after transplantation was 18% at 1 year after surgery.[1] The analysis also showed that, in contrast to other indications for lung transplantation, the 1-year mortality for patients with iPAH is predominantly driven by the mortality occurring within the first 30 days after transplantation.[1] According to the registry from the International Society for Heart and Lung Transplantation, patients with iPAH surviving beyond 30 days after transplantation have long-term outcomes similar to those of patients undergoing lung transplantation for indications other than iPAH.[2]

During the past several years, the perioperative management of patients undergoing lung transplantation has improved substantially, and several experienced centers have reported an overall 30-day mortality of less than 5% after lung transplantation.[3,4] The implementation of extracorporeal life support (ECLS) in the pretransplant setting has also helped to successfully bridge an increasing number of patients with respiratory failure to lung transplantation.[5] The effect of these improvements on the pre- and post-transplant outcome of patients with PAH is unclear.

The population of patients with PAH undergoing lung transplantation can be divided into three categories

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Abbreviations and Acronyms

CHD = congenital heart disease
CT = computed tomography
CTD = connective tissue disease
CTEPH = chronic thromboembolic pulmonary hypertension
ECLS = extracorporeal life support
GERD = gastroesophageal reflux disease
iPAH = idiopathic pulmonary arterial hypertension
PAH = pulmonary arterial hypertension
PGD = primary graft dysfunction

according to the most recent pulmonary hypertension classification: iPAH, PAH associated with congenital heart disease (CHD-PAH), and PAH associated with connective tissue disease (CTD-PAH). The number of patients with a diagnosis of iPAH, CHD-PAH, and CTD-PAH represents less than 5% of all patients undergoing lung transplantation worldwide; therefore, few studies have compared the outcomes of patients with PAH before and after lung transplantation.[2] In the present study, we reviewed our experience with all patients with PAH referred to the Toronto Lung Transplant Program during the past 14 years and compared the outcomes before and after lung transplantation for iPAH, CHD-PAH, and CTD-PAH. The changes over time were analyzed by comparing two cohorts of patients: 1997 to 2004 and 2005 to 2010.

MATERIALS AND METHODS

All patients referred for lung or heart–lung transplantation in our program from January 1, 1997 to September 10, 2010 were retrospectively reviewed from a prospectively collected database after the University Health Network Research Ethics Board had approved the study and waived the need for informed consent. The diagnosis was reviewed for all patients with PAH. Patients with PAH were then classified into different categories according to the Dana Point classification.[6] Heritable and anorexigen-mediated PAH were classified with iPAH, because these conditions only involve the pulmonary vasculature. Patients with associated conditions were divided into those with CTD-PAH and CHD-PAH. Patients with PAH related to portal hypertension, chronic hemolytic anemia, human immunodeficiency virus infection, and schistosomiasis were excluded from the present study, because these patients are rarely or never referred for lung transplantation.

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) who had pulmonary endarterectomy and recurrence of pulmonary hypertension or patients with CTEPH deemed not to be candidates for pulmonary endarterectomy were included in the present study, because these patients can have an underlying PAH component to their disease.[6] We were also interested in determining the number of patients with CTEPH referred for lung transplantation since we had started the pulmonary endarterectomy program in our institution in 2005. Ventilation/perfusion scans were used to differentiate PAH from CTEPH. CTEPH was then confirmed by pulmonary angiography and computed tomography (CT) pulmonary angiography. Our indication for pulmonary endarterectomy has evolved over the years, but we currently considered pulmonary endarterectomy for all patients with evidence of chronic thromboembolic disease localized in the segmental arteries or more proximally on the pulmonary angiogram and/or CT pulmonary angiogram, regardless of the degree of right ventricular dysfunction or the severity of the pulmonary vascular resistance.

We recommend that patients with PAH be assessed for transplantation when intravenous epoprostenol is being considered, with a plan to list them when they deteriorate clinically to New York Heart Association class III or IV despite optimal medical therapy, including intravenous epoprostenol. We believe that early assessment is crucial for these patients, even if the time of listing is delayed by several years (through the use of medical treatment) to ensure that patients understand the implication of the transplant option and to be able to provide rapid listing in the event their clinical course is more precarious than expected. The use of intravenous epoprostenol started in 1997 in our institution. In 2006, we implemented the option of ECLS to bridge patients with PAH to lung transplantation. The pumpless Novalung (Novalung GmbH, Hechingen, Germany) connected between the pulmonary artery and the left atrium was used as the preferred option for these patients.[7]

All patients with PAH listed for lung transplantation underwent right heart catheterization before their referral or before being listed. Pulmonary hypertension was defined as a mean pulmonary artery pressure greater than 25 mm Hg with a pulmonary capillary wedge pressure of less than 15 mm Hg. Occasionally, patients with CTD who were deemed too healthy to be listed had their right heart catheterization delayed until the time of listing. In these situations, if right heart catheterization had not been done by September 2010, a calculated pulmonary artery systolic pressure greater than 40 mm Hg at rest on the echocardiogram was used to define pulmonary hypertension to ensure that the denominator of patients with CTD-PAH was as complete as possible. Patients with severe interstitial lung disease defined by a total lung capacity less than 60% were excluded from the present study.

The donor and recipient management has been reviewed in detail elsewhere.[8] In brief, all donors received intravenous methylprednisolone (15 mg/kg, Solu-Medrol, Upjohn, Don Mills, ON, Canada) after brain death declaration. The donors were maintained euvolemic to avoid excess fluid administration, and vasopressin and/or noradrenaline were often used to maintain adequate blood pressure. Low potassium dextran solution (Perfadex, Vitrolife, Goteborg, Sweden) has been used for all lung preservation since April 1998. A retrograde flush has been added to the anterograde flush since 2001. Severe primary graft dysfunction (PGD) was defined according to the International Society for Heart and Lung Transplantation definition as grade III PGD during the initial 72 hours after transplantation.

Since 1994, the policy in our program has been to offer bilateral lung transplantation to all patients diagnosed with PAH. Heart–lung transplantation was considered only for patients with evidence of severe left ventricular dysfunction (left ventricular ejection fraction <40%) on the echocardiogram and/or the presence of technical limitations to conduct bilateral lung transplantation. Bilateral lung transplantations were performed through a clamshell incision and heart–lung transplantations through a clamshell incision or sternotomy. The approach to bilateral lung transplantation has not changed over time, and all but 1 patient underwent bilateral sequential lung transplantation in the present series. One patient with CHD underwent en bloc double lung transplantation for anatomic reasons.

Organ allocation in Canada has remained the same during the study period. All lung donors located in Ontario were allocated to Toronto. Donors from other provinces were allocated to the local program if there was one. If there was no program, the lungs were sequentially offered to the different lung transplant centers throughout Canada. Transplant physicians from the selected transplant center then chose the recipient on the basis of blood group, size match, patient status, and duration on the waiting list.

To define the changes over time, the patients were divided into 2 cohorts, 1997 to 2004 and 2005 to 2010. The cutoff between the 2 cohorts was at the time of referral, point of listing, and time of transplantation. Follow-up was complete until September 2010 for all patients.