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ORIGINAL ARTICLE

Double-lung Transplantation in 15 Patients With Pulmonary Hypertension

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ABSTRACT

Background: Pulmonary hypertension is a serious disease that, in its terminal phase, requires lung transplantation.
Patients and methods: A retrospective study was undertaken of 15 patients with pulmonary hypertension who underwent lung transplantation between 1994 and 2004.
Results: Pulmonary hypertension was reported as idiopathic in 8 patients (53%) and related to consumption of toxic oil in 2. The remaining causes were documented as chronic peripheral pulmonary embolism, histiocytosis X, venoocclusive disease, scleroderma, and simple corrected congenital heart defect in 1 patient each. The mean values of the hemodynamic variables were 100, 50, and 67 mm Hg for systolic, diastolic, and mean pulmonary artery pressure, respectively; 2.63 L/min for cardiac output; and 20.9 Wood units for total pulmonary resistance. The mean time between diagnosis of pulmonary hypertension and lung transplantation was 5.9 years (range, 0.4-20 y). Seven patients were in functional class III and 8 in functional class IV. The mean 6-minute walk distance was 204 m (range, 0-360 m). Four patients (26%) died during the during the perioperative period and 9 (60%), 7 (46%), and 6 (40%) were still alive at 1, 3, and 5 years, respectively.
Conclusions: Double-lung transplantation is a therapeutic option that, in certain cases, has similar outcomes to those achieved with the most aggressive medical treatment for pulmonary hypertension.

Trasplante bipulmonar en hipertensión pulmonar. Una serie de 15 pacientes

Palabras clave:
Hipertensión pulmonar
Trasplante pulmonar
Trasplante bipulmonar

RESUMEN

Introducción: La hipertensión pulmonar (HP) es una enfermedad grave tributaria de trasplante pulmonar (TP) en su fase terminal.
Pacientes y métodos: Se ha realizado un estudio retrospectivo de 15 pacientes con HP, a los que se trató con un TP en el período 1994–2004. Se revisan los datos clínicos antes del trasplante y el seguimiento tras éste.
Resultados: En 8 pacientes (53%) la HP fue idiopática y en 2 estuvo relacionada con el consumo de aceite tóxico; el resto de etiologías, con un paciente cada una, fueron: embolia pulmonar crónica periférica, histiocitosis X, enfermedad venooclusiva, esclerodermia y cardiopatía congénita simple corregida. Los valores hemodinámicos medios fueron: presión arterial pulmonar sistólica, diastólica y media, 100, 50 y 67 mmHg, respectivamente; gasto cardíaco, 2,63 l/min; resistencia pulmonar total, 20,9 UW. El tiempo desde el diagnóstico de HP hasta el TP fue de 5,9 (rango: 0,4-20) años. Siete pacientes estaban en clase funcional III y 8 en clase funcional IV. La distancia media recorrida en la prueba de la marcha de 6 min fue de 204 m (rango: 0–360). La mortalidad perioperatoria fue de 4 pacientes (26%). La supervivencia a 1, 3 y 5 años fue de 9 (60%), 7 (46%) y 6 (40%) pacientes, respectivamente.
Conclusiones: El TP bilateral es una opción terapéutica que, en casos seleccionados, presenta resultados comparables al tratamiento médico más activo de la HP.

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Introduction

Pulmonary hypertension is an uncommon and serious disease for which there is currently no known cure. It is defined as resting mean pulmonary artery pressure above 25 mm Hg or above 30 mm Hg during exercise. On average, the natural course of the disease leads to death within 3 years of diagnosis.[1,2]

Specific medical treatment has been developed over the past 30 years, but only in the last 10 years have most of the drugs useful in this disease actually started to be used. Thus from the mid 1980s until the beginning of 2000s, the only therapeutic option for these patients was lung transplantation. The type of lung transplantation for pulmonary hypertension has varied over the years. Initially heart-lung transplantation was preferred, with favorable outcomes in some series.[3] Subsequently, some groups opted for single-lung transplantation[4] before, finally, in recent years, double-lung transplantation became the treatment of choice in many hospitals.[5-7] With regard to medical treatment, the first specific drug for the disease to become available was epoprostenol, approved by the regulatory agencies at the end of the 1990s.[8] From 2002 onwards, pivotal trials with subcutaneous treprostinil,[9] inhaled iloprost,[10] oral beraprost,[11] and bosentan[12] were published. Three years later, clinical trials with sildenafil,[13] sitaxsentan,[14] and ambrisentan[15] started to be published. These drugs have been shown to partially improve exercise tolerance and hemodynamics, but not all treated patients achieve sustained benefit, indicating that we are still some way from curing the disease. Lung transplantation therefore remains the ultimate option in the therapeutic algorithm for treatment of pulmonary hypertension.[16] The decision of when to refer a patient for transplantation has been made more difficult with the availability of these new drugs. All transplant groups agree that patients should not be allowed to reach a terminal state because lung transplantation cannot be done in such cases.[17] Although some lung transplant recipients die as a result of the procedure, the pulmonary hemodynamics in those who survive quickly returns to normal, allowing the recovery of right ventricular function and structure.[18,19]

The present study reviews a series of patients with pulmonary hypertension who underwent transplantation in our hospital over a 10-year period.

Patients and Methods

Data were retrospectively collected for patients who underwent lung transplantation for pulmonary hypertension in our hospital between August 1994 and December 2004. From December 2004 until the end of follow-up in December 2007, no patients received a lung transplantation for pulmonary hypertension. Of a total of 243 transplantation procedures in the study period, 15 (6%) corresponded to patients with pulmonary hypertension–11 women (73%) and 4 men (27%) with a mean age of 37.3 years (range, 23-56 years) on diagnosis of the disease. In all cases, diagnosis of pulmonary hypertension was made by right heart catheterization. By etiology, and according to the traditional clinical classification,[20] 13 belonged to group I (8 cases of idiopathic pulmonary hypertension, 2 cases of toxin [rapeseed oil]-induced pulmonary hypertension, 1 case secondary to scleroderma, 1 case of pulmonary veno-occlusive disease, and 1 case of corrected patent ductus arteriosus), 1 to group IV (pulmonary embolism associated with Paget-Schrötter syndrome), and 1 to group V (histiocytosis X). In the diagnostic pulmonary hemodynamics study, the following mean values were recorded: systolic pulmonary artery pressure, 100 mm Hg (range, 65-141 mm Hg); diastolic pulmonary artery pressure, 50 mm Hg (range, 28-72 mm Hg), average pulmonary artery pressure, 67.3 mm Hg (range, 42-97 mm Hg); cardiac output, 2.63 L/min (range, 1.9-3.24 L/min); and total pulmonary resistance, 20.9 UW (range, 12.8-30.4 UW). The acute vasodilator test with intravenous epoprostenol was negative in all 13 patients in whom it was performed (Table).

These patients were considered eligible for lung transplantation given that they met the established criteria, namely: advanced disease with limited life expectancy; age under 60 years; no progressive, irreversible disease in other organs; absence of active infections or other contraindications for immunosuppressive therapy; acceptable nutritional status; and no evidence of surgical contraindications or psychosocial problems. The patients were studied according to the hospital's preoperative protocol and added to the waiting list for lung transplantation with the prior approval of the hospital's lung transplant committee.

For this indication, double-lung transplantation was the only type of procedure considered. The technique has been described previously.[21] Briefly, the lung was accessed by anterior transversal and submammary thoracosternotomy (clamp shell access) with sequential implantation. Elective cardiopulmonary bypass was practiced in all patients.

Postoperative immunosuppressive therapy consisted in all cases of a combination of cyclosporine, methylprednisolone, and azathioprine, while tacrolimus, mofetil mycophenolate, and rapamycin were reserved for second-line immunosuppression. The drugs used during the induction phase were the same as those

Table
Characteristics of the Sample Before Transplantation

	Age, y/Sex	Etiology	Year of Transplantation	Survival After Transplantation	mPAP, mm Hg	CO, L/min	FC	6MWD, m	Treatment	FVC, %
1	32/F	Rapeseed oil	1994	4927[a]	75	2.2	III	47	–	86
2	33/F	IPAH	1996	124	64	2.6	IV	180	–	85
3	34/F	IPAH	1996	770	64	1.9	IV	252	–	107
4	27/F	PE	1996	1	49	2.6	III	323	–	98
5	23/M	IPAH	1996	4197[a]	70	3.2	IV	–	Inhaled iloprost	104
6	46/F	Rapeseed oil	1998	3325[a]	45	2.9	III	240	–	103
7	52/F	IPAH	1999	1080	64	2.6	IV	228	Epoprostenol	110
8	45/F	IPAH	1999	6	62	2.6	III	204	–	78
9	36/M	IPAH	1999	37	64	3.1	III	210	–	97
10	26/F	Corrected ductus arteriosus	2000	1	97	2.4	III	360	–	62
11	51/F	Scleroderma-CREST	2000	2628[a]	42	2.6	III	255	–	71
12	56/F	IPAH	2000	2615[a]	85	2.9	IV	336	Epoprostenol	91
13	34/M	VOPD	2001	1365	64	2.6	IV	–	–	85
14	39/F	Histiocytosis X	2002	2035[a]	70	2.6	IV	312	Epoprostenol	56
15	26/F	IPAH	2004	1	78	2.6	IV	372	Epoprostenol	50

Abbreviations: CO, cardiac output; CREST, calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; F, female; FC, functional class; FVC, forced vital capacity; IPAH, idiopathic pulmonary artery hypertension; M, male; mPAP, mean pulmonary artery pressure; PE, pulmonary thromboembolism; VOPD, veno-occlusive pulmonary disease; 6MWD, 6-minute walk distance.

[a] Patients alive at the end of follow-up.

administered during maintenance. Treatment with cyclosporine was started on the day of the operation and the dose was adjusted to give a residual concentration (C_0) of between 200 and 400 ng/mL. Treatment with methylprednisolone was started during the procedure, before reperfusing the transplanted lungs, at a dose of 10 mg/kg; the dose on the first day was 375 mg, followed by 0.5 mg/kg/d for the first 3 months. After this period, 0.1-0.2 mg/kg/d were administered indefinitely. Cytomegalovirus prophylaxis was given to all patients. This consisted of intravenous ganciclovir before 2000, oral ganciclovir between 2000 and 2002, and valganciclovir between 2002 and 2004 for 4 to 6 months after the procedure.

A retrospective description of the results in these patients was obtained from a systematic chart review. For the descriptive presentation of the quantitative variables, means (SD) were given, with the range and/or median when these values might provide additional information. Qualitative variables were expressed as frequency and percentage. Survival was analyzed using the Kaplan-Meier method.

Results

Between August 1994 and February 2004, the 15 lung transplant operations for pulmonary hypertension accounted for 6% of all lung transplantation procedures in our hospital. The mean time between diagnosis of pulmonary hypertension and lung transplantation was 5.9 years (range, 0.4-20 years). The mean time on the waiting list was 222 days (range, 6-684 days). At the time of transplantation, 7 patients were in functional class III and 8 in functional class IV. Five patients, all in functional class IV, were receiving specific medication (prostaglandins) for pulmonary hypertension (4 intravenously and 1 by inhalation). The 13 patients able to do a 6-minute walk test covered a mean distance of 255 m (range, 47-372 m). Two patients were unable to perform the test because they were in a critical state. On joining the waiting list, the patients had a mean forced vital capacity of 85% (range, 50%-110%), forced expiratory volume in 1 second of 83% (range, 49%-112%), and a diffusing capacity of lung for carbon monoxide of 58% (range, 21%-100%).

In all cases, double-lung transplantation was performed with elective cardiopulmonary bypass. The mean duration of cardiopulmonary bypass was 386 minutes (range, 180-480 minutes) and the mean duration of ischemia of the second lung was 500 minutes (range, 290-570 minutes). No deaths were recorded during the operation. After the operation, patients were on mechanical ventilation for a mean duration of 270 hours (range, 8-1680 hours). Of the patients who survived the immediate postoperative period, 6 (54.5%) were extubated within 7 days of the operation.

The mean stay in hospital after lung transplantation lasted 38 days (range, 1-150 days), with 22 days in the intensive care unit (range, 1-112 days) and 16 days on the hospital ward (range, 0-68 days). For the patients who were finally discharged from hospital, the overall mean stay in hospital after lung transplantation was 46 days (range, 15-150 days), with 19 days in the intensive care unit (range, 5-82 days) and 26 days on the hospital ward (range, 8-43 days).

Perioperative Complications

Perioperative deaths occurred in 4 patients (26.6%), 3 of whom died within 24 hours of the operation. Causes of death were massive postoperative pleural hemorrhage (n=2), pulmonary thromboembolism (n=1), and primary graft dysfunction (n=1).

Eight-six percent of the patients experienced at least 1 perioperative complication. Pleuropulmonary complications (pleural hemorrhage, anastomotic dehiscence, bleeding from the suture line, atelectasis, and anastomotic ischemia) were reported in 7 patients (46%). Four patients (26%) experienced hemodynamic complications (severe cold ischemia, pulmonary thromboembolism, cardiac tamponade) and 3 (20%) experienced hematologic complications (persistent thrombocytopenia, disseminated intravascular coagulation, postoperative hemorrhagic diathesis).

During the perioperative period 5 patients (33%) presented infectious complications (2 cases of *Staphylococcus aureus* bacteremia, 1 case of *Candida* bronchitis, 1 case of *Pseudomonas aeruginosa* bronchitis, and 1 case of bronchitis caused by several microorganisms [*Stenotrophomona maltophilia*, *Acinetobacter* species, and *Candida* species]) and there was 1 case of *Acinetobacter* sepsis.

Late Complications

Five patients died in the late postoperative period (from day 30 after transplantation until the end of follow-up). The causes of death were bronchiolitis obliterans (3 patients), toxoplasmosis on day 37 after the operation (1 patient), and multiorgan failure on day 124 (1 patient). After the first month of follow-up, 7 out of 11 patients experienced a total of 23 episodes of infection, with a mean of 2.09 episodes per patient. The types of infection were as follows: 15 bacterial infections, 3 infections with *Aspergillus* species, 1 infection with *Candida* species, 2 herpes zoster infections, and 2 cytomegalovirus infections.

Acute and Chronic Rejection

Five episodes of acute symptomatic rejection (within the first month) were diagnosed by transbronchial biopsy a mean of 12.6 days after transplantation (range, 9-16 days). No relapses associated with acute rejection were reported. The overall rate of acute rejection was 45% (corresponding to 5 of the 11 patients who survived for more than 1 week).

Bronchiolitis obliterans was diagnosed in 7 of the 11 long-term survivors. The mean time between diagnosis of bronchiolitis obliterans and lung transplantation was 2.4 years (range, 0.3-5.8 years). Deaths attributed to bronchiolitis obliterans were reported in 3 of the 7 patients at study completion. The mean duration of follow-up in the patients diagnosed with bronchiolitis obliterans was 3.3 years (range, 1.3-6.7 years).

Survival

The mean survival was 4.2 years (Figure). Four patients died during the immediate postoperative period and 2 later while still in

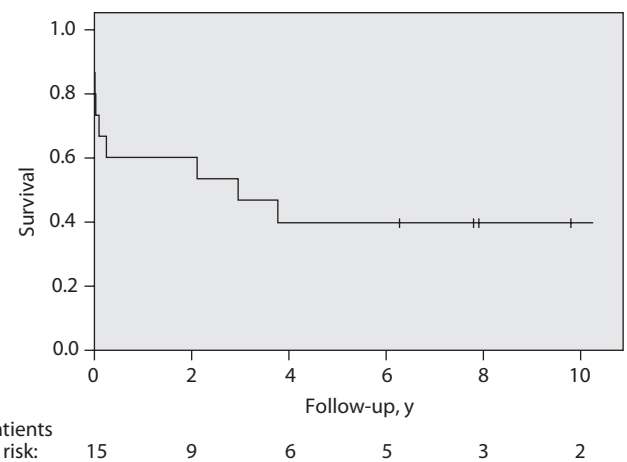

Figure 1. Actuarial survival of 15 patients with pulmonary hypertension who underwent lung transplantation.

hospital. All of the 9 patients who were discharged after transplantation led a normal and independent life, with normal pulmonary blood pressure and no right heart failure in the long-term follow-up. The mean survival in this group was 6.9 years (range 2.1-13.5 years).

During the study, 5 patients (33.3%) remained in follow-up at our hospital and 1 had been lost to follow-up. The mean survival in this group at the end of follow-up was 10.8 years (range 5.5-13.5 years).

Discussion

Mean long-term survival in this series was 4.2 years. The lung transplant operations for pulmonary hypertension accounted for 6% of all lung transplantation procedures in our hospital. These levels of activity are in line with those of the international registry,[6] in which the percentage of transplantations for pulmonary hypertension ranges from 10% of all double-lung transplantations in the 1990s to 3% of the total at present, with survival at 1 and 5 years of 65% and 46%, respectively. Similar results have been reported in other series of patients. A group in St Louis, United States, published a series of 100 patients–the largest series of lung transplant recipients at a single site–in which actuarial survival at 5 years was 57%.[4] This figure shows a marked contrast with that reported for the Baltimore program, in which actuarial survival at 4 years in a small number of patients was 80%.[22] The results of the present study are, however, consistent in terms of both long-term survival and perioperative mortality with those of the international registry, which covers most of the world's lung transplantation activity. Perioperative mortality in our series was 26%, which can be considered as comparable with published data.[6] It is known that patients undergoing lung transplantation for pulmonary hypertension are at high surgical risk. In addition, transplantation procedures performed in the 1990s are subject to a learning curve, an effect which has also been evaluated in the international registry, with improved outcomes reported as the transplant teams acquire experience.

The causes of death in the perioperative period in our series were pleural hemorrhage in 2 patients, pulmonary thromboembolism in 1 patient, and primary graft failure in 1 patient. Apart from pulmonary thromboembolism, which is an uncommon complication, these causes of death might be expected in view of the nature of the disease and the difficulty of the operation. According to data reported from both the international registry[6] and single-center series,[4,22] the main cause of death-and therefore the mean reason for lower perioperative survival-in patients after transplantation for pulmonary hypertension is primary graft failure.[6,23] In the present series, this cause was reported only once.

Other nonfatal perioperative complications were 4 episodes of pleural hemorrhage, 2 cases of anastomotic ischemia, 2 cases of anastomotic dehiscence, and 1 case of bleeding from the suture line. In this period, the incidence and characteristics of infectious complications were no different to those of other lung transplant recipients. Bronchiolitis obliterans resulting from chronic rejection has been reported as the most common long-term complication in lung transplant recipients for pulmonary hypertension.[24,25] Indeed, in our study, 63% of the long-term survivors presented with bronchiolitis obliterans, although these results are in disagreement with those presented in series from other reference hospitals[4,22]: bronchiolitis obliterans in the series at the St Louis Hospital was reported in 38% of a group of double-lung transplant recipients for pulmonary hypertension while in the Baltimore group, only 18% in a group of 55 patients experienced this complication. The lack of agreement with our data might be explained by the duration of follow-up, which ranged from 3 to 5 years in those series in contrast to a mean of 6.9 years in our patients.

The advantage of double-lung transplantation over other techniques is recognized in the medical literature, even by groups who initially opted for single-lung transplantation.[4,26] The main reason is that postoperative management is easier, given that reperfusion injury is less severe than in single-lung transplantation. Some authors are also of the opinion that double-lung transplantation provides a greater pulmonary functional reserve when bronchiolitis obliterans appears.[22,27] In the long term, it seems that the most important advantage of double-lung transplantation is the longer survival compared to single-lung procedures.[4,6] This debate had already been held at the beginning of the 1990s when the type of lung transplantation for pulmonary hypertension used in the present series started to be practiced.

The indications for heart-lung transplantation have decreased in recent years, given that it has been demonstrated that right ventricular function and structure recover once pulmonary hemodynamics has normalized after lung transplantation.[18,19] Currently this technique is therefore limited to instances of pulmonary hypertension associated with Eisenmenger syndrome resulting from complex congenital heart disease.[6,28]

The arrival of new specific treatments for pulmonary hypertension has forced a reevaluation of the role of lung transplantation in the management of these patients. Although the proportion of lung transplantation procedures indicated for pulmonary hypertension has clearly decreased relative to other diseases in recent years, the absolute number of procedures has remained constant, confirming that pulmonary transplantation remains an important part of the treatment algorithm for pulmonary hypertension. It is difficult to decide when exactly to perform the transplantation. The possibility of lung transplantation is considered on starting treatment with epoprostenol, as overall survival with this treatment is similar to that of lung transplantation for this disease.[29] Lung transplantation is indicated when the patient remains in functional class III or IV despite receiving intravenous epoprostenol.[16] Given that patients must usually wait a long time for lung transplantation, evaluation for transplantation and their inclusion on the waiting list should be done before failure of intravenous treatment, which can be anticipated by markers of poor prognosis (6-minute walk distance less than 380 m after 3 months' treatment with intravenous epoprostenol, onset of pericardial effusion, high right atrial pressure, low cardiac index). A detailed clinical and hemodynamic assessment after 3 or 4 months of intravenous treatment would therefore seem appropriate as it would enable timely referral for lung transplantation. If the patient showed a very favorable response to epoprostenol, achieving a stable condition and recovering to functional class I or II, lung transplantation could be postponed. Otherwise, the patient should be added to the waiting list as delays often lead to the need for emergency transplantation and a markedly worse prognosis.[30]

In conclusion, the outcomes of lung transplantation for pulmonary hypertension in our hospital were comparable with those reported for other published series, and we can affirm that it is a therapeutic option that, in selected patients, offers encouraging results for a serious and progressive disease. The favorable impact of new treatments on the management of pulmonary hypertension has led to the referral of fewer patients for lung transplantation in recent years. However, it seems that, given the absence of curative medical treatment, lung transplantation will continue to play a role in this field. Health professionals who work in this area should be aware of the potential of this procedure and ensure that our patients enjoy a genuine chance of success when they undergo lung transplantation.

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