Abstract

Objective: To evaluate the changes in lung function in the first year after single lung transplantation in patients with idiopathic pulmonary fibrosis (IPF). Methods: We retrospectively evaluated patients with IPF who underwent single lung transplantation between January of 2006 and December of 2012, reviewing the changes in the lung function occurring during the first year after the procedure. Results: Of the 218 patients undergoing lung transplantation during the study period, 79 (36.2%) had IPF. Of those 79 patients, 24 (30%) died, and 11 (14%) did not undergo spirometry at the end of the first year. Of the 44 patients included in the study, 29 (66%) were men. The mean age of the patients was 57 years. Before transplantation, mean FVC, FEV₁, and FEV₁/FVC ratio were 1.78 L (50% of predicted), 1.48 L (52% of predicted), and 83%, respectively. In the first month after transplantation, there was a mean increase of 12% in FVC (400 mL) and FEV₁ (350 mL). In the third month after transplantation, there were additional increases, of 5% (170 mL) in FVC and 1% (50 mL) in FEV₁. At the end of the first year, the functional improvement persisted, with a mean gain of 19% (620 mL) in FVC and 16% (430 mL) in FEV₁. Conclusions: Single lung transplantation in IPF patients who survive for at least one year provides significant and progressive benefits in lung function during the first year. This procedure is an important therapeutic alternative in the management of IPF.

Keywords: Pulmonary fibrosis; Respiratory function tests; Lung transplantation.

Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia that is fatal. This poor prognosis is always associated with deterioration of lung function, and estimated median survival after diagnosis is 2.8–4.8 years. Although IPF can remain stable indefinitely in some patients, it progresses to loss of lung function in the vast majority of cases. It has recently been found that the therapeutic strategy adopted worldwide, i.e., the use of corticosteroids and immunosuppressants, is possibly associated with increased mortality in patients with IPF. In view of the inefficacy of currently available therapeutic measures and the rapid and inexorable progression of IPF, lung transplantation remains one of the few effective treatment options.

The first single lung transplantation was performed at the University of Toronto in 1983 in order to treat IPF, being successful and resulting in prolonged patient survival. In recent years, lung transplantation has been increasingly recommended for the management of IPF, and, in many centers, it is the standard of care for IPF.

Current data on lung transplantation for the treatment of IPF show that the procedure has a significant impact on patient survival, estimated 1-, 5-, and 10-year survival rates being 74%, 45%, and 22%, respectively.
The patients who died before the first year of follow-up and those who were unable to undergo lung function assessment at the end of the first year after transplantation were excluded.

Before transplantation, patients had been receiving follow-up care from the clinical team at our lung transplant center, in accordance with then-current national and international guidelines for the treatment of IPF. All patients were enrolled in a pulmonary rehabilitation program for patients with fibrosing interstitial lung disease.

The lung that was to be removed was chosen on the basis of international guidelines for lung transplantation, the degree of lung impairment and lung size compatibility having previously been analyzed. As a rule, IPF patients at our center undergo single lung transplantation only.

Pulmonary function testing

All patients underwent pulmonary function testing before transplantation and during the first year of follow-up. All tests were performed at the same location, i.e., the Laboratório de Função Pulmonar of the Pavilhão Pereira Filho of the Santa Casa de Porto Alegre, being performed by a team of technicians trained in pulmonary function testing. All tests were performed with a MasterScreen IOS device (Viasys Health Care Global, Loma Linda, CA, USA), the results obtained in the first month, in the third month, and at the end of the first year after transplantation being analyzed. All pulmonary function tests were performed in accordance with the Brazilian Thoracic Association criteria and the American Thoracic Society criteria, and the predicted values were those derived for the Brazilian population.

We analyzed the following spirometric parameters: FVC; FEV\textsubscript{1}; and the FEV\textsubscript{1}/FVC ratio.

Statistical analysis

Data were expressed as mean and standard deviation. Lung function variables were analyzed by the paired t-test. The level of significance was set at 5% (p ≤ 0.05). The Wilcoxon test was used in order to determine the differences among pulmonary function test results.

Results

During the study period, 218 patients underwent lung transplantation at the Santa Casa de Misericórdia de Porto Alegre. Few studies conducted in Brazil or any other country and including a significant number of patients have determined the beneficial impact of transplantation on lung function in patients with IPF. In addition to providing symptom relief and improving quality of life, stable or improved lung function is associated with reduced mortality in patients with IPF. The objective of the present study was to evaluate lung function in the first year after single lung transplantation in patients with IPF in order to show the real functional benefit of this therapeutic strategy.

Methods

We retrospectively reviewed the medical records of IPF patients undergoing lung transplantation at the Santa Casa de Misericórdia de Porto Alegre lung transplant center, in the city of Porto Alegre, Brazil, between January of 2006 and December of 2012. All of the patients in the sample underwent single lung transplantation, and 1-year survival was evaluated.

Study sample and inclusion and exclusion criteria

We included patients diagnosed with IPF in accordance with the latest American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association consensus statement. The diagnostic criteria for IPF are as follows: a) exclusion of other known causes of interstitial lung disease, such as occupational or household exposure, connective tissue disease, and drug toxicity; b) a usual interstitial pneumonia pattern on HRCT in patients not undergoing surgical biopsy; and c) HRCT findings suggestive of IPF and a histopathological pattern consistent with the disease in patients undergoing surgical lung biopsy.

Radiological and histopathological criteria were in accordance with the recommendations of national and international guidelines, and in all of the patients included in the study the histopathological diagnosis was confirmed by analysis of the lung removed during transplantation. Radiological and histopathological analyses were performed in the thoracic radiology and diagnostic pathology departments of the Santa Casa de Misericórdia de Porto Alegre.
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third month and the first year after transplantation (Figure 2), a total of 24 deaths having occurred (30%).

Discussion

The data of the present study show that patients with IPF have a significant improvement in lung function during the first year after single lung transplantation. Improved lung function occurs as early as one month after the procedure, with a mean increase in FVC and FEV₁ of 12% from baseline. The most important finding is that the functional improvement persists for 12 months following transplantation, with an additional mean increase of 19% from baseline. Lung function improvement persisted despite the fact that patients underwent single lung transplantation rather than bilateral lung transplantation and the fact that the fibrotic process that had led to their being on the waiting list for lung transplantation persisted in the remaining lung. One limitation of the present study is that 14% of the patients who were eligible for inclusion did not undergo pulmonary function testing at the end of the first year after transplantation. Therefore, the study results refer exclusively to the lung transplant recipients who underwent all of the required spirometry tests. Among the IPF patients who underwent single lung transplantation at our center during the study period, 1-year survival was 70%.

Given that IPF is a disease for which there is no pharmacological treatment whose efficacy in improving or even stabilizing lung function has been confirmed, the results of the present study underscore the need for lung transplantation in patients with IPF, transplantation being the only therapeutic measure that has any impact on lung function. Another reason why lung transplantation is the only viable treatment option for patients with advanced IPF is that disease severity and mortality rates in IPF patients waiting for lung transplantation are far superior to those in other lung transplant candidates. Hayden et al. reported six-month survival rates of 38% and 81%, respectively, in patients with IPF and pulmonary emphysema undergoing lung transplantation.

Few studies have assessed functional improvement in IPF patients undergoing lung transplantation, many of which have shown incomplete data. Tomaszek et al.
Pêgo-Fernandes et al. [28] observed a similar functional improvement at the end of the first year after transplantation, the increase in FVC being greater in the patients who had undergone bilateral lung transplantation than in those who had undergone single lung transplantation. Given that this was a retrospective cohort study, design-related limitations should be taken into consideration. Given that measurements of lung volumes and pulmonary diffusing capacity were not always available or reproducible, we chose to evaluate only FVC and FEV₁ (as assessed by spirometry). All lung transplant procedures were performed by the same surgical team at the same location, the same technique being demonstrated that functional improvement does not depend on patient age at transplantation. Chacon et al. [26] evaluated 7 IPF patients undergoing single lung transplantation. Pulmonary function tests were performed 6-12 months after lung transplantation, mean FVC and FEV₁ having improved by 92% and 78%, respectively. No such results were obtained at other centers.

Lanuza et al. [27] evaluated lung function in 10 patients undergoing lung transplantation (bilateral lung transplantation in 2 and single lung transplantation in 8). Reasons for lung transplantation included pulmonary fibrosis, in 1 patient, cystic fibrosis, in 4, and COPD, in 5. In the third month after transplantation, mean FVC and FEV₁ had increased by 58% and 55%, respectively, from baseline.

Table 2 - Lung function in the study sample (N = 44) before and after single lung transplantation.

| Variable       | Waiting list | After LTx | p² | p³ | p⁴ | p⁵ | p⁶ | p⁷ |
|----------------|--------------|-----------|----|----|----|----|----|----|
|                | 1st month    | 3rd month | 1st year |
| FEV₁, L        | 1.48 ± 0.48  | 1.83 ± 0.53 | 1.91 ± 0.62 | < 0.001 | < 0.001 | < 0.001 | 0.144 | 0.112 | 0.047 | 0.001 |<ref>Table 2 - Lung function in the study sample (N = 44) before and after single lung transplantation.</ref>
| FEV₁, % of predicted | 52 ± 17 | 64 ± 18 | 65 ± 19 | 68 ± 22 | < 0.001 | < 0.001 | < 0.001 | 0.480 | 0.064 | 0.061 | 0.001 |
| FVC, L         | 1.78 ± 0.60  | 2.22 ± 0.68 | 2.39 ± 0.65 | 2.40 ± 0.65 | < 0.001 | < 0.001 | < 0.001 | 0.005 | 0.084 | < 0.001 |
| FVC, % of predicted | 50 ± 18 | 62 ± 16 | 67 ± 18 | 69 ± 19 | < 0.001 | < 0.001 | < 0.001 | 0.003 | 0.002 | 0.053 | 0.001 |
| FEV₁/FVC       | 83 ± 19      | 84 ± 10   | 80 ± 12 | 80 ± 10 | < 0.001 | < 0.001 | < 0.001 | 0.006 | 0.024 | 0.937 | 0.361 |

LTx: lung transplantation. *Waiting list vs. 1st month. †Waiting list vs. 3rd month. ¶Waiting list vs. 1st year. ‡1st month vs. 3rd month. ¶*1st month vs. 1st year. ¶†3rd month vs. 1st year. ¶¶The entire period.

Figure 1 - Functional response to lung transplantation in the 44 patients who survived the one-year follow-up period. ¶All comparisons. *Waiting list vs. 1st month vs. 3rd month vs. 1st year. †The entire period.

Figure 2 - One-year survival curve for patients with idiopathic pulmonary fibrosis undergoing single lung transplantation (N = 79).
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used in all procedures. One of the limitations of the study was that only single lung transplant procedures were performed and only single lung transplant recipients were analyzed; in several international centers, bilateral lung transplantation is preferred, being more beneficial in terms of patient survival. The decision to perform single lung transplantation (rather than bilateral lung transplantation) is mainly due to the scarcity of donor lungs, which are not enough to meet the demand of patients waiting for lung transplantation. Therefore, when both donor lungs are viable, two different patients can undergo transplantation at the same time, thus reducing waiting time for lung transplantation (which is crucial for the survival of patients with advanced lung disease). All pharmacological treatments available for IPF at the time of the study were in accordance with international guidelines and were found to have no impact on functional outcome measures. As was the case with the surgical procedures, all pulmonary function tests were performed by the same team (of technicians) using the same equipment, thus contributing to a homogeneous analysis.

On the basis of the data of the present study, we conclude that IPF patients undergoing single lung transplantation have a significant improvement in lung function during the first year of follow-up. These data are significant because IPF inexorably progresses to loss of lung function, being an important marker of poor prognosis. The impact that new drugs such as pirfenidone and nintedanib have on the survival of patients with IPF has yet to be examined. Lung transplantation is currently considered the only treatment modality that can have a significant impact on disease progression and should always be discussed in cases in which the risk of respiratory failure and death is high. However, further studies are needed in order to determine exactly how lung function improves after lung transplantation in patients with IPF.

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